# Indian Consensus Guidelines for the Management of Pancreatic Cancer

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## Abstract

Pancreatic cancer needs a multidisciplinary approach to treatment. These consensus statements encompass all aspects of treatment of pancreatic cancer within the Indian context. This article outlines consensus-based Indian guidelines for pancreatic cancer (PC), created by a national panel of 39 experts using NCCN and ESMO frameworks. Recommendations were systematically developed via evidence review, expert discussion, and conflict-of-interest exclusions. Guidance covers standardized diagnostic workup, risk stratification and multidisciplinary management involving surgical oncology, medical oncology and radiation oncology. Tumor subtypes (resectable, borderline resectable, locally advanced) determine treatment pathways: upfront surgery for eligible patients and neoadjuvant therapy for downstaging, as appropriate. Preferred regimens for advanced/metastatic disease are outlined. Recommendations are tailored to Indian practice, integrating resource stratification and local access issues. Each guideline is graded for evidence strength and consensus level as per ESMO standards. Emphasis on surveillance and early integrated palliative care aims to optimize patient outcomes. These evidence-based guidelines seek to standardize and elevate PC care across diverse settings in India.

**Keywords**
- guideline
- medical oncology
- pancreatic cancer treatment

## Introduction

Pancreatic cancer (PC) is a relatively rare malignancy, ranking 14th in incidence and 7th in mortality globally. In India, it ranks 24th in incidence, with 1% of new cancer cases, and 18th in mortality, but this could have been marred by under-reporting.[1] Despite its rarity, PC is among the leading causes of cancer-related deaths worldwide, with incidence highest in individuals aged 65 to 75 years and particularly prevalent in Northeast India. Metastatic pancreatic cancer (MPC) has a

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dismal prognosis with incidence and mortality curves running in parallel, with only 5% people surviving at 5 years of diagnosis. Given worldwide variations in PC management (as given in NCCN and ESMO guidelines) and diverse financial circumstances in India (government schemes/out-of-pocket expenses), consensus recommendations suited to local needs are essential to guide the management of PC for low- or middle-income countries.

## Materials and Methods

The PC management recommendations were based on existing NCCN[2] and ESMO[3] guidelines. A panel of 39 recognized PC experts was convened to ensure a balanced and thorough evaluation, with members voting on specific questions while abstaining in cases of potential conflicts of interest (►**Supplementary Material**, available in the online version only). The panel discussed areas of significant disagreement or controversy, integrating recent advances and addressing inaccuracies before circulating the revised recommendations for further review via email. Each recommendation follows the ESMO guideline framework,[4] including a level of evidence and grade of recommendation to indicate the strength of the evidence and the consensus level among experts. The degree of agreement was determined by the proportion of experts endorsing each recommendation. This meticulous process ensures that recommendations are based on a systematic evidence review and reflect the collective expertise of the panel. This review addresses key considerations related to the management of PC, including diagnosis, staging, risk stratification, treatment modalities, and palliative care.

## Imaging

Multidetector computed tomography (MDCT) angiography is the gold standard for PC imaging. The pancreatic protocol (PP) mandates intravenous iodinated contrast injection at 1.5 mL/kg at 4 to 5 mL/s with biphasic acquisitions. These include a pancreatic phase (15–20 seconds post-trigger or 35–40 seconds post-contrast injection), which offers maximum contrast differentiation between the hypodense lesion and pancreatic parenchyma. A portal venous phase (30 seconds after the pancreatic phase or 65–70 seconds post-injection) with slice thickness $\leq$2.5 mm aids in assessing vascular invasion and extrapancreatic tumor spread. Furthermore, dynamic imaging during peak pancreatic and liver enhancement phases allows for evaluating vascular invasion, extrapancreatic extension, and liver metastases. This protocol is pivotal for preoperative therapy monitoring and posttreatment reassessment to evaluate resectability. Submillimeter axial slices and multiplanar reconstruction are essential, as studies demonstrate that 70 to 85% of patients can undergo resection when MDCT confirms tumor resectability.[2]

Additionally, the accuracy of MDCT in determining resectability diminishes over time due to the aggressive nature of PC, necessitating preoperative imaging within 4 weeks before surgery. Usually, patients come with CT scans from outside; reimaging with a PP is often required as these scans are suboptimal. MDCT alters management in 56% of patients following repeat imaging.[5] Magnetic resonance imaging (MRI) is a valuable adjunct to CT in the staging of PC whenever CT is not feasible due to contrast allergies or renal insufficiency. This also includes instances where pancreatic tumors are inconclusive or isoattenuating, as seen in 5 to 17% of cases. MRI also plays a critical role in characterizing pancreatic cystic lesions, providing detailed imaging with sequences such as T2-weighted, fat-suppressed T1-weighted, and diffusion-weighted imaging (DWI).[6] If an MRI scan is planned, it should ideally precede any interventions, such as stent placement or biopsies, to prevent procedure-related changes, such as postintervention pancreatitis, from obscuring diagnostic accuracy.[2] However, regardless of the abdominal imaging modality used, staging must always include chest CT to evaluate for thoracic metastases and complete the staging workup. Prior to surgery, liver CEMRI is recommended to exclude the presence of small liver metastases, particularly in cases where tumor markers are elevated or CT findings are inconclusive. MRI has also demonstrated superior sensitivity to CT for detecting small hepatic and peritoneal metastases. Studies, including three case series and a meta-analysis, have shown that MRI, particularly with DWI sequences, identified liver metastases in 10 to 23% of cases that were not visible on CT. This increased sensitivity reduces the risk of unnecessary laparotomies in patients initially deemed operable based on CT findings.[6]

While positron emission tomography-computed tomography (PET-CT) is not routinely recommended for the primary diagnosis of PC due to its overlap with findings from autoimmune conditions and chronic pancreatitis, it can serve as a valuable tool in specific scenarios where distant metastases are uncertain. For instance, PET-CT is beneficial in cases of equivocal or indeterminate findings on standard imaging or high-risk patients with markedly elevated CA19–9 levels, large primary tumors, or concerning symptoms such as excessive weight loss or extreme pain. Notably, PET demonstrated a sensitivity of 61% in detecting metastatic disease, which improves to 87% when combined with standard CT imaging, as opposed to 57% with CT alone. Additionally, PET-CT findings have been shown to influence clinical management, leading to changes in treatment plans in 11% of cases with invasive PC. Moreover, in the neoadjuvant setting, PET-CT can provide valuable information before and after initiating therapy to assess treatment response and restaging. However, limitations include a 7.8% false-positive rate and a 9.8% false-negative rate, as demonstrated in a meta-analysis of 17 clinical studies involving 1,343 patients.[7] Thus, while PET-CT should not replace high-quality contrast-enhanced CT, it remains a useful adjunct in select cases where metastatic disease is suspected but not confirmed. Before initiating chemotherapy for localized PC, cytologic or biopsy confirmation is mandatory to establish a definitive diagnosis.[2] Fibroblast activation protein inhibitor (FAPI) PET imaging shows a promising emerging role in staging workup. It can effectively detect small lesions due to its capability of detecting tumors with strong desmoplastic reactions and higher tumor-to-background contrast, resulting in superior

**Table 1** Imaging

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 1** | | | |
| Utilize multiphasic contrast-enhanced CT for initial imaging of suspected pancreatic cancer, incorporating late arterial and portal venous phases. If obstructive head pancreatic cancer is causing jaundice, perform imaging prior to biliary drainage or stenting. CT of the chest is to be done to complete the initial staging | III | A | 35/35 |
| **Statement 2** | | | |
| Abdominal MRI may be considered when CT is not feasible, yields inconclusive findings, or for the evaluation of pancreatic cystic lesions; in such instances, chest CT is preferable for staging | IV | C | 37/38 |
| **Statement 3** | | | |
| Before surgery, CEMRI of the liver may be considered to verify the absence of small liver metastases in case of equivocal findings on CT | III | B | 9/13 |
| **Statement 4** | | | |
| While PET-CT is not recommended for initial tumor diagnosis, it can be beneficial in situations where the presence of distant metastases is uncertain, such as doubtful initial imaging or elevated CA19-9 levels despite biliary drainage | III | C | 32/35 |

sensitivity and positive predictive value compared with FDG-PET/CT. Notably, FAPI-PET improved TNM staging in 25% of PC patients and altered clinical management in 12% of cases[7] (►**Table 1**).

## Tissue Diagnosis

EUS-FNA is preferred due to its high accuracy and reliability in determining malignancy, with sensitivity and specificity values of 90.8 and 96.5%, respectively. This approach is essential for patients with neoadjuvant therapy or those with locally advanced, borderline resectable, or metastatic PC. If EUS-FNA is not feasible, alternatives like endoscopic cholangioscopy, percutaneous or laparoscopic biopsies, or pancreatic ductal brushings may be used. If malignancy is unconfirmed, repeat biopsy is recommended, with EUS-FNA and core needle biopsy at a high-volume center preferred. For borderline resectable cases, advanced evaluation at specialized centers is advised. Surgery may proceed without biopsy in localized PC with R0 resection potential if clinical and radiographic findings strongly support PC, as biopsy is not mandatory. A nondiagnostic biopsy should not delay surgical intervention when clinical suspicion of malignancy is high. In such cases, multidisciplinary tumor board (MDTB) discussion is critical in diagnostic and surgical management decisions. In instances where tissue diagnosis is unavailable, serum IgG4 levels may aid in distinguishing type-I autoimmune pancreatitis from PC.[8] Transabdominal core needle biopsy is generally not recommended unless EUS-FNA is unavailable or not feasible. EUS-FNA is the preferred method in patients with resectable pancreatic disease due to its superior diagnostic yield, safety profile, and significantly reduced risk of peritoneal seeding. Unlike transabdominal approaches, EUS-FNA minimizes the need to traverse vascular and bowel structures, lowering bleeding and infection risks. Moreover, EUS-FNA provides critical staging information during the biopsy procedure, which is vital for treatment planning and prognostication.

CA19–9 is a biomarker frequently expressed and shed in pancreatic and hepatobiliary diseases but is not tumor-specific. The sensitivity of CA19–9 ranges from 79 to 81%, with specificity between 80 and 90% in symptomatic patients, making it useful in disease management rather than initial screening. Due to false elevation in conditions such as biliary obstruction, cholangitis, or inflammation, its low positive predictive value limits its utility as a reliable screening tool. Measurement of CA19–9 levels is most accurate when performed after biliary decompression and normalization of bilirubin. Preoperative CA19–9 levels strongly predict resectability, with values exceeding 250 U/mL increasing the likelihood of staging laparoscopy.[9] Moreover, elevated levels above 500 IU/mL are associated with advanced pathological stage and poor survival outcomes, warranting careful consideration before surgical intervention. It is also critical to recognize that CA19–9 is undetectable in ~15% of the population with blood groups having Lewis antigen-negative phenotypes, further limiting its diagnostic reliability. CA19–9 is a valuable prognostic marker and a tool for monitoring treatment response, particularly in advanced PC, where its levels are elevated in nearly 80% of patients (►**Table 2**).

## Molecular Testing

BRCA and microsatellite instability (MSI) testing are essential in PC management, particularly for identifying germline variants linked to hereditary cancer syndromes. BRCA1 pathogenic or likely pathogenic (P/LP) variant rates range

**Table 2** Tissue diagnosis

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 5** | | | |
| Prior to commencing chemotherapy for localized pancreatic cancer, it is essential to obtain cytology or biopsy confirmation, preferably guided by EUS | III | A | 33/33 |
| **Statement 6** | | | |
| It is reasonable to perform a surgical procedure without a biopsy if the tumor is resectable and R0 resection is feasible, as suggested by the imaging findings, and provided the facility of frozen section analysis is available | IV | C | 35/37 |
| **Statement 7** | | | |
| Transabdominal core needle biopsy is not indicated unless EUS is unavailable or unfeasible for resectable pancreatic cancer. | III | C | 32/36 |
| **Statement 8** | | | |
| CA19.9 levels can be used to assess disease burden and follow disease course, but it is not a substitute for the diagnosis of pancreatic cancer | III | A | 38/38 |

from 1 to 11%, and BRCA2 rates from 0 to 17%, with higher prevalence in familial PC cases and Ashkenazi Jewish populations (5.5–19%).[10] Recent studies report actionable BRCA1 variants at 0 to 3% and BRCA2 at 1 to 6%, underscoring the importance of genetic testing for targeted therapies like PARP inhibitors. BRCA1/2 P/LP variants confer a lifetime PC risk of 3% in males and 2.3% in females, emphasizing tailored risk assessment.[11] Genetic counseling is recommended for individuals with a family history of PC, early-onset disease (<45 years), or associated cancers, supported by tools like PancPRO.[12] Evaluation should include family history of pancreatitis, melanoma, and colorectal, breast, ovarian, or PCs. Counseling is crucial for patients with mutations in genes such as ATM, BRCA1/2, CDKN2A, and MLH1. Preventive strategies, including smoking cessation and weight management, are strongly advised.[13,14] Comprehensive genomic profiling and next-generation sequencing facilitate the identification of mutations and fusions, aiding personalized treatment[2] (►**Table 3**).

## Staging and Risk Stratification

The UICC TNM 8th edition provides a standardized staging system, categorizing PC into resectable, borderline-resectable, locally advanced, or metastatic stages, guiding treatment planning. Staging criteria incorporate the primary tumor's size and extent and the metastatic disease's presence and distribution. Suspicious lymph nodes are defined by enlargement (>1 cm in the short axis) or abnormal morphology, including hypodensity, irregular margins, or involvement of adjacent vessels. Distant metastases are present in over half of PDAC patients at diagnosis, with liver, peritoneal cavity, and lungs being the most commonly affected sites.[15]

**Table 3** Molecular testing

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 9** | | | |
| Germline genetic testing (particularly, HRR pathway genes like BRCA, PALB2) is recommended in all Pancreatic Cancer patients. Genetic Counselling can be considered prior to performing genetic tests | III | A | 35/36 |
| **Statement 10** | | | |
| People with a family history of pancreatic cancer, those diagnosed at a younger age (below 45), or those at an elevated risk should consider seeking genetic counseling | III | A | 35/35 |
| **Statement 11** | | | |
| Comprehensive genomic profiling for advanced pancreatic cancer is suggested if resources permit | IV | C | 33/35 |

 

**Table 4** Resectability criteria in pancreatic cancer (NCCN criteria)[2]

| | Arterial | Venous |
|---|---|---|
| Resectable | | |
| | *SMA, CA, CHA*: no arterial tumor contact | *SMV/PV*: no tumor contact, or contact of <180° without vein contour irregularity |
| Borderline resectable (BRPC) | | |
| BR-PV (SMV/PV invasion alone) | | *SMV/PV*: solid tumor contact of 180° or more, contact of less than 180° with contour irregularity of the vein or thrombosis of the vein, but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction.<br>*IVC*: solid tumor contact |
| BR-A (arterial invasion) | **Pancreatic head/uncinate process:**<br>*SMA*: solid tumor contact of <180°<br>*CHA*: solid tumor contact without extension to CA/hepatic artery bifurcation, allowing for safe and complete resection and reconstruction.<br>Presence of variant arterial anatomy (RHA, CHA) and the presence of tumor contact, as it may affect surgical planning<br>*Pancreatic body/tail*:<br>*CA*: solid tumor contact of < 180°<br>*CA*: solid tumor contact of 180° or more without involvement of the aorta and with intact and uninvolved GDA | |
| Unresectable | | |
| UR-LR (locally advanced) (LAPC) | **Head/uncinate process:**<br>*SMA, CA*: solid tumor contact of 180° or more<br>Solid tumor contact with the 1st jejunal SMA branch<br>**Body and tail**<br>*SMA, CA*: solid tumor contact of 180° or more<br>Solid tumor contact with the CA and aortic involvement | **Head/uncinate process**:<br>*SMV/PV*: unreconstructible due to tumor involvement/occlusion<br>Contact with the most proximal draining jejunal branch into the SMV<br>**Body and tail:**<br>*SMV/PV*: unreconstructible due to tumor involvement/occlusion |
| UR-M (metastatic) | Distant metastasis (including nonregional lymph node metastasis) | |

Abbreviations: SMV, superior mesenteric vein; CA, celiac artery; CHA, common hepatic artery; GDA, gastroduodenal artery; IVC, inferior vena cava; LR, locally advanced; PV, portal vein; RHA, right hepatic artery; SMA, superior mesenteric artery.

PC resectability assessment is guided by anatomical criteria outlined by the NCCN guidelines (►**Table 4**) and biological or conditional factors defined by the IAP consensus. Radiographic evaluation focuses on detecting peritoneal or hepatic metastases, assessing the patency of key vascular structures, including the superior mesenteric vein (SMV), portal vein, and the tumor's spatial relationship with the superior mesenteric artery (SMA), celiac axis, and hepatic artery. Borderline-resectable tumors are those tumors where there are sufficient proximal and distal vessels for reconstruction.[16,17]

The integration of biological factors such as serum CA 19–9 levels is critical for predicting metastatic risk or recurrence. Elevated CA 19–9 levels above 500 U/mL often signal hidden metastatic disease, necessitating a detailed preoperative evaluation.[18,19] Conditional factors focus on patient fitness for major surgery, assessing comorbidities, nutritional status, and functional reserve. Additionally, responses to neoadjuvant therapy, such as reduced tumor size or vascular encasement and normalized CA 19–9 levels, may reclassify borderline-resectable or unresectable cases as potentially resectable.[19]

A multidisciplinary tumor board (MDTB) involving specialists in imaging, surgery, oncology, and gastroenterology is pivotal in managing PC, influencing diagnosis and treatment strategies.[20] MDTB decisions have been shown to alter treatment plans in 18.3% of cases. The cornerstone of managing a patient with newly diagnosed PC is the integration of a multidisciplinary team approach. Endoscopic biliary drainage is advised for patients with resectable or borderline resectable disease presenting with cholangitis, undergoing neoadjuvant therapy, or facing treatment delays exceeding 2 weeks, especially when bilirubin levels exceed 250 µmol/L (~15 mg/dL) or in cases of nutritional compromise. A fully covered, self-expandable metallic stent is preferred.[21]

Only one in five patients presents with resectable disease. Even in this group, 5-year survival remains low at 25%, with a median survival of ~2 years following resection and adjuvant therapy. The most significant prognostic factors for long-term survival include negative margin status (R0 resection), smaller tumor size, and the absence of lymph node

metastases. Nonmetastatic PC is classified into resectable, borderline resectable (BRPC), and locally advanced (LAPC) categories (►**Table 4**). Resectability status should be determined through a consensus at an MDTB, considering imaging findings, serum CA 19–9 levels, performance status, and clinical response.[22] A pooled analysis of 17 studies involving 2,242 patients demonstrated that a >50% reduction or normalization of CA 19–9 levels following neoadjuvant therapy was significantly associated with improved OS ($p < 0.0001$).[23]

The recent international consensus on BRPC defines it across three dimensions[24]:

1. **Anatomical (A):** Tumors with a high risk of margin-positive resection (R1 or R2).
2. **Biological (B):** Indicators suggestive of, but not definitive for, extrapancreatic metastatic disease, such as elevated serum CA 19–9 or suspected metastases on imaging.
3. **Conditional (C):** Increased surgical risk due to host-related factors, including poor performance status and significant comorbidities.

A systematic review and meta-analysis concluded that chronological age is not a contraindication for resection in experienced centers. However, in patients with severe comorbidities (ECOG PS >2) or refractory malnutrition, avoiding surgery may be warranted despite technical feasibility.[25] Hence, the decision to proceed with surgical resection for PC should consider not only anatomical criteria but also the tumor's biological behavior and the patient's ability to tolerate the physiological demands of surgery (►**Table 5**).

## Resectable Pancreatic Cancer

Research suggests that ~80% of patients with localized PC exhibit micrometastases at the time of diagnosis, as reflected by the high recurrence rates observed even among those undergoing cancer therapy.[26,27] Can neoadjuvant therapy before surgery lead to better oncologic outcomes compared with upfront surgery followed by adjuvant chemotherapy? The phase II NORPACT-1 trial evaluated whether neoadjuvant therapy improves outcomes compared with upfront surgery in resectable PC. A total of 140 patients were randomized to receive 4 cycles of neoadjuvant FOLFIRINOX followed by surgery and adjuvant therapy or upfront surgery followed by 12 cycles of adjuvant FOLFIRINOX. Median overall survival (mOS) was 25.1 months in the neoadjuvant group versus 38.5 months in the upfront surgery group, suggesting a detrimental effect of neoadjuvant therapy. However, several limitations need to be considered that might have influenced the outcomes. The study exclusively included patients with tumors located in the pancreatic head and excluded patients with tumors in the body and tail. Also, the patients in the neoadjuvant arm often required biliary drainage and diagnostic confirmation, delaying treatment initiation by almost 2 weeks, unlike those in the upfront surgery arm.[28] A meta-analysis of trials, including PACT-15, PREP-02/JSAP-05, PREOPANC, and NEONAX, demonstrated that neoadjuvant chemotherapy or chemoradiation improves R0 resection rates by 20% but does not significantly improve DFS or OS in resectable PC.[29] Hence, neoadjuvant treatment for resectable PC is not recommended outside the clinical trial setting.

Surgical treatment for PC includes procedures such as pancreaticoduodenectomy, distal pancreatectomy with splenectomy, or total pancreatectomy, depending on tumor location and the extent of pancreatic involvement.[30] Patients with tumors located in the head of the pancreas typically undergo a pancreatoduodenectomy (Whipple procedure). To achieve optimal medial clearance and enhance the likelihood of an R0 resection, dissection of the right hemi-

**Table 5** Staging and risk stratification

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 12** | | | |
| Utilize the UICC TNM 8th edition staging system for the staging of pancreatic cancer. All pancreatic adenocarcinomas should be classified as resectable, borderline-resectable, locally advanced, or metastatic | III | A | 34/34 |
| **Statement 13** | | | |
| Assessment of resectability can be conducted through the application of both anatomical NCCN (National Comprehensive Cancer Network) criteria or biological and conditional features as outlined by the IAP (International Association of Pancreatology) consensus | III | A | 38/38 |
| **Statement 14** | | | |
| For individuals with localized disease, it is preferable to have their imaging assessed at a multidisciplinary tumor board (MDTB) comprising experts in pancreas imaging, pancreas surgery, medical/radiation oncology, and gastroenterology | III | A | 36/36 |

circumference of the SMA up to the right side of the celiac trunk is recommended.[31] In cases of venous involvement, complete resection of the portal vein or SMV, followed by reconstruction, can be performed to achieve an R0 resection. However, venous or arterial resections are associated with a lower likelihood of attaining R0 margins and reduced survival outcomes, likely reflecting the intrinsic aggressiveness of the tumor.[32] An R1 resection is defined as microscopic tumor involvement within 1 mm of the resection margin.[33] The following margins, when applicable, must be clearly identified: anterior, posterior, medial (superior mesenteric groove), SMA, pancreatic transection, bile duct, and enteric margins. For tumors in the body or tail of the pancreas, distal pancreatectomy with splenectomy is typically performed. Radical anterograde modular pancreatosplenectomy, involving dissection of the left hemicircumference of the SMA to the left of the celiac trunk, improves the likelihood of R0 resection.[34]

While minimally invasive techniques may reduce morbidity, data on their oncologic outcomes remain limited, making open surgery the standard of care.[35] Minimally invasive techniques, such as laparoscopic distal pancreatectomy, have shown equivalent survival outcomes to open surgery, with additional benefits of shorter hospital stays and faster recovery, as supported by the LEOPARD-1 trial.[36] Conversely, laparoscopic pancreaticoduodenectomy is technically demanding, with high morbidity rates leading to the premature termination of the LEOPARD-2 trial, highlighting its limited feasibility in general practice.[37]

Standard lymphadenectomy should include the excision of at least 16 lymph nodes, requiring the removal of lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b.[38] The survival benefit of extended resections, including wide para-aortic lymphadenectomy, nerve plexus excision, and multivisceral resections, lacks robust high-level evidence. Consequently, these procedures are not routinely recommended, as they may significantly impair quality of life, potentially causing complications such as intractable diarrhea. Postoperatively, reconstruction involves restoring pancreatic, biliary, and gastric continuity. Clinically relevant postoperative pancreatic fistula remains the most significant complication, with pancreaticojejunostomy and pancreaticogastrostomy being commonly employed for pancreatico-enteric anastomosis, though neither has demonstrated clear superiority.

However, in highly selected patients with stable or nonprogressive disease after neoadjuvant therapy, these procedures may offer survival benefits over palliative care. Similarly, radical surgery for oligometastatic disease has shown potential advantages in select cases. The SMA-first approach, involving six distinct variations, has been proposed to improve margin positivity in borderline resectable PC, with systematic reviews reporting reduced blood loss and transfusion needs. A literature review identified six surgical techniques described as “artery first,” each offering a distinct route to the SMA: via the retroperitoneum (posterior approach), the uncinate process (medial uncinate approach), the infracolic region medial to the duodenojejunal flexure (inferior infracolic/mesenteric approach), the infracolic retroperitoneum lateral to the duodenojejunal flexure (left posterior approach), the supracolic region (inferior supracolic approach), and through the lesser sac (superior approach). These six strategies allow early assessment of arterial involvement based on tumor size and location, before a definitive commitment to resection. Whether their use translates into higher rates of negative surgical margins, better locoregional control, or improved long-term survival remains to be determined. For BRPC and LAPC, arterial resection after induction therapy is generally not recommended but may be considered. The most common procedure involves resection of the common or proper hepatic artery with direct or graft reconstruction. En bloc resection of the common hepatic artery and celiac axis during distal pancreatectomy is feasible without reconstruction.[39] Resection and reconstruction of the SMA are occasionally performed when required for radical tumor removal.[40] Patients with PC are at significantly elevated risk for venous thromboembolic events. Therefore, perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin is recommended for surgical patients unless contraindications are present.[41]

Among patients who undergo surgical resection for PC, the majority experience recurrence, with ~15% developing local recurrence and around 65% presenting with distant recurrence.[42] There is a universal consensus among expert groups on the necessity of adjuvant treatment for all stages of resected PC. However, variations in practice exist across continents. In Europe, adjuvant chemotherapy alone is the standard approach, whereas in the United States, a combination of chemoradiotherapy (CRT) and chemotherapy is more commonly utilized.[43]

The role of adjuvant radiotherapy or CRT remains controversial, with potential benefits observed in margin-positive and node-positive patients. Conflicting evidence exists from various trials. In Europe and Japan, chemotherapy alone is preferred, guided by data from the CONKO-001, EORTC, and ESPAC-1 trials. The EORTC trial showed minimal benefit from adding radiotherapy, while the ESPAC-1 trial suggested it might be detrimental. In contrast, American practice often includes radiotherapy, particularly for node-positive and margin-positive cases, drawing on findings from the GITSG and EORTC trials, along with criticisms of the ESPAC-1 methodology. Even meta-analyses have failed to resolve this ongoing debate on the optimal adjuvant approach.[44]

The ESPAC-1 trial first demonstrated a survival benefit from adjuvant chemotherapy in resected PC, despite some criticism. Building on it, a German phase III trial (CONKO-1), involving 364 patients, established the superiority of adjuvant chemotherapy with gemcitabine over surgery alone in patients with resected PC, irrespective of the achievement of tumor-free resection margins. An updated analysis of this trial revealed a marked improvement in 5-year OS, which was 21% in the gemcitabine group compared with 10% in the surgery-alone group.[45] Subsequently, the ESPAC-3 trial showed comparable survival benefits with adjuvant gemcitabine or 5-fluorouracil (5-FU) plus leucovorin.[46]

The ESPAC-4 trial, a large Phase III study involving 732 patients, compared adjuvant gemcitabine monotherapy with a combination regimen of gemcitabine and capecitabine (GemCap). The study demonstrated a modest improvement in survival outcomes with the combination therapy. The mOS was 28.0 months for the combination group versus 25.5 months for the gemcitabine-alone group ($p = 0.032$). Additionally, the 5-year OS rate was 29% with the combination therapy, compared with 16% with gemcitabine alone.[47]

The Phase III PRODIGE-24 trial represents a landmark study in the treatment of resected PC, comparing 6 months of adjuvant FOLFIRINOX (a combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin) to gemcitabine monotherapy. The trial demonstrated a significant improvement in median disease-free survival (DFS), with FOLFIRINOX achieving 21.6 months compared with 12.8 months. This translated into a notable mOS benefit, extending from 35 to 54 months, with a 3-year OS of 63 versus 49%. This represents the longest median survival reported in a Phase III trial of adjuvant therapy for PC and has established FOLFIRINOX as the standard of care for patients with resected PC who are fit for this regimen.[48] These findings have established mFOLFIRINOX as the preferred adjuvant chemotherapy regimen for patients with good performance status. In a recent ESPAC4 update at 104 months, 732 patients were randomized to gemcitabine ($n = 367$) or GemCap ($n = 365$). mOS was 29.5 months with gemcitabine versus 31.6 months with GemCap ($p = 0.031$). In R0 patients, mOS was 32.2 months on gemcitabine versus 49.9 months on GemCap ($p = 0.002$). Lymph node–negative patients had a higher 5-year OS with GemCap (59%) than with gemcitabine (53%; $p = 0.04$). Among PRODIGE24-ineligible patients ($n = 193$), GemCap also improved survival (25.9 vs. 20.7 months; $p = 0.038$). GemCap remains a standard option for those ineligible for mFOLFIRINOX, with particular benefit in R0 and lymph node–negative disease.[49]

The recent Phase III APACT (Adjuvant Therapy for Patients with Resected Pancreatic Cancer) trial evaluated gemcitabine alone versus gemcitabine combined with nab-paclitaxel in the adjuvant setting. While the study did not achieve its primary endpoint of improved mDFS and hence gemcitabine and nab-paclitaxel (GN) is not a recommended regimen for adjuvant therapy.[50] Regular follow-up after curative-intent treatment is encouraged despite the evidence being limited regarding its impact. Although active surveillance may detect recurrence earlier and facilitate treatment, the effect on OS is still uncertain[51] (►**Table 6**).

## Borderline Resectable Pancreatic Cancer

Evidence supporting neoadjuvant therapy remains limited, with literature-based meta-analyses comparing it to upfront surgery followed by adjuvant chemotherapy yielding conflicting results regarding R0 resection rates and potential survival benefits.[52,53] The benefit of adjuvant chemotherapy following neoadjuvant therapy and pancreatectomy has yet to be determined, as randomized trial data addressing this question are currently unavailable. Several recent trials, including Southwest Oncology Group (SWOG) 1505, PREOPANC, A021501, and ESPAC-5F, have provided valuable insights into the role of neoadjuvant therapy in this context.[54–57]

In borderline resectable PC, the SWOG 1505 trial comparing perioperative mFOLFIRINOX with GN found no significant differences in outcomes among patients who underwent surgery (72%) or in median survival.[55] The primary endpoint of achieving a 2-year survival rate of 58% was not met. Notably, the trial highlighted the critical importance of evaluating patients at high-volume centers within a multidisciplinary setting, as nearly one-third of patients initially classified as having resectable disease were determined to be unresectable upon central review.

The ESPAC-5F trial, presented at the ASCO 2020 Annual Meeting, evaluated surgery alone versus several perioperative regimens (CRT, mFOLFIRINOX, and gemcitabine plus capecitabine) in patients with borderline resectable PC. Approximately two-thirds of patients in all arms underwent primary tumor resection. R0 resection rates were significantly higher with CRT (37 vs. 14% for surgery alone), and 1-year OS was improved in all neoadjuvant arms compared with the surgery-alone arm (77 vs. 42%). Among the neoadjuvant strategies, mFOLFIRINOX achieved the highest 12-month OS (84%), although the trial was not powered for direct comparisons between neoadjuvant regimens.[56]

The Dutch PREOPANC study provides additional evidence supporting neoadjuvant CRT for patients with resectable or borderline resectable PC. While the resection rate was high in the upfront surgery group, the R0 resection rate was significantly higher in the neoadjuvant therapy group (71 vs. 40%). Additionally, among patients who underwent surgery, the NACT arm demonstrated improved OS (35 vs. 20 months; $p = 0$ 0.029).[57] This study questions the benefit of adding radiotherapy to neoadjuvant chemotherapy. PREOPANC reported a 5-year OS of 20.5% with NACRT versus 6.5% with upfront surgery; notably, the OS in the control arm fell below the historical landmark of 10%.[45] Given the relatively young, good-performance-status population with more than half of the patients having resectable tumors in this study, as well as the conflicting data related to the correlation between R0 resection and improvement in OS, the role of radiotherapy in the neoadjuvant setting remains unsubstantiated. The results of the ALLIANCE A021806 study are eagerly awaited. This randomized trial aims to assess the efficacy of perioperative FOLFIRINOX compared with upfront surgical resection followed by adjuvant FOLFIRINOX.[58]

The benefit of adding radiation therapy in R1 resection to improve local control in a disease often marked by systemic failure remains debated. ESPAC-1 showed no survival advantage with adjuvant radiation added to chemotherapy, regardless of margin status.[59] However, prospective and retrospective analyses, including over 1,200 patients, demonstrated improved outcomes with adjuvant chemoradiation, particularly in the R1 subset.[60] A meta-analysis of four RCTs further supported greater survival benefit in R1 over R0 resections.[61] Hence, adjuvant radiotherapy in addition to chemotherapy may be considered on the basis of the individual patient if the resection margins are positive. Radiation therapy in PC is typically administered concurrently with

**Table 6** Resectable pancreatic cancer

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 15** | | | |
| Surgical patients should be provided with perioperative thromboprophylaxis, using either unfractionated heparin or low-molecular-weight heparin unless otherwise contraindicated | I | A | 28/35 |
| **Statement 16** | | | |
| Endoscopic biliary drainage is advisable for patients with cholangitis or those scheduled for neoadjuvant treatment or those facing any inordinate delay exceeding 2 weeks when the bilirubin level exceeds 250 mmol/L (~15 mg/dL) or if they are nutritionally compromised. Placement of a fully covered, self-expandable metallic biliary stent is preferred for resectable and borderline resectable disease; the stent should be a "short SEMS" | I | A | 35/36 |
| **Statement 17** | | | |
| The use of neoadjuvant therapy is not advised for resectable pancreatic cancer, primarily due to the limited availability of phase III evidence, unless within the framework of clinical trials. However, it may be considered in cases of equivocal imaging or elevated tumor markers | II | B | 34/36 |
| **Statement 18** | | | |
| For patients with tumors in the body of the pancreas, it is recommended to undergo radical anterograde modular pancreato-splenectomy, including dissection of the SMA to the left of the coeliac trunk | IV | B | 25/26 |
| **Statement 19** | | | |
| A standard lymphadenectomy, involving the removal of 16 lymph nodes, is advised for adequate pathological staging. Pathological analysis should report the total number of examined lymph nodes and the lymph node ratio. Additionally, frozen section analysis of pancreatic neck transection and common bile duct transection margins for a minimum of 4 mm is suggested | IV | B | 36/36 |
| **Statement 20** | | | |
| Adjuvant chemotherapy for 6 months is recommended for all patients | I | A | 37/37 |
| **Statement 21** | | | |
| mFOLFIRINOX should be a preferred option for adjuvant therapy for patients with ECOG PS 0 or 1 | I | A | 39/39 |
| **Statement 22** | | | |
| Gemcitabine with or without capecitabine is an acceptable alternative for patients unfit for mFOLFIRINOX | I | B | 39/39 |
| **Statement 23** | | | |
| Gemcitabine and nab-paclitaxel are not recommended for adjuvant therapy in resected pancreatic cancer | II | B | 32/33 |
| **Statement 24** | | | |
| Adjuvant radiotherapy may be considered on an individual patient basis if the resection margins are positive | I | B | 34/37 |
| **Statement 25** | | | |
| Regular follow-up is recommended for patients who have undergone resection for pancreatic cancer, even though there is insufficient evidence demonstrating an impact on overall survival | IV | B | 35/36 |

gemcitabine- or fluoropyrimidine-based chemotherapy. Retrospective analyses showed improved outcomes with hypofractionated or stereotactic body radiotherapy (SBRT) over conventionally fractionated RT, including better mOS (13.9 vs. 11.6 months; $p < 0.001$) and 2-year OS (21.7 vs. 16.5%; $p = 0.001$)[62] (►**Table 7**).

## Locally Advanced Pancreatic Cancer

For patients with locally advanced, unresectable PC, an initial 6-month course of systemic combination chemotherapy is recommended. In case of absence of disease progression following induction therapy, the addition of CRT may be

**Table 7** Borderline resectable pancreatic cancer (BRPC)

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 26** | | | |
| Neoadjuvant strategy is recommended in all patients with BRPC due to the high risk of R1/R2 resection and potential survival advantage | II | A | 39/39 |
| **Statement 27** | | | |
| Duration of 3–6 months of neoadjuvant therapy is recommended before proceeding to surgery; the exact duration can be decided on an individual case-by-case basis | IV | B | 37/37 |
| **Statement 28** | | | |
| mFOLFIRINOX or gemcitabine with nab-paclitaxel are both acceptable systemic therapy options for neoadjuvant setting. GEM-CIS can be used in cases of germline BRCA mutation | III | A | 36/36 |
| **Statement 29** | | | |
| Moderately hypofractionated radiation therapy or SBRT may be considered on individual patient basis before surgical exploration | III | C | 29/35 |
| **Statement 30** | | | |
| Surgically eligible patients displaying no disease progression radiologically and a decrease in CA 19-9 following neoadjuvant therapy should undergo exploration, unless contraindicated | III | C | 33/36 |

considered.[63] As with resectable disease, the role of CRT in locally advanced unresectable PC remains debated. The international Phase III LAP07 trial evaluated gemcitabine with or without erlotinib, followed by a second randomization for patients with at least stable disease after 4 months to either continue chemotherapy or transition to CRT with capecitabine as a radiation sensitizer. The trial was terminated at its first planned interim analysis due to a lack of efficacy, showing no improvement in OS or PFS with consolidative CRT. However, a subsequent analysis revealed that patients receiving radiation therapy experienced significantly lower rates of local tumor progression (34 vs. 65%; $p < 0.0001$) and a longer interval before reinitiation of chemotherapy (159 vs. 96 days; $p = 0\ 0.05$).[64]

The NEOLAP trial recently compared a continuous regimen of GN with a sequential approach involving GN followed by FOLFIRINOX. Approximately two-thirds of patients in both arms proceeded to surgery, with no significant differences observed in R0 resection rates or mOS.[54] In the NRG-RTOG 0848 step 2 randomization ($n = 354$), at a median follow-up of 2.2 years, adjuvant fluoropyrimidine plus radiotherapy improved DFS across all patients, with additional DFS and OS benefit in node-negative disease. Five-year OS for node-negative patients was 48% (chemo + CRT) versus 29% (chemo), while node-positive patients showed no OS improvement. Overall, 5-year DFS was 21% (chemo + CRT) versus 15% (chemo) with similar grade 4–5 adverse events. This study suggests that the addition of RT might benefit a particular subset of population.[65]

A study on chemo-naive advanced PC patients aged >65 years with ECOG PS <2 evaluated a modified biweekly regimen of gemcitabine (1,000 mg/m$^2$) and nab-paclitaxel (125 mg/m$^2$) on days 1 and 15 of a 28-day cycle. Among 73 elderly patients, mOS and PFS were 9.1 and 4.8 months, respectively. This regimen demonstrated efficacy comparable to MPACT historical controls, with fewer dose reductions, lower costs, and a favorable toxicity profile.[66] Upon completing planned chemotherapy, patients should undergo reevaluation by a multidisciplinary team with extensive expertise in PC. This assessment determines potential eligibility for surgical resection. For those deemed potentially resectable, consideration should be given to incorporating CRT (►**Table 8**).

## Metastatic Pancreatic Cancer

The insidious progression and nonspecific clinical manifestations of PC often lead to delayed diagnosis.[67] The molecular heterogeneity of PC, combined with the desmoplastic and immunosuppressive characteristics of its tumor microenvironment, significantly limits the efficacy of treatment options for patients with MPC. To date, conventional chemotherapy remains the cornerstone of treatment, offering the primary means of improving survival outcomes in patients with MPC.[68]

A pivotal clinical trial published in 1997 compared gemcitabine versus fluorouracil, demonstrating median survival durations of 4.4 months in the fluorouracil group and 5.7 months in the gemcitabine group. Following these results, gemcitabine was established as the standard of care for chemotherapy in this setting.[69] Subsequent studies explored various doublet combinations with gemcitabine, including cisplatin,[70] 5-FU,[71] and capecitabine,[72] yielding only modest benefits. The emergence of triplet regimens ultimately established the standard of care.

**Table 8** Locally advanced pancreatic cancer (LAPC)

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 31** | | | |
| All patients should receive chemotherapy for at least 6 months before evaluating for potential resectability/conversion. The preferred regimen is mFOLFIRINOX; however, gemcitabine and nab-paclitaxel is an acceptable option | I | A | 35/35 |
| **Statement 32** | | | |
| Consideration for resection exploration may arise in the presence of a substantial CA19-9 level decrease, clinical improvement, and tumor downstaging. While arterial resection post-induction therapy is generally not recommended, experienced centers may contemplate it on a case-by-case basis for selected patients | IV | C | 35/35 |
| **Statement 33** | | | |
| Patients not undergoing surgery after systemic therapy may be considered for consolidated RT | IV | C | 33/36 |

The phase III ACCORD-11 trial showed that FOLFIRINOX significantly outperformed gemcitabine in treating MPC in patients younger than 75 years. The regimen achieved higher response rates, progression-free survival, and OS with a median survival of 11.1 months versus 6.8 months for gemcitabine ($p < 0.001$).[73] While FOLFIRINOX offers significant clinical benefits, it is associated with a higher incidence of febrile neutropenia, sensory neuropathy, and gastrointestinal toxicities. Consequently, this regimen is recommended primarily for patients aged 75 years or younger with good performance status and no substantial risk of cholestasis or cholangitis.

The phase III MPACT trial demonstrated that GN combination therapy outperformed gemcitabine alone as a first-line treatment for MPC. Among 861 patients (ECOG 0–2), mOS was 8.5 months with the addition of nab-paclitaxel versus 6.7 months with gemcitabine alone ($p < 0.001$). Additionally, the adverse effects associated with this regimen appear to be less severe than those observed with FOLFIRINOX, making it a suitable option for a broader patient population.[74] Based on the current evidence, FOLFIRINOX and GN are the preferred treatment regimens for patients with good performance status. Retrospective studies suggest FOLFIRINOX shows greater activity and is often used in fit patients with better ECOG PS. However, a meta-analysis of 3,813 patients found no significant OS or PFS advantage over GN as first-line therapy for MPC.[75]

Gemcitabine combined with erlotinib may be a viable alternative.[76] For patients with ECOG PS 2 or significant comorbidities, other acceptable first-line therapies include single-agent gemcitabine, 5-FU/capecitabine, FOLFOX, or gemcitabine–capecitabine. Where available, S-1 monotherapy offers a convenient oral alternative to gemcitabine. The NAPOLI-3 trial compared NALIRIFOX (liposomal irinotecan, 5-FU, and oxaliplatin) with nab-paclitaxel and gemcitabine in 770 de novo MPC patients. NALIRIFOX demonstrated superior mOS (11.1 vs. 9.2 months, $p = 0.036$). Based on these results, the FDA approved NALIRIFOX as a first-line treatment for metastatic pancreatic adenocarcinoma.[77] The SEQUENCE trial evaluated sequential GN followed by mFOLFOX versus GN as first-line therapy for MPC. The sequential regimen significantly improved mOS (13.2 vs. 9.7 months) and median PFS (mPFS; 7.9 vs. 5.2 months) compared with standard therapy.

Less than half of the patients with advanced PC receive second-line therapy.[78] Second-line therapy selection depends on ECOG PS, comorbidities, and organ function. Most studies in this setting, conducted pre-FOLFIRINOX, assessed oxaliplatin-based chemotherapy post-gemcitabine failure, now applicable only to a small subset of patients in the current era. The phase III NAPOLI-1 trial demonstrated improved outcomes with nanoliposomal irinotecan plus 5-FU over 5-FU alone in MPC, with mOS of 6.1 versus 4.2 months ($p = 0.012$). Secondary endpoints, including PFS, objective response rates (ORRs), and time to treatment failure, were also significantly better. Additionally, contrasting findings on FOLFOX as a second-line regimen merit consideration. The CONKO-003 trial reported a significant OS benefit with FOLFOX compared with 5-FU/LV monotherapy, while the PANCREOX study did not. Differences may stem from lower oxaliplatin doses and better tolerance in the CONKO-003 trial.[79,80] Following gemcitabine-based regimens, nanoliposomal irinotecan plus 5-FU is preferred. If unavailable, 5-FU with irinotecan or oxaliplatin may be used, with the choice guided by neuropathy status, though meta-analysis favors irinotecan combinations.[81]

In a systematic review of seven phase III trials ($N = 2,581$) testing first-line NALIRIFOX, FOLFIRINOX, or GN for MPC, mPFS was longer with NALIRIFOX (7.4 months) or FOLFIRINOX (7.3 months) than with GN (5.7 months). Similarly, mOS was lower with GN (10.4 months) compared with NALIRIFOX (11.1 months) and FOLFIRINOX (11.7 months), while there was no statistically significant difference in ORRs among the three regimens, with NALIRIFOX having

considerably fewer grade 3 toxicities.[82] Hence, NALIRIFOX has emerged as a feasible regimen for patients ineligible for FOLFIRINOX, particularly those requiring a triplet regimen like body or tail pancreatic tumors, where DNA adduct accumulation augments the efficacy of platinum-based therapies.[82] Based on retrospective data, gemcitabine plus cisplatin, FOLFIRINOX, or modified FOLFIRINOX are suitable treatment options for patients with MPC and known BRCA1/2 or PALB2 mutations, as they achieve good response to platinum-based chemotherapy regimens.[83]

Maintenance strategies are seldom utilized in PC, where mPFS ranges from 3 to 5 months and mOS remains below 9 to 10 months, largely due to the disease's aggressive nature and limited life expectancy. The POLO study evaluated maintenance therapy with olaparib versus placebo in 154 patients with MPC and germline BRCA1/2 mutations who had not progressed after $\geq$16 weeks of platinum-based chemotherapy. Olaparib significantly improved mPFS (7.4 vs. 3.8 months, $p = 0.004$); however, final OS data showed no significant benefit (19.0 vs. 19.2 months, $p = 0.3487$).[84] Olaparib is FDA-approved for this indication, yet certain limitations warrant caution. Chemotherapy was administered for only 4 months instead of the standard 6, and 11% of the placebo group demonstrated disease regression, suggesting sustained chemotherapy effects. Additionally, no quality-of-life improvement was observed, and olaparib poses significant tolerability challenges.

MSI-high (MSI-H) or mismatch repair-deficient (dMMR) PC and NTRK fusion-positive PC are rare entities and are seen in less than 1% of cases.[85] In the phase II KEYNOTE-158 study, 22 MSI-H/dMMR PC patients treated with pembrolizumab showed an ORR of 18% (one complete response and three partial responses), with mPFS and mOS of 2.1 and 3.7 months, respectively.[86] Although anecdotal, dual immune checkpoint inhibition has shown promising responses. In a study of 10 MSI-H MPC patients treated with nivolumab and ipilimumab, an ORR of 30% (including two complete responses) and a disease control rate of 50% were observed.[87] A phase I/II study on NTRK fusion-positive tumors, including 2% PC cases, demonstrated the promising efficacy of targeted inhibitors like larotrectinib and entrectinib, with a 75% response rate and sustained responses.[88]

The DESTINY-PanTumor2 trial led to tumor-agnostic approval for Fam-trastuzumab deruxtecan-nxki in HER2-positive (IHC3 + )/IHC2+ FISH-positive solid tumors, and this trial included 25 patients with MPC that showed 4% ORR and 3.2 months mPFS with T-DXd.[89] Dabrafenib–trametinib combination also has tumor-agnostic approval in BRAFV600E mutation in solid tumors based on the NCI-MATCH platform trial that included patients with MPC. KRAS mutations are present in almost 90% of MPC, most commonly bG12D, G12V, and G12R, which make these mutations important targets for future therapies. However, the KRAS12GC mutation is detected in only 2 to 3% of MPC. Sotorasib and adagrasib have shown efficacy in the KRAS G12C mutation. In a Phase I/II trial with KRAS G12C-mutated advanced PC, 8 of 38 patients had confirmed objective response with sotorasib.[90] A multicohort phase I/II study evaluating adagrasib showed partial responses in 50% of patients with advanced pancreatic adenocarcinoma.[91]

Less than 10% of patients with MPC present with limited metastatic spread, which might be amenable to local ablative therapy in combination with systemic therapy. A proposed criterion to define oligometastatic PC is characterized by (1) $\leq$4 liver or lung metastatic lesions, (2) CA 19–9 levels <1,000 U/mL, and (3) response to systemic therapy.[92] The role of metastatectomy remains unclear and is recommended only for select patients, particularly those with durable radiologic and biochemical responses and low-volume lung-only metastases.[93] A systematic review and meta-analysis of six retrospective studies demonstrated improved survival in patients receiving chemotherapy followed by surgery compared with chemotherapy alone, with mOS ranging from 23 to 56 months versus 11 to 16 months, respectively. FOLFIRINOX was the most commonly used chemotherapy regimen.[94] A single-center study involving 85 patients reported a mOS of a little over 1 year and a 5-year survival rate of 8%.[95] Another study on 78 patients suggested prolonged mOS in lung-only metastasis treated with surgery or stereotactic radiotherapy (67.5 months) compared with chemotherapy alone (33.8 months) or observation (29.9 months)[96] (►**Table 9**).

## Palliative Setting

Early palliative care integration is essential in MPC to address symptoms such as pain secondary to celiac plexus involvement, jaundice from biliary obstruction, and gastric outlet obstruction due to locoregional disease. Management includes palliative care interventions with analgesics like morphine, palliative chemotherapy, and often involves interventional pain management and endoscopy specialists. Although preoperative biliary drainage is not routinely performed due to increased risk of complications,[21] it is indicated for patients presenting with cholangitis, significant comorbidities, poor nutritional status, or deranged renal dysfunction.[97] Operative bilioenteric bypass, such as Roux-en-Y hepatico- or choledochojejunostomy, was historically preferred for locally advanced, incurable PC. Currently, endoscopic biliary stenting with ERCP is the standard for palliating obstructive jaundice.[98] Exercise is increasingly recognized as a therapeutic approach for mitigating fatigue, enhancing psychological health, preserving muscle mass, improving physical function, and maintaining quality of life in PC patients, who are predisposed to sarcopenia and cachexia, while also potentially normalizing tumor vasculature to optimize chemotherapy delivery and activating immune responses through the interleukin-15 (IL-15) axis.[99–101] Pancreatic enzyme replacement therapy, administered in divided doses during meals, is effective in managing symptoms of exocrine insufficiency in PC patients, including weight loss, abdominal discomfort, and steatorrhea, with initial dosing recommendations of 30,000 to 40,000 IU per meal and 15,000 to 20,000 IU per snack along with proton pump inhibitors as adjuncts arising due to tumor-induced parenchymal damage, ductal obstruction, or surgical resection.[102]

**Table 9** Metastatic pancreatic cancer (MPC)

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 34** | | | |
| mFOLFIRINOX remains the preferred systemic therapy option for newly diagnosed patients with MPC who have ECOG PS—0 or 1 | I | A | 36/36 |
| **Statement 35** | | | |
| Gemcitabine and nab-paclitaxel may be an acceptable alternative for patients with MPC who have ECOG PS $>1$ | II | A | 33/34 |
| **Statement 36** | | | |
| For elderly and/or frail individuals, gemcitabine monotherapy can be considered | I | B | 33/33 |
| **Statement 37** | | | |
| Sequential/alternating treatment with nab-GEM followed by mFOLFOX or treatment with NALIRIFOX may be considered for some patients | III | C | 16/27 |
| **Statement 38** | | | |
| For patients with BRCA mutation, platinum-based chemotherapy (mFOLFIRINOX or GEM-CIS) is suggested | III | A | 31/31 |
| **Statement 39** | | | |
| Maintenance with olaparib is suggested in patients with BRCA germline mutation who have completed 4–6 months of induction chemotherapy and if it has not progressed | I | C | 28/29 |
| **Statement 40** | | | |
| For patients with dMMR or MSI-high pancreatic cancer, immunotherapy (pembrolizumab preferred) should be considered for second line and beyond | II | A | 30/30 |
| **Statement 41** | | | |
| For patients with NTRK fusion, larotrectinib or entrectinib should be considered for second line and beyond | III | A | 30/30 |

Discussions about various management options should include prognosis and a balanced assessment of risks and benefits. Intensive care unit (ICU) admission is common in the final month of life[103] and should be avoided in view of poor outcomes and financial toxicity with such strategies. Proactive incorporation of end-of-life (EOL) care discussions facilitates better understanding of disease trajectory for patients and caregivers and must be part of the palliative care goals in every institution (►**Table 10**).

In the context of India as a low- to middle-income country with limited resources, the consensus guidelines emphasize cost-effective, pragmatic approaches to PC management, prioritizing MDTBs in high-volume centers to optimize decision-making and avoid unnecessary interventions, given prevalent out-of-pocket expenses and reliance on government schemes like Pradhan Mantri Jan Arogya Yojana—Ayushman Bharat (PMJAY—Ayushman Bharat). For diagnosis and staging, MDCT with PP remains the gold standard, but reimaging should be judiciously performed only when prior scans are suboptimal, while MRI is reserved for cases with CT contraindications or inconclusive findings to minimize costs; PET-CT is not routine and recommended only for equivocal metastases in high-risk patients. Tissue diagnosis via EUS-FNA is preferred at specialized centers, with alternatives like percutaneous biopsies used when EUS is unavailable, and CA19–9 monitoring is advocated post-biliary decompression for its prognostic value without over-reliance due to false positives. Molecular testing for BRCA and MSI is essential for targeted therapies like PARP inhibitors, but genetic counseling should integrate family history assessments using accessible tools like PancPRO, focusing on high-risk groups such as those with familial syndromes. For resectable PC, upfront surgery followed by adjuvant chemotherapy (mFOLFIRINOX for fit patients or gemcitabine-capecitabine for others) is standard, avoiding neoadjuvant therapy outside trials to reduce delays and costs; in borderline resectable cases, neoadjuvant regimens like FOLFIRINOX or GN are considered, but radiation is debated and not routinely added unless margins are positive. In locally advanced and metastatic settings, first-line therapies prioritize FOLFIRINOX or GN for good performance status patients, with gemcitabine monotherapy or capecitabine for those with ECOG PS 2 or comorbidities, and second-line options like nanoliposomal irinotecan plus 5-FU if available; maintenance olaparib is limited to germline BRCA mutants post-platinum therapy. Early palliative care integration, including endoscopic stenting for jaundice, analgesics for pain, pancreatic enzyme replacement for exocrine insufficiency, and exercise for cachexia, is crucial to enhance quality of life while

**Table 10** Palliative setting

| Guidelines | Level of evidence | Grade of recommendation | Consensus |
|---|---|---|---|
| **Statement 42** | | | |
| Preferential management of duodenal obstruction involves considering endoscopic placement of an expandable metal stent or palliative surgical bypass whenever feasible | IV | C | 20/22 |
| **Statement 43** | | | |
| It is highly advisable to have early involvement of a pain control specialist and a nutritionist for effective pain control and expert nutritional management | III | A | 29/30 |
| **Statement 44** | | | |
| Engaging in physical activity is advised as a beneficial treatment for patients to cope with fatigue and emotional strain, to prevent muscle atrophy, to improve physical abilities, and to sustain a good quality of life | III | A | 27/27 |
| **Statement 45** | | | |
| The use of pancreatic enzyme replacement therapy is effective in alleviating symptoms associated with exocrine insufficiency, including weight loss, abdominal discomfort, and steatorrhea may be considered | III | A | 26/27 |

**Table 11** Standard-of-care systemic therapy in the management of pancreatic cancer

| Setting | Treatment context | ECOG PS 0/1 | ECOG PS $>1$ or age $>75$ y | Duration | Special considerations |
|---|---|---|---|---|---|
| Resectable pancreatic cancer | Adjuvant | mFOLFIRINOX (PRODIGE 24)[48] | Gemcitabine $\pm$ capecitabine (ESPAC-4)[49] | 6 mo | |
| Borderline resectable pancreatic cancer (BRPC) | Neoadjuvant | mFOLFIRINOX[56] | Gemcitabine + nab-paclitaxel | 3–6 mo | If germline BRCA mutation: gemcitabine + cisplatin<br>If R1 resection: consider adjuvant radiation with gemcitabine or fluoropyrimidine-based chemotherapy[60] |
| Locally advanced pancreatic cancer | Neoadjuvant | mFOLFIRINOX | Gemcitabine + nab-paclitaxel | 6 mo | If R1 resection: consider adjuvant radiation with gemcitabine or fluoropyrimidine-based chemotherapy[61] |
| Metastatic pancreatic cancer (MPC) | 1st line | mFOLFIRINOX (ACCORD-11)[75] or NALIRIFOX (NAPOLI-3)[77] or sequential gemcitabine + nab-paclitaxel followed by mFOLFOX (NEOLAP)[54] | Gemcitabine + nab-paclitaxel (MPACT)[66,74] | If germline BRCA mutation: gemcitabine + cisplatin for 6 mo followed by maintenance Olaparib[84] | |
| MPC | 2nd line[81] | | | | If dMMR/MSI-H: immunotherapy (pembrolizumab preferred)[86]<br>If NTRK fusion: larotrectinib or entrectinib[88] |

avoiding aggressive end-of-life ICU admissions to mitigate financial toxicity, ensuring equitable access through resource-stratified adaptations (►**Table 11**).

### Authors' Contributions

B.S. and V.L. contributed to the conception and design of the manuscript. All the authors contributed to the definition of intellectual content, literature search, manuscript preparation, manuscript editing, and manuscript review. All the authors have read and approved the manuscript, met the requirements for authorship, and believe that the manuscript represents honest work.

### Patient Consent

Patient consent is not required.

### Conflict of Interest

None declared.

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