

## Supplementary Materials

### Exploring chatbot applications in pancreatic disease treatment: potential and pitfalls

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## CHATGPT

1. What are the known risk factors for sporadic Pancreatic cancer?

Risposta 1.

Sporadic pancreatic cancer, which occurs without a clear hereditary or familial predisposition, is associated with several known risk factors. Here's a summary of the key risk factor

1. Smoking: One of the most significant and well-established risk factors. Cigarette smokers are about twice as likely to develop pancreatic cancer compared to non-smokers. The risk increases with the number of years and amount of smoking, but it decreases after smoking cessation, with risk dropping significantly after 10-15 years of quitting.

2. Age: The risk of pancreatic cancer increases with age, particularly after the age of 60.

Most cases are diagnosed in individuals over 65 years old.

3. Chronic Pancreatitis: Long-term inflammation of the pancreas can increase the risk of pancreatic cancer. Chronic pancreatitis may result from a variety of causes, including alcohol abuse and genetic factors (though the latter is more often linked to hereditary forms of the disease).

4. Diabetes: New-onset diabetes, particularly in older adults, is considered both a risk factor and an early symptom of pancreatic cancer.

Long-standing type 2 diabetes has also been associated with an increased risk, though the relationship is complex and not entirely understood.

5. Obesity: Obesity (BMI > 30) has been associated with an increased risk of pancreatic cancer. Fat tissue increases insulin resistance and chronic inflammation, both of which are believed to contribute to the development of cancer.

6. Diet: Diets high in processed meats (such as bacon, sausages, and hot dogs) and red meat have been linked to a higher risk of pancreatic cancer.

Conversely, diets rich in fruits, vegetables, and fiber are thought to have a protective effect.

7. Alcohol Abuse: Excessive and long-term alcohol use can increase the risk of chronic pancreatitis, which is a known risk factor for pancreatic cancer.

Alcohol may also have a direct carcinogenic effect on the pancreas, but the evidence for this remains mixed.

8. Exposure to Certain Chemicals: Occupational exposure to certain chemicals used in dry cleaning, metalwork, and petroleum industries has been linked to a higher risk.

Chemicals such as pesticides, benzene, and chlorinated hydrocarbons have been implicated.

9. Non-O Blood Type: People with blood types A, B, and AB have a slightly higher risk of developing pancreatic cancer compared to those with blood type O.

The reason for this association is not entirely clear, but it might be related to the role of blood group antigens in the pancreatic ductal epithelium.

10. Helicobacter pylori (H. pylori) Infection: Some studies suggest that chronic infection with H. pylori, the bacteria that causes stomach ulcers, may increase the risk of pancreatic cancer, though this link is not as strong as for other gastrointestinal cancers like stomach cancer.

11. Family History (Without Known Genetic Mutations): While this is a smaller contributor compared to familial pancreatic cancer syndromes, individuals with one or more first-degree relatives who have had pancreatic cancer have a modestly increased risk of developing the disease themselves, even in the absence of known hereditary mutations.

12. Gallstones and Biliary Tract Disease: Some studies have suggested a possible association between a history of gallstones or other biliary tract diseases and an increased risk of pancreatic cancer, possibly due to chronic inflammation in the region.

These risk factors contribute to the development of sporadic pancreatic cancer through mechanisms such as chronic inflammation, DNA damage, and impaired immune

surveillance. In addition to these established risk factors, researchers are continuously exploring other potential contributors, such as the gut microbiome and metabolic diseases.

## Risposta 2.

Sporadic pancreatic cancer, which occurs in individuals without a known hereditary predisposition, is the most common form of pancreatic cancer. Several environmental, lifestyle, and medical factors have been identified as contributing to the risk of developing sporadic pancreatic cancer. These include:

### 1. Smoking:

- Cigarette smoking is the most established modifiable risk factor, responsible for about 20-25% of cases.
- Risk increases with the number of cigarettes smoked and the duration of smoking.
- Quitting smoking reduces the risk, but former smokers remain at higher risk compared to non-smokers for many years.

### 2. Chronic Pancreatitis:

- Chronic inflammation of the pancreas, often due to long-standing alcohol abuse or hereditary pancreatitis, increases the risk.
- Chronic pancreatitis leads to changes in pancreatic tissue over time, increasing susceptibility to cancer.

### 3. Diabetes Mellitus:

- Long-standing type 2 diabetes (especially more than 5 years) is a risk factor.
- New-onset diabetes in older adults may be an early indicator of pancreatic cancer, often referred to as a “paraneoplastic” manifestation.

### 4. Obesity and Diet:

- Obesity, particularly abdominal or central obesity, is associated with an increased risk of pancreatic cancer.
- Diets high in red and processed meats, as well as high-fat diets, have been linked to a higher risk.
- Conversely, diets rich in fruits, vegetables, and whole grains are believed to reduce the risk.

### 5. Age:

- Pancreatic cancer predominantly affects older individuals. Most cases are diagnosed after age 60, with the median age at diagnosis being around 70 years.

### 6. Alcohol Consumption:

- Heavy alcohol consumption, particularly when it leads to chronic pancreatitis, may elevate the risk of pancreatic cancer.
- The association is stronger when alcohol use results in chronic inflammation of the pancreas.

#### 7. Family History of Pancreatic Cancer (Without Known Genetic Syndromes):

- While this can be part of familial pancreatic cancer syndromes, even in the absence of a clearly defined genetic syndrome, having a first-degree relative with pancreatic cancer increases one's risk of developing the disease.

#### 8. Gallstones and Biliary Tract Disease:

- Some studies suggest a relationship between gallstone disease or gallbladder surgery and an elevated risk of pancreatic cancer, possibly due to bile reflux and chronic irritation.

#### 9. Helicobacter pylori (H. pylori) Infection:

- There is some evidence that chronic infection with H. pylori, especially strains associated with more virulent forms, may be linked to pancreatic cancer.

#### 10. Workplace Exposures:

- Occupational exposure to certain chemicals, such as pesticides, dyes, and petroleum products, has been associated with an increased risk of pancreatic cancer in some studies.

#### 11. Non-O Blood Group:

- Individuals with blood types A, AB, or B may have a slightly higher risk of developing pancreatic cancer compared to those with blood type O. The exact mechanisms are unclear but may involve differences in immune responses or inflammation pathways.

#### 12. Physical Inactivity:

- Sedentary lifestyles are linked to an increased risk of many cancers, including pancreatic cancer. Regular physical activity is believed to offer some protective effect.

#### 13. Coffee Consumption (Debatable):

- Early studies suggested an association between heavy coffee drinking and pancreatic cancer, but subsequent studies have largely discounted this link. Current evidence does not strongly support coffee as a significant risk factor.

#### 14. Non-hereditary Gene Mutations:

- Accumulation of somatic mutations in genes like KRAS, TP53, CDKN2A, and SMAD4 can occur sporadically due to environmental exposures, inflammation, or other unknown factors, contributing to the development of pancreatic cancer.

In summary, the key modifiable risk factors for sporadic pancreatic cancer include smoking, chronic pancreatitis, diabetes, obesity, and certain dietary habits. Non-modifiable factors

include age, family history, and blood type. Given the aggressiveness of pancreatic cancer, addressing these modifiable risk factors through lifestyle changes (e.g., smoking cessation, maintaining a healthy weight) can reduce the risk of developing this disease.

Risposta 3.

#### 1. Smoking

- A significant risk factor, with smokers having a higher likelihood of developing pancreatic cancer compared to non-smokers.

#### 2. Obesity

- Excess body weight increases the risk, likely due to metabolic changes and chronic inflammation.

#### 3. Age

- Risk increases with age, particularly in individuals over 65.

#### 4. Diabetes

- New-onset diabetes, especially in older adults, can be both a risk factor and a symptom of pancreatic cancer.

#### 5. Chronic Pancreatitis

- Long-standing inflammation of the pancreas can elevate risk, particularly in those with hereditary pancreatitis.

#### 6. Diet

- High consumption of red and processed meats, and low intake of fruits and vegetables, may be linked to increased risk.

#### 7. Family History

- While sporadic, a family history of pancreatic cancer can increase risk, even without known genetic syndromes.

#### 8. Alcohol Consumption

- Heavy alcohol use has been associated with an increased risk, likely through its role in chronic pancreatitis.

#### 9. Exposure to Certain Chemicals

- Occupational exposure to substances like pesticides, dyes, and some industrial chemicals may be linked to higher risk.

#### 10. Genetic Factors

- While sporadic, some individuals may have genetic predispositions that do not fit classic hereditary syndromes.

Understanding these risk factors can help in identifying high-risk individuals and potentially improving early detection and intervention strategies. If you want to discuss any specific risk factor in more detail, let me know!

The diagnostic pathway for pancreatic cancer involves a series of steps to confirm the diagnosis and determine the stage of the disease. Since early detection is challenging, timely and accurate diagnosis is crucial to improving patient outcomes. Here is the typical diagnostic approach:

2. Is the new onset of diabetes mellitus considered a risk factor for pancreatic cancer?

Risposta 1.

Yes, new-onset diabetes mellitus, particularly in older adults, is considered both a risk factor and a potential early symptom of pancreatic cancer. This connection is significant, and there are a few key aspects to consider regarding the relationship between new-onset diabetes and pancreatic cancer:

1. Bidirectional Relationship: Long-standing type 2 diabetes has been associated with an increased risk of pancreatic cancer, particularly in people who have had diabetes for more than five years. Chronic hyperglycemia and insulin resistance may contribute to carcinogenesis.

New-onset diabetes, especially in individuals over the age of 50, can sometimes be an early manifestation of pancreatic cancer, as the tumor itself can cause changes in glucose metabolism.

2. Early Warning Sign: In about 1-2% of individuals who develop new-onset diabetes after age 50, pancreatic cancer may be diagnosed within three years. The onset of diabetes in these patients is believed to be related to the cancer interfering with insulin secretion and glucose regulation.

Pancreatic cancer-induced diabetes tends to be more severe and progresses rapidly, sometimes leading to insulin resistance and weight loss despite hyperglycemia.

3. Potential Mechanism: The exact mechanism by which pancreatic cancer leads to diabetes is not fully understood, but it is thought that:

Tumor cells may secrete substances (e.g., islet amyloid polypeptide) that impair insulin secretion and action.

The inflammation associated with the tumor and damage to the insulin-producing beta cells of the pancreas may also disrupt normal glucose metabolism.

4. Clinical Implication: The development of new-onset diabetes, especially when accompanied by other symptoms like weight loss or abdominal pain, should raise suspicion for pancreatic cancer, particularly in patients without traditional risk factors for type 2 diabetes (such as obesity or a family history of diabetes).

In some screening strategies, individuals with new-onset diabetes and certain high-risk profiles (such as older age and a rapid decline in body weight) may be targeted for imaging to rule out pancreatic cancer.

Conclusion: New-onset diabetes mellitus is indeed considered a risk factor and possible early marker for pancreatic cancer, particularly in older adults. The association has prompted some experts to recommend screening

Risposta 2.

Yes, new-onset diabetes mellitus (particularly in individuals over the age of 50) is considered an important risk factor and, in some cases, an early warning sign of pancreatic cancer. This association has been increasingly recognized in recent years.

1. Bidirectional Relationship:

- Pancreatic cancer and diabetes mellitus have a complex, bidirectional relationship. Long-standing type 2 diabetes is a known risk factor for pancreatic cancer, but new-onset diabetes may also be a manifestation of the cancer itself.

2. Paraneoplastic Phenomenon:

- In some cases, pancreatic cancer causes diabetes, rather than the other way around. This is thought to be due to the tumor disrupting the normal function of insulin-producing beta cells in the pancreas. Cancer-related diabetes often presents as new-onset diabetes in individuals who had no prior history of blood sugar issues.

3. Timing:

- New-onset diabetes that develops within 1 to 3 years before the diagnosis of pancreatic cancer is sometimes referred to as "diabetes of recent onset" or "paraneoplastic diabetes". It is often more severe and progresses faster than typical type 2 diabetes.

4. Clinical Features:

- Individuals over the age of 50 who suddenly develop diabetes without typical risk factors (like obesity, a sedentary lifestyle, or a family history) may warrant further investigation.
  - These patients may also have unexplained weight loss, which is atypical for most cases of newly diagnosed type 2 diabetes.
5. Early Detection Opportunity:
- Recognizing the association between new-onset diabetes and pancreatic cancer provides a potential window for early diagnosis. Since pancreatic cancer is usually diagnosed late, identifying those at higher risk based on new-onset diabetes could enable earlier interventions.
6. Biomarkers and Screening:
- Some research is focused on identifying biomarkers (e.g., CA 19-9 levels, microRNAs) in people with new-onset diabetes to help distinguish between typical type 2 diabetes and cancer-related diabetes. Imaging studies (such as abdominal CT or MRI) may be considered in patients with new-onset diabetes who present with other warning signs, such as weight loss or abdominal discomfort.
  - Studies suggest that approximately 1-2% of people with new-onset diabetes over the age of 50 may be diagnosed with pancreatic cancer within 1 to 3 years of their diabetes diagnosis. In summary, new-onset diabetes, especially in older adults and in the absence of traditional risk factors for type 2 diabetes, can indeed be a harbinger of pancreatic cancer and should raise clinical suspicion, prompting further diagnostic evaluation.

Risposta 3.

Yes, new-onset diabetes mellitus is considered a risk factor for pancreatic cancer. The relationship between diabetes and pancreatic cancer is complex and bidirectional:

1. Risk Factor:

- Long-standing Diabetes: Individuals with long-term diabetes have an increased risk of developing pancreatic cancer compared to those without diabetes. Chronic hyperinsulinemia and hyperglycemia may promote pancreatic tumorigenesis.

2. Early Indicator:

- New-Onset Diabetes: Recent onset of diabetes, especially in individuals over the age of 50 without typical risk factors for diabetes (such as obesity or family history), can be an early sign of pancreatic cancer. In some cases, pancreatic tumors may disrupt insulin production, leading to diabetes.

3. Screening Considerations:



- High-Risk Individuals: For patients who develop diabetes later in life without obvious causes, healthcare providers might consider screening for pancreatic cancer, particularly if other risk factors (like weight loss, abdominal pain, or family history) are present.

#### 4. Mechanisms:

- Biological Links: The exact mechanisms linking diabetes and pancreatic cancer are still under investigation, but they may involve insulin resistance, inflammatory processes, and changes in the tumor microenvironment.

#### Clinical Implications:

- Monitoring: Healthcare providers should monitor patients with new-onset diabetes for signs and symptoms of pancreatic cancer, especially if they fall into higher-risk categories.
- Research: Ongoing research aims to better understand the temporal relationship and underlying mechanisms between diabetes and pancreatic cancer to improve early detection and outcomes.

#### Conclusion:

While diabetes is both a risk factor and a potential early sign of pancreatic cancer, it is important for clinicians to assess the overall clinical context when evaluating new-onset diabetes in older adults or those with other risk factors for pancreatic malignancies.

if you or someone you know is experiencing new-onset diabetes along with other concerning symptoms, it's advisable to consult a healthcare professional for a comprehensive evaluation.

### 3. what is the correct diagnostic pathway for pancreatic cancer diagnosis?

#### Risposta 1.

The diagnosis of pancreatic cancer often requires a combination of clinical evaluation, imaging studies, and laboratory tests. Due to its often late presentation, a systematic approach is essential for early detection and appropriate staging. Here's the correct diagnostic pathway for pancreatic cancer:

#### 1. Clinical Evaluation:

History and Physical Examination: Symptoms to watch for include jaundice, weight loss, abdominal or back pain, and new-onset diabetes, especially in older adults.

Family history of pancreatic or other cancers may raise suspicion, particularly in cases of hereditary cancer syndromes.

Risk Factors: Smoking, chronic pancreatitis, and obesity should be noted.

#### 2. Laboratory Tests:

**Tumor Marker - CA 19-9:** Elevated CA 19-9 levels can support the diagnosis and are often used for monitoring treatment response or recurrence. However, CA 19-9 is not specific or sensitive enough to be used alone for diagnosis.

It can be falsely elevated in cases of obstructive jaundice or cholangitis, so it must be interpreted cautiously.

**Other blood tests:** Routine liver function tests may show elevated bilirubin and liver enzymes in cases of biliary obstruction due to pancreatic head tumors.

### 3. Initial Imaging:

**Abdominal Ultrasound:** Often the first imaging test performed, particularly if the patient presents with jaundice. It may identify a mass or signs of biliary obstruction (such as dilated bile ducts), prompting further evaluation.

**Contrast-enhanced CT Scan (Pancreas Protocol):** This is the gold standard for initial imaging of suspected pancreatic cancer. It provides high-resolution images of the pancreas, can identify the size and location of the tumor, and assesses involvement of surrounding structures (vessels, lymph nodes, etc.). A CT scan helps classify the tumor as resectable, borderline resectable, locally advanced, or metastatic, which is crucial for treatment planning.

**4. Further Diagnostic Imaging (if needed): MRI or MRCP (Magnetic Resonance Cholangiopancreatography):** MRI may be used as an alternative to CT, especially for patients who cannot tolerate contrast. MRCP is particularly useful for evaluating the bile and pancreatic ducts, detecting small tumors or cystic lesions, and further characterizing biliary obstruction.

**Endoscopic Ultrasound (EUS):** EUS is a highly sensitive test for detecting small pancreatic tumors, and it allows for fine-needle aspiration (FNA) to obtain tissue samples for histologic diagnosis. It can assess local invasion and guide biopsy of lymph nodes or suspicious masses.

**Positron Emission Tomography (PET) Scan:** Sometimes used to evaluate for distant metastases, especially when the primary tumor is detected but metastatic disease is suspected. PET may be particularly useful for identifying occult metastatic disease not seen on CT or MRI.

### 5. Histologic Confirmation

**Biopsy via Endoscopic Ultrasound (EUS):** EUS-guided fine-needle aspiration (FNA) biopsy is the preferred method for obtaining tissue from the pancreatic mass or involved lymph nodes. This provides a definitive diagnosis of pancreatic cancer and can also help differentiate between types (adenocarcinoma, neuroendocrine tumors, etc.).

CT- or Ultrasound-guided Biopsy: If EUS is not feasible, a percutaneous biopsy of a mass or metastatic lesion (e.g., liver metastasis) may be performed.

ERCP (Endoscopic Retrograde Cholangiopancreatography): ERCP is not routinely performed for diagnostic purposes, but it may be used if bile duct obstruction requires relief, such as stenting. During ERCP, brushings from the biliary ducts can be obtained for cytology. This is more often used in patients with obstructive jaundice or when other biopsy methods are not accessible.

6. Staging (to guide treatment decisions):

CT Scan (as part of the diagnostic process) is also key for staging pancreatic cancer according to the TNM (Tumor, Node, Metastasis) system.

Laparoscopy: Diagnostic laparoscopy may be performed in some cases to evaluate for peritoneal metastases, particularly in patients with locally advanced disease to determine if they are candidates for surgery.

7. Molecular and Genetic Testing (Optional but becoming more important): In some cases, especially in patients with a strong family history or younger age, genetic testing for mutations such as BRCA1/2 or PALB2 may be indicated. Next-generation sequencing of tumor tissue is sometimes used to identify mutations that could guide the use of targeted therapies (e.g., PARP inhibitors for BRCA-mutated cancers).

Diagnostic Pathway Summary:

Clinical suspicion based on symptoms and risk factors.

Initial imaging (abdominal ultrasound or CT scan with contrast).

Confirmatory imaging (MRI/MRCP, EUS with FNA biopsy).

Histological confirmation via biopsy (EUS-FNA, ERCP brushings, or percutaneous biopsy).

Staging via CT or other advanced imaging, and possibly diagnostic laparoscopy.

Molecular testing if applicable, especially in younger patients or those with familial risk.

This systematic approach ensures the accurate diagnosis, staging, and appropriate treatment planning for patients with pancreatic cancer.

Risposta 2.

The diagnostic pathway for pancreatic cancer involves a combination of clinical evaluation, imaging techniques, laboratory tests, and biopsy confirmation. Because pancreatic cancer

often presents late and mimics other conditions, the diagnostic process must be thorough and systematic. Here's a typical pathway followed when pancreatic cancer is suspected:

### 1. Clinical Evaluation:

- **History and Symptoms:** Initial presentation often includes nonspecific symptoms such as jaundice, weight loss, abdominal pain, new-onset diabetes, or steatorrhea. Sudden-onset diabetes, especially in patients over 50, can be a warning sign.
- **Physical Examination:** Look for signs such as jaundice, palpable abdominal mass, or hepatomegaly. Cachexia and malnutrition are common in advanced cases.

### 2. Initial Laboratory Investigations:

- **Liver Function Tests (LFTs):** To check for elevated bilirubin and liver enzymes, which may indicate biliary obstruction.
- **Tumor Markers:**
  - **CA 19-9:** The most commonly used serum tumor marker for pancreatic cancer, though it is not specific or sensitive enough for early diagnosis. It's useful for monitoring disease progression and treatment response.
  - **CEA:** Sometimes measured but less commonly used.
- **Fasting Blood Glucose / HbA1c:** Assess for diabetes, especially new-onset or worsening glycemic control.

### 3. Imaging Studies:

- **Abdominal Ultrasound:**
  - Often the first imaging test, especially in patients with jaundice. It can detect biliary tract dilatation or large pancreatic masses, but it is not sensitive for detecting small tumors or for staging.
- **Multiphase Contrast-Enhanced CT Scan (Pancreatic Protocol):**
  - This is the gold standard imaging test for diagnosing pancreatic cancer. A triphasic CT scan (precontrast, arterial, and venous phases) helps assess the tumor, its relationship to blood vessels, and possible metastases.
  - It provides key information about tumor size, location, resectability, and the involvement of major vessels (e.g., celiac axis, superior mesenteric artery, and portal vein).
- **Endoscopic Ultrasound (EUS):**
  - EUS is particularly useful for detecting smaller pancreatic tumors (<2 cm) and assessing vascular invasion or lymph node involvement.
  - It also allows for fine-needle aspiration (FNA) to obtain tissue samples for cytology, which is crucial for confirming the diagnosis.

- Magnetic Resonance Imaging (MRI) and MRCP (Magnetic Resonance Cholangiopancreatography):
  - MRI with MRCP is used if more detailed imaging of the bile duct or pancreatic duct is needed. It's especially useful when CT findings are inconclusive or if there's concern for biliary or pancreatic duct obstruction.
- Positron Emission Tomography (PET-CT):
  - May be used in selected cases to detect distant metastases or assess for recurrent disease. It's not typically used for initial diagnosis but can be valuable for staging.

#### 4. Endoscopic Procedures:

- Endoscopic Retrograde Cholangiopancreatography (ERCP):
  - ERCP is primarily therapeutic (e.g., for placing biliary stents to relieve jaundice) but can also help with diagnosis in certain cases, particularly when the tumor obstructs the bile duct.
  - During ERCP, brush cytology or biopsy can be taken from the bile duct or pancreatic duct.
  - Biliary stenting may be performed to relieve obstruction and improve quality of life in patients with jaundice, even before final diagnosis.

#### 5. Tissue Diagnosis:

- Fine-Needle Aspiration (FNA) or Core Biopsy:
  - Performed during EUS or sometimes via percutaneous routes (CT-guided) to obtain tissue samples for cytological or histological confirmation.
  - Biopsy is essential for confirming malignancy before starting chemotherapy or radiation therapy.
  - Liquid biopsy (analysis of circulating tumor DNA) is being researched as a less invasive diagnostic method, but it is not yet a standard practice.

#### 6. Staging Investigations:

- After the diagnosis is confirmed, accurate staging is critical to guide treatment decisions, particularly regarding surgical resectability. Common methods for staging include:
  - CT or MRI of the chest, abdomen, and pelvis: To assess for metastasis, particularly in the liver or lungs.
  - PET-CT: May be used in staging, especially if metastasis is suspected or for recurrence evaluation.
  - Laparoscopy: Sometimes performed preoperatively in borderline resectable cases to detect small peritoneal or liver metastases not seen on imaging.

#### 7. Multidisciplinary Review:

- Once the diagnosis and staging are confirmed, a multidisciplinary tumor board (involving surgeons, oncologists, gastroenterologists, and radiologists) reviews the case to determine the best treatment approach, especially considering:
  - Resectability of the tumor (resectable, borderline resectable, or unresectable).
  - Possible need for neoadjuvant chemotherapy or radiation therapy before surgery.

#### Diagnostic Pathway Summary:

1. Clinical suspicion → Initial lab tests and imaging (ultrasound, CT)
2. If suspicion persists → Contrast-enhanced CT (Pancreatic protocol) or MRI/MRCP
3. Tissue diagnosis (FNA via EUS or CT-guided biopsy)
4. Further staging with CT, PET-CT, or laparoscopy
5. Multidisciplinary team decision on treatment

This systematic approach ensures timely diagnosis, accurate staging, and the most appropriate treatment for pancreatic cancer. Would you like more detail on any specific diagnostic step or treatment strategies based on staging?

Risposta 3.

#### 1. Clinical Evaluation

-History and Symptoms: The diagnostic process usually begins with a detailed medical history and symptom assessment. Common symptoms of pancreatic cancer include:

- Jaundice (yellowing of the skin and eyes)
- Abdominal pain radiating to the back
- Unexplained weight loss
- New-onset diabetes, especially in older adults
- Nausea, vomiting, or loss of appetite

- Physical Examination: The physician will look for physical signs like jaundice, abdominal masses, or enlarged liver.

#### 2. Initial Laboratory Tests

-Blood Test:

- Liver Function Tests (LFTs): These may show elevated bilirubin levels or abnormal liver enzymes, particularly in cases with bile duct obstruction.

- Tumor Markers:

- CA 19-9: A commonly used tumor marker for pancreatic cancer. Elevated levels can suggest pancreatic cancer, but it is not specific and may also be elevated in benign conditions. It is mainly used to monitor treatment response or recurrence, rather than as a primary diagnostic tool.

3. Imaging Studies: Imaging is critical for detecting pancreatic tumors, assessing the extent of disease, and guiding further diagnostic procedures.

- Abdominal Ultrasound: Often used as an initial screening tool, especially if jaundice is present, to evaluate the liver, bile ducts, and pancreas.

- Contrast-Enhanced Computed Tomography (CT) Scan: Multiphasic Pancreatic CT is the gold standard imaging modality for diagnosing pancreatic cancer. It helps visualize the tumor, assess local spread, and evaluate distant metastases. A high-quality CT scan with pancreatic protocol is typically the first-line diagnostic test.

- Magnetic Resonance Imaging (MRI): An alternative to CT scans, particularly Magnetic Resonance Cholangiopancreatography (MRCP), which provides detailed images of the pancreatic ducts and bile ducts

- Endoscopic Ultrasound (EUS): EUS provides high-resolution images of the pancreas and is more sensitive than CT or MRI for detecting small tumors. It can also be used for fine-needle aspiration (FNA) to obtain tissue samples for biopsy.

#### 4. Endoscopic Procedures

- Endoscopic Retrograde Cholangiopancreatography (ERCP): This is used to assess and treat bile duct obstructions caused by pancreatic tumors. During the procedure, stents can be placed to relieve obstruction, and tissue samples may be collected.

- EUS-Guided Fine-Needle Aspiration (EUS-FNA): If a suspicious mass is detected, EUS-FNA is often performed to obtain a biopsy sample for histopathological examination. This is essential to confirm the diagnosis of pancreatic cancer.

#### 5. Histopathology and Cytology

- Biopsy Confirmation:

- A definitive diagnosis of pancreatic cancer requires microscopic examination of tissue obtained via FNA, core needle biopsy, or during surgical procedures. Cytology from ERCP brushings or fluid from cystic lesions can also provide diagnostic information.

- Pathology reports classify the type of pancreatic cancer, typically adenocarcinoma, and provide information about the tumor's grade.

6. Staging (if cancer is confirmed): Accurate staging is crucial for determining the best treatment plan.

- CT Scan (Chest/Abdomen/Pelvis): Further imaging may be performed to check for metastases in the liver, lungs, or other areas.

- Positron Emission Tomography (PET) Scan: May be used to detect distant metastasis, although it is not part of the routine diagnostic process for all patients.

-Laparoscopy: Sometimes performed to look for small metastatic lesions in the peritoneum or liver that might not be visible on imaging.

7. Molecular and Genetic Testing (Optional): In some cases, molecular testing (e.g., KRAS, BRCA mutations, MSI status) may be recommended, especially for patients with a family history of pancreatic cancer or those being considered for targeted therapies or clinical trials.

#### Summary of Diagnostic Pathway:

1. Clinical Assessment: History, physical exam, symptoms
2. Laboratory Tests: CA 19-9, liver function tests
3. Initial Imaging: Abdominal ultrasound, multiphasic pancreatic CT scan
4. Advanced Imaging: MRI, MRCP, EUS
5. Biopsy: Tissue sampling via EUS-FNA, ERCP, or surgical methods
6. Staging: CT, PET scans, laparoscopy for metastasis detection
7. Histopathology: Definitive cancer diagnosis from biopsy
8. Optional Testing: Genetic and molecular profiling

Once the diagnosis is confirmed and the cancer is staged, the medical team will determine the most appropriate treatment plan, which may include surgery, chemotherapy, radiation, or palliative care.

4. Is positron emission tomography (PET) recommended as a diagnostic method in patients with suspected pancreatic cancer?

Risposta 1.

Positron emission tomography (PET) is not routinely recommended as a first-line diagnostic method for suspected pancreatic cancer. However, it can play a role in specific clinical scenarios. Here's a breakdown of PET's role in the diagnostic workup of pancreatic cancer:

1. Primary Role: PET is primarily used to detect occult metastatic disease, particularly in cases where CT or MRI imaging suggests localized disease but there is a clinical suspicion of metastases. PET can be useful in staging, as it helps detect distant metastatic disease that may not be visible on conventional imaging, thus aiding in treatment planning, especially when curative surgery is being considered.

2. Limitations: PET alone does not provide the same detailed anatomic information as CT or MRI, which are essential for assessing tumor resectability, local invasion, and involvement of surrounding structures. PET can lead to false positives in cases of inflammatory conditions



(e.g., pancreatitis) because inflammation also causes increased glucose uptake, similar to cancer cells. PET-CT (a combination of PET and CT imaging) is more commonly used than standalone PET in this context, as it provides both metabolic and anatomic details.

### 3. When PET Might Be Used:

Indeterminate or borderline resectable cases: PET-CT can help clarify whether a suspicious lesion is metastatic or benign, particularly if CT or MRI results are equivocal.

Suspected metastases: PET-CT is valuable in detecting small, distant metastases (e.g., in the liver or peritoneum) that might not be visible on CT scans.

Differentiation of benign vs. malignant lesions: In some cases, PET can help distinguish between inflammatory lesions (such as chronic pancreatitis) and pancreatic cancer, though this is not always reliable.

### 4. Post-treatment Monitoring:

PET-CT can sometimes be used for follow-up in patients after treatment (e.g., surgery, chemotherapy) to detect recurrence or residual disease.

### Summary of PET in Suspected Pancreatic Cancer:

Not first-line: PET is not a primary diagnostic tool for initial evaluation but can complement other imaging modalities, especially for detecting metastases.

PET-CT: The combined modality of PET-CT is more useful for providing both metabolic and anatomical data.

Selective use: It may be considered in specific clinical circumstances, such as unclear findings from CT/MRI or suspected metastatic disease.

In most cases, contrast-enhanced CT and endoscopic ultrasound (EUS) are more commonly used as first-line imaging modalities for diagnosing and staging pancreatic cancer. PET is typically reserved for further investigation or staging in select cases.

## Risposta 2

Positron Emission Tomography (PET), often combined with CT scanning (PET-CT), is not typically recommended as a first-line diagnostic tool in the initial evaluation of suspected pancreatic cancer. Its primary role is in staging or detecting metastasis in certain specific cases rather than routine diagnosis.

Here are some important details regarding PET-CT in pancreatic cancer:

### 1. Primary Diagnostic Use:

- PET-CT is not a standard tool for initial diagnosis of pancreatic cancer. Imaging modalities such as contrast-enhanced CT (pancreatic protocol) and MRI/MRCP are considered the gold standard for diagnosing and assessing the local extent of the tumor, including its relationship to adjacent vascular structures.
- PET-CT has limited sensitivity in detecting small pancreatic lesions (<2 cm) and may not offer additional value over high-quality CT or MRI in the detection of primary pancreatic tumors.

## 2. Role in Staging:

- PET-CT can be useful in certain cases for identifying distant metastases, especially in locations that may not be clearly visualized on CT or MRI, such as small peritoneal or bone metastases.
- It may also be helpful in assessing the extent of disease when borderline resectability is suspected, as it can reveal occult metastatic disease that might contraindicate surgery.

## 3. Evaluation of Suspected Recurrence:

- PET-CT is more commonly used in the follow-up of pancreatic cancer patients, particularly when recurrence is suspected after surgery or treatment.
- It can help in differentiating between scar tissue and active malignancy or between inflammation and residual cancer.

## 4. Detection of Occult Metastases:

- In patients where there is uncertainty regarding the presence of metastatic disease based on conventional imaging, PET-CT can provide valuable information. For example, it can detect metastases in lymph nodes or distant sites that might be missed on standard CT or MRI.

## 5. Limitations of PET-CT:

- False positives: PET-CT scans can show uptake in areas of inflammation, infection, or benign conditions, leading to false-positive results. This is particularly relevant in cases of chronic pancreatitis, where inflammation can mimic malignancy.
- False negatives: Small tumors or lesions with low metabolic activity may not show up on PET-CT, making it less reliable for detecting early or small tumors.

## 6. When PET-CT is Considered:

- PET-CT may be recommended in selected cases, especially if:
  - There is clinical suspicion of distant metastases not evident on conventional imaging (e.g., unexplained weight loss, elevated CA 19-9 with negative CT scans).
  - Resection is being planned but occult metastases are suspected based on clinical or biochemical findings (e.g., a rising tumor marker with a negative CT).

- The case involves recurrent disease where the source or extent of cancer recurrence is unclear from other imaging modalities.

#### Summary of PET-CT Use in Pancreatic Cancer:

- Not first-line for diagnosis: Contrast-enhanced CT and MRI are preferred for initial evaluation.
- Used in staging: To identify distant metastases not seen on CT/MRI.
- Recurrence evaluation: Helpful in detecting cancer recurrence or distinguishing between residual cancer and post-treatment changes.
- Not sensitive for small tumors or early-stage disease.

In conclusion, PET-CT is reserved for specific clinical scenarios where further clarification on metastasis or recurrence is needed. It complements other imaging techniques but is not the primary tool for initial diagnosis of pancreatic cancer

#### Risposta 3.

Positron Emission Tomography (PET) is not routinely recommended as a primary diagnostic method in patients with suspected pancreatic cancer, but it can be valuable in specific clinical situations, especially for staging and detecting metastasis.

#### When PET Scans Are Used in Pancreatic Cancer:

##### 1. Staging and Detection of Metastasis:

- PET/CT scans can be useful for detecting distant metastases that might not be visible on conventional imaging such as a CT or MRI. It is particularly helpful in identifying small, hidden metastases in the liver, lungs, bones, or lymph nodes.

##### 2. Clarifying Indeterminate Findings:

- When there are indeterminate lesions on CT or MRI (e.g., small liver or lung lesions), a PET scan can help determine whether these are malignant or benign. PET detects areas of high metabolic activity, which is a hallmark of cancerous cells

##### 3. Preoperative Assessment:

- In patients being considered for surgical resection (such as the Whipple procedure), PET/CT can be used to ensure that there is no distant metastatic disease that would make surgery inappropriate.

##### 4. Detection of Recurrence:

- PET/CT is also helpful in detecting recurrent pancreatic cancer, especially when tumor markers like CA 19-9 are elevated but standard imaging does not show clear evidence of recurrence.

Limitations of PET in Pancreatic Cancer:

-False Positives: PET scans detect areas of high glucose metabolism, which can also be present in benign conditions such as inflammation or infection, leading to false-positive results.

- Not a First-Line Diagnostic Tool: PET is generally not used to diagnose pancreatic cancer in the initial workup. Multiphasic contrast-enhanced CT or MRI is typically preferred because these provide better anatomic detail and are more cost-effective for detecting the primary tumor and assessing local invasion.

Current Guidelines:

Most clinical guidelines (e.g., NCCN, ASCO) recommend using PET/CT selectively:

- For detecting distant metastases in patients with localized pancreatic cancer.
- In cases where conventional imaging (CT or MRI) results are unclear or indeterminate.
- Before planned curative surgery to rule out occult metastases.

PET scans are not recommended as a routine diagnostic tool for all patients with suspected pancreatic cancer but can be very helpful in specific clinical scenarios such as staging, identifying distant metastases, and clarifying ambiguous findings on other imaging modalities.

## 5. When is the surgical approach indicated as first-line therapy for pancreatic cancer?

Risposta 1.

Surgery is considered the first-line therapy for pancreatic cancer only in cases where the tumor is resectable or, in some cases, borderline resectable. Surgical resection offers the best chance for long-term survival and potential cure. However, the decision to proceed with surgery depends on careful assessment of the tumor's location, extent, and involvement of surrounding structures. Here are the indications for surgery as first-line therapy:

### 1. Resectable Pancreatic Cancer:

Definition: A tumor that is confined to the pancreas or only minimally involves nearby structures (e.g., blood vessels), without evidence of distant metastases.

**Imaging Criteria:** On high-quality imaging (CT, MRI, or EUS), the tumor should not involve major arteries (such as the celiac axis or superior mesenteric artery) or veins (such as the portal vein or superior mesenteric vein), or the involvement should be minimal and potentially resectable.

**Key Points:**

No distant metastases (e.g., liver, peritoneum).

Clear surgical margins can be achieved.

The patient is medically fit to undergo a major operation

## 2. Borderline Resectable Pancreatic Cancer:

**Definition:** A tumor that involves nearby blood vessels (usually veins, sometimes arteries) but may still be removable with careful surgical planning and vascular reconstruction.

**Typical Approach:** Surgery may be performed upfront in certain cases where vascular involvement is minimal and can be managed intraoperatively.

More often, neoadjuvant therapy (chemotherapy and/or radiation) is given first to shrink the tumor and improve the chances of achieving clear margins during surgery.

After neoadjuvant therapy, reimaging is performed to assess whether the tumor has become resectable, and surgery is then considered.

## 3. Surgical Procedures for Pancreatic Cancer:

**Whipple Procedure (Pancreaticoduodenectomy):** This is the most common surgery for tumors located in the head of the pancreas. It involves removing the head of the pancreas, part of the small intestine (duodenum), the bile duct, and sometimes a portion of the stomach, followed by reconstruction.

**Distal Pancreatectomy:** Used for tumors located in the body or tail of the pancreas. It involves removal of the affected portion of the pancreas, sometimes along with the spleen.

**Total Pancreatectomy:** Rarely performed but may be necessary if the tumor involves the entire pancreas. The entire pancreas is removed, leading to lifelong insulin dependence and enzyme replacement.

## 4. Patient Criteria for Surgery:

**Good Performance Status:** Patients must be in good general health, as pancreatic surgery is a major procedure with significant risks.

**Absence of Significant Comorbidities:** Conditions such as severe heart disease or uncontrolled diabetes may contraindicate surgery.

Absence of Distant Metastases: Surgery is generally only performed if imaging confirms the absence of metastatic disease to distant organs like the liver, lungs, or peritoneum.

#### 5. When Surgery is NOT Indicated as First-Line Therapy:

Locally Advanced Pancreatic Cancer: The tumor involves major blood vessels to the extent that surgical resection is not feasible.

Neoadjuvant therapy (chemotherapy and/or radiation) is the first-line approach, with surgery considered later if the tumor becomes resectable.

Metastatic Pancreatic Cancer: Surgery is not indicated in cases where the cancer has spread to distant organs (liver, lungs, peritoneum).

In these cases, systemic chemotherapy is the mainstay of treatment, with surgery reserved for palliation (e.g., relieving biliary obstruction).

#### 6. Emerging Approaches:

In some borderline resectable cases, there is increasing evidence supporting the use of neoadjuvant therapy (chemotherapy, sometimes with radiation) before surgery. This approach may downstage the tumor, making surgery more feasible and increasing the likelihood of complete resection.

##### Summary of Indications for Surgery:

Resectable pancreatic cancer: Tumor is localized, with no involvement of major blood vessels or distant metastases.

Borderline resectable pancreatic cancer: Tumor involves nearby vessels, but surgery may still be possible with or without neoadjuvant therapy.

Patient eligibility: The patient must be medically fit to undergo a major operation with a reasonable chance of recovery.

Surgery is the most effective treatment for long-term survival in pancreatic cancer, but only a minority of patients are candidates for upfront surgery due to the often advanced stage of the disease at diagnosis.

#### Risposta 2.

A surgical approach is indicated as the first-line therapy for pancreatic cancer only when the cancer is deemed resectable, which means it is localized and can be surgically removed with

curative intent. However, this applies to a minority of cases, as most patients are diagnosed at later stages when the cancer has already spread or involves critical blood vessels.

#### Criteria for Surgery as First-Line Therapy:

Surgery is typically indicated when pancreatic cancer falls into one of the following categories:

##### 1. Resectable Pancreatic Cancer:

- Definition: The tumor is confined to the pancreas without involving nearby arteries (such as the celiac axis or superior mesenteric artery) or critical veins (such as the portal vein or superior mesenteric vein). There is no evidence of distant metastasis (e.g., liver, lungs, or peritoneum).
- Surgical Options:
  - Whipple Procedure (Pancreaticoduodenectomy): For tumors located in the head of the pancreas, this surgery removes the head of the pancreas, part of the small intestine, bile duct, and sometimes part of the stomach.
  - Distal Pancreatectomy: For tumors located in the body or tail of the pancreas, this surgery involves removing the distal portion of the pancreas, and often the spleen.
  - Total Pancreatectomy: Rarely performed, this surgery removes the entire pancreas and spleen. It is considered for certain extensive tumors.

#### Indications for First-Line Surgical Therapy:

- Tumor is localized and not invading major vascular structures.
- No metastasis to distant organs, such as the liver, peritoneum, or lungs.
- Good performance status of the patient, meaning they are medically fit to undergo a major surgery, as pancreatic surgery is complex and associated with significant risks.
- Absence of severe comorbidities that would make surgery too risky.

##### 2. Borderline Resectable Pancreatic Cancer:

- Definition: The tumor is close to major blood vessels (e.g., celiac axis, superior mesenteric artery, or vein) but may still be surgically resectable with vascular reconstruction or other complex surgical techniques.
- Approach:
  - In these cases, neoadjuvant therapy (chemotherapy or chemoradiotherapy) is often given before surgery to shrink the tumor and improve the chances of complete resection. If the tumor responds well to neoadjuvant therapy, surgery is then performed.
  - Surgical resection may still be the first-line option if the tumor is deemed removable with acceptable margins.

### Key Criteria for Determining Resectability:

- No arterial involvement: No tumor encasement of the superior mesenteric artery (SMA), celiac axis, or common hepatic artery.
- Venous involvement: If there is limited involvement of the superior mesenteric vein (SMV) or portal vein (PV), the tumor may still be considered resectable, as vascular reconstruction can be attempted.

### Pre-Surgical Evaluation:

Before surgery is considered, several factors are assessed:

- High-quality imaging: Contrast-enhanced CT or MRI is used to assess resectability by determining the tumor's relationship to critical blood vessels and ruling out distant metastasis.
- Multidisciplinary review: A team including surgeons, medical oncologists, and radiologists typically assesses whether the tumor is resectable and whether the patient is fit for surgery.
- CA 19-9 levels: Tumor marker levels can be elevated in pancreatic cancer. Dramatically high levels of CA 19-9 may raise suspicion of metastatic disease, prompting further evaluation before surgery.

### 3. Palliative Surgery:

In some cases, surgery may be performed even if the tumor is not resectable, but this is not with curative intent:

- Biliary bypass or stenting: For tumors causing bile duct obstruction (resulting in jaundice), biliary bypass surgery or stenting may be done to relieve the obstruction.
- Gastrojejunostomy: To bypass a blocked stomach or duodenum in cases where the tumor has caused gastric outlet obstruction.

### When Surgery is Not Indicated as First-Line Therapy:

- Locally advanced, unresectable cancer: Tumors that have invaded major vessels or surrounding structures, making them too difficult to remove.
- Metastatic disease: Surgery is not recommended when the cancer has spread to distant organs (such as the liver, lungs, or peritoneum), as surgery will not offer a survival benefit in these cases.
- Poor performance status: Patients who are not medically fit to undergo a major surgical procedure due to age, comorbidities, or frailty.

### Post-Surgical Considerations:

Even after successful resection, pancreatic cancer has a high recurrence rate, and adjuvant therapy (typically chemotherapy, sometimes combined with radiation) is often recommended to reduce the risk of recurrence and improve overall survival.



#### Summary of Indications for Surgery:

- First-line surgical therapy is indicated primarily for resectable pancreatic cancer and select cases of borderline resectable cancer.
- Neoadjuvant therapy is typically used in borderline cases before surgery to improve outcomes.
- Surgery is not indicated as first-line treatment in locally advanced or metastatic disease, where chemotherapy and/or radiation are the preferred options.

#### Risposta 3.

Surgery is considered the first-line therapy for pancreatic cancer in patients who are diagnosed with resectable or borderline resectable pancreatic cancer, as it offers the best chance for long-term survival or cure. However, surgery is only feasible in a minority of cases because pancreatic cancer is often diagnosed at an advanced stage when the tumor is no longer operable.

#### Indications for Surgery as First-Line Therapy:

Surgery is indicated when the cancer is localized and has not spread beyond the pancreas or to nearby major blood vessels and organs. The specific scenarios include:

##### 1. Resectable Pancreatic Cancer:

- Definition: In resectable pancreatic cancer, the tumor is confined to the pancreas and has not invaded nearby major blood vessels (like the superior mesenteric artery or celiac axis) or distant organs (such as the liver or lungs).

- Surgical Candidate: Patients with tumors that are classified as resectable based on imaging studies, such as CT scan or MRI, and who are healthy enough to withstand surgery, are the best candidates for surgical resection.

##### -Types of Surgery:

- Whipple Procedure (Pancreaticoduodenectomy): This is the most common surgery for tumors located in the head of the pancreas. It involves removing the head of the pancreas, part of the small intestine, gallbladder, bile duct, and sometimes part of the stomach.

- Distal Pancreatectomy: Used for tumors in the body or tail of the pancreas. It involves removing the tail or the tail and body of the pancreas, often along with the spleen.

- Total Pancreatectomy: Rarely performed, this involves removing the entire pancreas and other nearby organs.

- Outcome: Surgical resection in resectable cases offers the only potential for a cure, but survival rates remain modest, often because microscopic metastases may already be present by the time of surgery. Surgery is typically followed by adjuvant chemotherapy to reduce the risk of recurrence.

## 2. Borderline Resectable Pancreatic Cancer:

- Definition: In borderline resectable pancreatic cancer, the tumor involves nearby blood vessels but is not extensively invading them. The tumor is considered surgically resectable, but with a higher risk of incomplete resection.

- Treatment Strategy:

- Patients with borderline resectable tumors often receive neoadjuvant therapy (chemotherapy, with or without radiation) before surgery to shrink the tumor and improve the chances of complete removal.

- After neoadjuvant treatment, the tumor is reassessed, and if it is deemed operable, surgery can then be performed.

- Rationale: Neoadjuvant therapy is aimed at increasing the likelihood of achieving a negative margin (R0) resection, meaning no cancer cells are left behind.

When Surgery is Not Indicated:

Surgery is generally not indicated as the first-line treatment in patients with:

- Locally Advanced (Unresectable) Pancreatic Cancer: The tumor involves critical blood vessels (like the superior mesenteric artery, celiac axis, or portal vein) too extensively to allow safe removal.

- Metastatic Pancreatic Cancer: The cancer has spread to distant organs (e.g., liver, lungs, peritoneum). In these cases, systemic chemotherapy is the first-line therapy, not surgery.

- Poor Functional Status or High Surgical Risk: Patients who are not medically fit for surgery due to other health issues, such as cardiovascular problems or severe malnutrition, are not candidates for surgical resection.

Factors Determining Surgical Eligibility:

- Tumor Location and Size: Resectability depends on whether the tumor is confined to the pancreas or has spread to nearby vessels or structures.

- Vascular Involvement: Tumors involving major blood vessels may require complex vascular reconstruction, which increases surgical risk.

- Metastasis: Surgery is contraindicated if there is evidence of distant metastases (stage IV disease).

-General Health: Patients need to be in good general health to tolerate major surgery, as pancreatic surgery is complex with a significant recovery period.

Role of Multidisciplinary Team (MDT):

Before surgery is considered, a multidisciplinary team (including surgeons, oncologists, radiologists, and gastroenterologists) evaluates the patient's case to determine if surgery is appropriate. This ensures that surgery is only performed on patients likely to benefit from it.

Summary of Indications for Surgery in Pancreatic Cancer:

1. Resectable Pancreatic Cancer: Surgery is indicated as the first-line therapy for patients with localized disease that has not spread to major blood vessels or distant organs.
2. Borderline Resectable Pancreatic Cancer: Surgery is performed after neoadjuvant therapy to shrink the tumor and increase the chance of a successful resection.
3. No Distant Metastasis: Surgery is not indicated if the cancer has spread beyond the pancreas.

In eligible patients, surgery offers the best chance of long-term survival, though it is often combined with chemotherapy or radiation for optimal outcomes.

6. Is prophylactic extended lymph node and nerve plexus dissection recommended in patients with resectable pancreatic cancer undergoing surgery?

Risposta 1.

Prophylactic extended lymph node and nerve plexus dissection is not routinely recommended in patients with resectable pancreatic cancer undergoing surgery. Here's why:

1. Standard Lymphadenectomy:

During surgery for resectable pancreatic cancer, a standard lymph node dissection is performed. This typically includes removal of regional lymph nodes in the vicinity of the pancreas, particularly around the head (for a Whipple procedure) or the body and tail (for a distal pancreatectomy).

This standard lymphadenectomy targets the nodes that are at the highest risk of harboring metastases and is essential for accurate staging, as lymph node involvement is a strong prognostic factor.

2. Extended Lymphadenectomy:

Extended lymphadenectomy involves the removal of additional lymph nodes beyond the standard ones, including nodes around the celiac axis, para-aortic region, and superior mesenteric artery.

Early studies suggested that extended lymphadenectomy might improve local control of the disease, but more recent high-quality studies and meta-analyses have not demonstrated a clear survival benefit from this approach compared to standard lymph node dissection.

Additionally, extended lymphadenectomy is associated with increased complications, such as delayed gastric emptying, diarrhea, and malabsorption, without a corresponding improvement in survival.

### 3. Nerve Plexus Dissection:

Prophylactic dissection of the nerve plexus (celiac and superior mesenteric nerve plexuses) has also been investigated with the goal of improving local control by removing potential microscopic spread of cancer.

However, studies have shown that this aggressive approach does not lead to a significant improvement in overall survival.

Nerve plexus dissection can also lead to increased postoperative complications, particularly severe diarrhea and neuropathic pain, as these plexuses are crucial for autonomic regulation of the gastrointestinal system.

### 4. Current Guidelines and Practice:

Current guidelines, including those from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), recommend standard lymphadenectomy during pancreatic cancer surgery.

Prophylactic extended lymph node dissection and nerve plexus dissection are not recommended due to the lack of survival benefit and the increased morbidity associated with these procedures.

### 5. Focus on R0 Resection:

The primary goal of surgery in resectable pancreatic cancer is achieving a complete (R0) resection, meaning no cancer cells at the margins of the resected tissue.

Studies have consistently shown that the completeness of the resection (R0 vs. R1) is the most important factor in improving long-term survival.

Extended lymphadenectomy or nerve plexus dissection has not been shown to improve the likelihood of achieving an R0 resection.

#### 6. Alternative Approaches:

Given the poor prognosis of pancreatic cancer even after resection, attention has shifted toward the use of neoadjuvant therapies (chemotherapy, sometimes combined with radiation) to shrink tumors and improve the chances of achieving a complete resection rather than extending the scope of lymph node dissection.

#### Conclusion:

Prophylactic extended lymph node dissection and nerve plexus dissection are not recommended in patients with resectable pancreatic cancer because they do not improve overall survival and increase postoperative complications.

The focus should remain on performing a standard lymphadenectomy and achieving an R0 resection to maximize the potential for cure.

#### Risposta 2.

In patients with resectable pancreatic cancer, prophylactic extended lymph node dissection and nerve plexus dissection (also known as extended lymphadenectomy or extended lymph node dissection) have been studied extensively to determine whether they improve outcomes. However, current evidence and expert guidelines do not recommend extended lymph node and nerve plexus dissection beyond standard lymphadenectomy during surgery for pancreatic cancer.

Here's an overview of the reasoning behind this recommendation:

##### 1. Standard Lymphadenectomy:

- During surgery for resectable pancreatic cancer, standard lymphadenectomy is performed, which involves the removal of regional lymph nodes around the pancreas, including nodes along the hepatoduodenal ligament, common hepatic artery, superior mesenteric vein, and sometimes celiac nodes.
- The goal is to remove lymph nodes that are at high risk of harboring metastatic cancer cells and to ensure complete tumor removal with clear margins.

##### 2. Extended Lymphadenectomy:

- In an extended lymph node dissection, surgeons remove additional lymph nodes outside the standard regional field, including nodes around the celiac trunk, para-aortic region, and superior mesenteric artery.
- The rationale behind extended lymphadenectomy was to improve local control of the cancer and potentially reduce recurrence by removing more potential sites of microscopic disease.

### 3. Nerve Plexus Dissection:

- The nerve plexus dissection involves removing the autonomic nerve plexuses (e.g., the celiac and superior mesenteric nerve plexuses) in the hope of better controlling local cancer spread.
- This can lead to a wider surgical field, but it is associated with increased morbidity, especially postoperative complications related to autonomic nerve damage, such as diarrhea, impaired gastrointestinal motility, and worsened quality of life.

### 4. Clinical Evidence:

- Multiple randomized controlled trials (RCTs) and meta-analyses have compared standard lymphadenectomy with extended lymphadenectomy for resectable pancreatic cancer, and the results consistently show:
  - No improvement in overall survival: Extended lymph node dissection does not lead to better long-term survival outcomes compared to standard lymphadenectomy.
  - Increased morbidity: Extended dissection increases the risk of complications such as diarrhea, delayed gastric emptying, and poor nutritional status due to injury to the autonomic nerve plexus.
  - No difference in local recurrence rates: Even with extended lymph node removal, there is no significant reduction in the rate of local cancer recurrence.

### 5. Current Guidelines:

- NCCN (National Comprehensive Cancer Network), European Society for Medical Oncology (ESMO), and other major guidelines recommend standard lymph node dissection rather than extended dissection for resectable pancreatic cancer.
- The International Study Group on Pancreatic Surgery (ISGPS) also concluded that extended lymphadenectomy should not be performed routinely due to lack of survival benefit and the increased morbidity.

### 6. Focus on Clear Margins:

- For patients with resectable pancreatic cancer, achieving a complete (R0) resection with negative margins is the most important prognostic factor. Surgeons prioritize removing the primary tumor and nearby structures with a clear margin, as this has the greatest impact on survival.

- Extended lymphadenectomy or nerve plexus dissection does not significantly contribute to better survival if clear margins (R0) can already be achieved with standard techniques.

#### 7. Exceptions and Individualized Decisions:

- In rare cases where there is suspicion of lymph node involvement outside the standard field based on preoperative imaging or intraoperative findings, surgeons may extend lymph node dissection. However, this is individualized and not routinely practiced.
- The involvement of large nerve plexuses or vascular structures may influence surgical decisions, but again, this would be based on specific tumor anatomy and not a prophylactic approach.

#### Conclusion:

Prophylactic extended lymph node dissection and nerve plexus dissection are not recommended for patients undergoing surgery for resectable pancreatic cancer. Standard lymphadenectomy, which targets the regional lymph nodes, is considered sufficient, and extended dissection has not been shown to improve survival while increasing the risk of postoperative complications.

#### Risposta 3.

Prophylactic extended lymph node and nerve plexus dissection is not routinely recommended in patients with resectable pancreatic cancer undergoing surgery. While extended lymph node dissection has been studied as a means of improving survival outcomes, evidence does not support its routine use because it has not demonstrated a significant survival benefit and may increase postoperative complications.

#### Key Points:

##### 1. Standard Lymphadenectomy:

- During pancreatic cancer surgery (e.g., Whipple procedure or distal pancreatectomy), regional lymph node dissection is routinely performed as part of the standard procedure. This involves removing lymph nodes around the pancreas, duodenum, and nearby vascular structures to ensure complete removal of the tumor and assess for nodal metastasis.

- The extent of standard lymph node dissection is well-defined and focused on removing the peri-pancreatic lymph nodes (N1 nodes), which are most likely to harbor metastases.

##### 2. Extended Lymphadenectomy:

- Extended lymphadenectomy involves removing additional lymph nodes beyond the standard regional nodes, such as those around the aorta, celiac axis, superior mesenteric artery, and along the para-aortic region (N2 nodes).

- Extended nerve plexus dissection involves resecting nerves that surround major arteries near the pancreas (e.g., the celiac nerve plexus and superior mesenteric nerve plexus). These areas may contain microscopic cancer spread but are also vital for normal bodily functions, and their removal can lead to complications.

### 3. Lack of Survival Benefit:

- Multiple randomized controlled trials (RCTs) and meta-analyses have shown no significant improvement in overall survival or disease-free survival with extended lymphadenectomy compared to standard lymph node dissection in patients with resectable pancreatic cancer.

- A notable study, the Japan Pancreas Society (JPS) trial, and others, compared standard and extended lymph node dissections and found no meaningful difference in long-term survival between the groups.

### 4. Increased Morbidity:

- Extended lymph node and nerve plexus dissections are associated with increased postoperative morbidity. Complications such as:

- Diarrhea

- Delayed gastric emptying

- Increased pain due to nerve damage

- Poor quality of life

- These complications arise from the disruption of autonomic nerve function, particularly when nerve plexuses are involved in the resection.

### 5. Current Guidelines:

- National Comprehensive Cancer Network (NCCN) and other professional guidelines recommend against the routine use of extended lymphadenectomy or nerve plexus dissection in resectable pancreatic cancer surgery.

- They advocate for standard lymphadenectomy, which focuses on removing the lymph nodes most likely to harbor metastatic disease without extending the resection to distant nodes or nerve plexuses.

### 6. Ongoing Research:



- Research is still ongoing to refine the surgical approach for pancreatic cancer, including understanding which patients may benefit from more extensive resections, but routine extended dissection remains not recommended in clinical practice.

Conclusion:

In patients with resectable pancreatic cancer, prophylactic extended lymph node and nerve plexus dissection is not recommended as it does not provide a survival benefit and is associated with increased postoperative complications. The current standard of care is to perform a standard lymphadenectomy, focusing on the regional lymph nodes most likely to be involved in the cancer's spread, while avoiding unnecessary dissection of distant nodes or nerve plexuses.

## 7. What is the definition of borderline resectable pancreatic cancer?

Risposta 1.

Borderline resectable pancreatic cancer refers to a tumor that involves nearby blood vessels to a degree that makes surgical resection challenging but potentially possible. It represents an intermediate stage between resectable and locally advanced, unresectable disease. While these tumors may have vascular involvement, they are not so extensively involved as to make surgery impossible.

Here is the detailed definition and criteria based on involvement of nearby vessels:

1. Definition: Borderline resectable pancreatic cancer is characterized by tumors that have limited involvement of major blood vessels but are not invading them to an extent that precludes the possibility of surgical removal.

These tumors may require complex surgical techniques, such as vascular resection and reconstruction, in order to achieve complete (R0) resection.

2. Vascular Involvement Criteria (Based on Imaging Findings): The classification of borderline resectable pancreatic cancer is primarily based on the relationship between the tumor and key nearby blood vessels, particularly the arteries and veins.

Venous Involvement (Superior Mesenteric Vein [SMV] or Portal Vein [PV]): Tumor abutment or encasement of the SMV or PV, but with a potential for venous resection and reconstruction.

Short segment occlusion of the SMV or PV, but the possibility of reestablishing venous continuity through resection and reconstruction exists.

Involvement does not extend to a degree that would preclude reconstruction or makes resection technically unfeasible.

Arterial Involvement (Superior Mesenteric Artery [SMA], Celiac Axis, or Common Hepatic Artery [CHA]): Superior Mesenteric Artery (SMA): Tumor abutment ( $\leq 180$  degrees of the circumference of the artery), but no full encasement or occlusion.

Celiac Axis: Tumor abutment or short segment encasement that might still allow resection with possible reconstruction.

Common Hepatic Artery (CHA): Involvement of the CHA without encroachment of the proper hepatic artery. Resection may be feasible if arterial continuity can be restored through reconstruction.

3. Imaging Modalities: Contrast-enhanced CT (pancreatic protocol): This is the preferred imaging modality to evaluate the relationship between the tumor and the blood vessels.

MRI and endoscopic ultrasound (EUS) can provide additional detail, especially if the initial CT is inconclusive.

Detailed imaging helps classify the tumor as resectable, borderline resectable, or locally advanced, guiding the treatment plan.

4. Criteria According to the NCCN (National Comprehensive Cancer Network): The NCCN defines borderline resectable pancreatic cancer based on vascular involvement as follows:

Venous involvement (SMV/PV): Tumor abutment or short segment occlusion, but resection and reconstruction are feasible.

Arterial involvement (SMA/CHA): Tumor abutment ( $\leq 180$  degrees) without full encasement or occlusion, with potential for resection.

No distant metastases (M0), and the tumor is confined to the pancreas and its surrounding structures.

5. Neoadjuvant Therapy:

Neoadjuvant therapy (chemotherapy and/or chemoradiation) is often used for borderline resectable pancreatic cancer. This approach aims to:

Shrink the tumor and reduce vascular involvement.

Improve the chances of achieving a clear surgical margin (R0 resection).

Allow for a more successful and less complex surgery.

After neoadjuvant treatment, patients are re-evaluated with imaging to determine if the tumor has responded well enough to proceed with surgery.

6. Prognosis:

The prognosis of borderline resectable pancreatic cancer is generally better than that of locally advanced unresectable disease but worse than resectable pancreatic cancer.

Surgical resection after neoadjuvant therapy, especially if an R0 margin is achieved, can lead to improved survival outcomes.

Summary: Borderline resectable pancreatic cancer is defined by tumors with limited involvement of major blood vessels (SMV, PV, SMA, CHA, celiac axis), where surgery might still be possible but requires more complex techniques, such as vascular resection and reconstruction. Neoadjuvant therapy is often employed to improve the chances of successful resection

Risposta 2.

Borderline resectable pancreatic cancer refers to tumors that are technically operable but have a higher risk of incomplete resection due to involvement of nearby blood vessels or other structures. These tumors are neither clearly resectable nor completely unresectable. The goal of classifying pancreatic cancer as borderline resectable is to identify patients who may benefit from neoadjuvant therapy (chemotherapy, chemoradiotherapy) to improve the chances of achieving a complete resection (R0), meaning no cancer cells remain at the surgical margins.

Key Characteristics of Borderline Resectable Pancreatic Cancer:

1. Tumor Involvement with Blood Vessels:
  - One of the defining features of borderline resectable pancreatic cancer is limited involvement of major blood vessels that are critical for surgery. While the tumor may encroach upon these vessels, there is a possibility of complete resection after neoadjuvant therapy. The major blood vessels involved include:
    - Superior mesenteric vein (SMV) or portal vein (PV): The tumor may involve these veins, but resection may still be possible with venous reconstruction or partial resection.
    - Superior mesenteric artery (SMA) or celiac axis: The tumor may abut (come into contact with) or minimally encase these arteries without completely surrounding them. Full encasement would classify the tumor as unresectable.
2. No Distant Metastasis:
  - Like resectable pancreatic cancer, borderline resectable tumors are localized, meaning they have not metastasized to distant organs such as the liver, lungs, or peritoneum. However, local extension to nearby vessels creates challenges for achieving a clean surgical margin.
3. Tumor Location:

- Borderline resectable cancers can be located in the head, neck, body, or tail of the pancreas. Most often, the involvement of blood vessels is a key factor in determining resectability, particularly in tumors of the pancreatic head due to the proximity to the superior mesenteric vessels and celiac axis.

#### Criteria for Borderline Resectability:

Several professional organizations, including the National Comprehensive Cancer Network (NCCN), have published guidelines to define borderline resectable pancreatic cancer. The classification is based on the relationship of the tumor to nearby vessels, and specific criteria are applied:

##### 1. Venous Involvement (SMV/PV):

- Tumor contact of  $\leq 180^\circ$  with the superior mesenteric vein (SMV) or portal vein (PV).
- Short-segment venous occlusion (narrowing or blockage), where the vein can still be reconstructed.
- Tumor may cause deformity or narrowing of the vein, but resection is possible with venous reconstruction.

##### 2. Arterial Involvement (SMA, Celiac Axis):

- Superior mesenteric artery (SMA): Tumor contact of  $\leq 180^\circ$  without full encasement or involvement of the surrounding tissue.
- Celiac axis: Tumor contact of  $\leq 180^\circ$  without encasement.
- In some cases, there is short-segment involvement of these arteries, but surgical resection is still feasible with complex surgical techniques or after neoadjuvant therapy.

##### 3. Gastroduodenal Artery (GDA):

- The tumor may involve the gastroduodenal artery but not extend to the common hepatic artery (CHA) beyond this point, meaning resection and reconstruction of the artery may be possible.

#### Multidisciplinary Approach:

- Borderline resectable pancreatic cancer cases require a multidisciplinary team approach, involving surgeons, medical oncologists, radiation oncologists, and radiologists.
- The goal of neoadjuvant therapy (chemotherapy and/or radiation) is to shrink the tumor, improve the chances of an R0 resection, and reduce the risk of local recurrence.
- After neoadjuvant therapy, re-imaging (CT or MRI) is done to reassess the tumor's relationship to the blood vessels and determine if the tumor has become more resectable.

#### Importance of Neoadjuvant Therapy:

- Neoadjuvant therapy is usually recommended before surgery for borderline resectable pancreatic cancer. The rationale is that treating the tumor with chemotherapy or chemoradiotherapy can shrink it, making surgery more likely to result in complete tumor removal.
- Neoadjuvant therapy can also help identify patients who have aggressive disease (based on their response to the therapy), sparing some patients from unnecessary surgery if the tumor progresses despite treatment.

Summary:

- Borderline resectable pancreatic cancer refers to tumors that are operable but involve key blood vessels in ways that complicate achieving an R0 resection.
- The tumor is confined locally with no distant metastasis.
- Surgery may be possible after neoadjuvant therapy, which is aimed at shrinking the tumor and improving the likelihood of a successful resection.

Key factors include venous and arterial involvement, with criteria based on the degree of tumor contact with vessels like the superior mesenteric vein (SMV), portal vein (PV), superior mesenteric artery (SMA), and celiac axis.

Risposta 3.

Borderline resectable pancreatic cancer refers to a stage of pancreatic cancer where the tumor involves nearby blood vessels but not to the extent that makes it completely unresectable. In this scenario, surgery may still be feasible, but with a higher risk of incomplete resection (i.e., leaving cancer cells behind). The goal in borderline resectable cases is often to shrink the tumor using neoadjuvant (pre-surgical) therapy, such as chemotherapy and/or radiation, before attempting surgery to improve the chances of a complete (R0) resection.

Key Characteristics of Borderline Resectable Pancreatic Cancer:

#### 1. Vascular Involvement

- Tumors in borderline resectable pancreatic cancer have a limited involvement with major blood vessels near the pancreas, such as the superior mesenteric artery (SMA), celiac axis, superior mesenteric vein (SMV), or portal vein. However, the involvement is not extensive enough to preclude surgery.
- Criteria for borderline resectability based on vascular involvement can vary slightly, but generally include:

- Superior Mesenteric Artery (SMA): Tumor abutment (less than 180° of the vessel circumference involved) without encasement.
- Celiac Axis: Tumor abutment (less than 180°) without encasement.
- Venous Involvement:
- Superior Mesenteric Vein (SMV) or Portal Vein: Tumor abutment or short-segment occlusion that may be reconstructable.

Tumors involving these vessels may require vascular resection and reconstruction during surgery, which increases the complexity of the procedure.

## 2. No Distant Metastasis:

- Borderline resectable pancreatic cancer has no evidence of distant metastasis (such as to the liver, lungs, or peritoneum), as this would categorize the disease as unresectable or metastatic.

## 3. Potential for R0 Resection:

- In borderline resectable cases, the goal is to achieve an R0 resection (meaning no cancer cells at the margins of the removed tissue), but the tumor's location and involvement with critical blood vessels make this more challenging. Neoadjuvant therapy is often used to shrink the tumor, reduce vascular involvement, and increase the likelihood of clear surgical margins.

## 4. Multidisciplinary Management:

- Patients with borderline resectable pancreatic cancer are typically managed by a multidisciplinary team (MDT), including surgeons, medical oncologists, and radiologists, to assess the tumor's resectability and plan treatment. Neoadjuvant therapy is often recommended to downstage the tumor and improve the odds of a successful resection.

## Definitions by Major Guidelines:

Several professional organizations provide specific criteria for defining borderline resectable pancreatic cancer, most notably:

### 1. National Comprehensive Cancer Network (NCCN) Guidelines:

The NCCN defines borderline resectable pancreatic cancer based on the tumor's relationship to nearby arteries and veins:

- Arterial Involvement:
- SMA or celiac axis: Tumor abutment  $\leq 180^\circ$  (less than half of the vessel's circumference).
- Venous Involvement:
- SMV or portal vein: Tumor abutment with short-segment occlusion or encasement that is technically reconstructable.

2. American Hepato-Pancreato-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), and Society for Surgery of the Alimentary Tract (SSAT): These organizations jointly define borderline resectable pancreatic cancer as having limited venous involvement or minimal arterial abutment but with the potential for complete resection after neoadjuvant treatment.

#### Management of Borderline Resectable Pancreatic Cancer:

##### 1. Neoadjuvant Therapy:

- Neoadjuvant (pre-surgery) chemotherapy, sometimes combined with radiation therapy, is recommended to shrink the tumor and increase the chances of a successful surgical resection (R0 resection). This approach also helps eliminate micrometastases that may not be detectable.

- Common chemotherapy regimens include FOLFIRINOX or gemcitabine-based therapies.

##### 2. Surgical Resection:

- After neoadjuvant therapy, patients are re-evaluated with imaging studies (such as a CT scan or MRI) to assess the tumor's response to treatment and determine if it has become resectable.

- If the tumor is deemed operable, surgery (e.g., Whipple procedure or distal pancreatectomy with vascular resection if necessary) is performed with the goal of achieving a complete resection.

##### 3. Postoperative Therapy:

- Following surgery, adjuvant chemotherapy is often given to reduce the risk of recurrence.

#### Conclusion:

Borderline resectable pancreatic cancer refers to tumors with limited but significant involvement of nearby blood vessels, making surgical resection technically challenging but potentially feasible. The goal is to achieve an R0 resection, often with the aid of neoadjuvant therapy to reduce tumor size and vascular involvement before surgery. This category of pancreatic cancer requires careful multidisciplinary evaluation and treatment planning.

#### 8. Is combined arterial resection recommended in patients with BR pancreatic cancer?

##### Risposta 1.

Combined arterial resection in patients with borderline resectable (BR) pancreatic cancer is not routinely recommended due to the high risk of complications and limited evidence of

improved survival outcomes. However, it can be considered in highly select cases where it is the only way to achieve an R0 resection (complete tumor removal with negative margins), but this approach is still controversial and not widely adopted.

#### Key Considerations Regarding Arterial Resection in BR Pancreatic Cancer:

##### 1. Technical Challenges and Risks:

Arterial resection, particularly of the superior mesenteric artery (SMA), celiac axis, or common hepatic artery, is a highly complex procedure.

It involves significant technical challenges due to the vital nature of these arteries, which supply blood to the liver, intestines, and other abdominal organs.

Risks: Arterial resection is associated with increased perioperative morbidity and mortality, including complications like: Bleeding, Ischemia of the liver or bowel, Delayed gastric emptying, Postoperative infections. These complications often lead to a prolonged recovery period and may negatively impact the patient's ability to undergo adjuvant chemotherapy, which is essential for improving long-term outcomes.

##### 2. Limited Evidence of Survival Benefit:

Studies have not consistently shown a significant survival advantage for patients undergoing combined arterial resection compared to those who have standard resections without arterial involvement. Some small, specialized centers have reported favorable outcomes in select patients, but these cases are rare and not reflective of broader practice patterns. Larger studies and meta-analyses generally show that venous resection in borderline resectable pancreatic cancer is more acceptable, while arterial resection remains associated with worse survival and higher complications.

3. Neoadjuvant Therapy First: In patients with borderline resectable pancreatic cancer, particularly those with arterial involvement, the preferred approach is to start with neoadjuvant therapy (chemotherapy with or without radiation). Neoadjuvant therapy aims to shrink the tumor, potentially reducing arterial involvement and converting the tumor to a more resectable state. This strategy also helps to select patients who may benefit from surgery by identifying those with more aggressive disease who develop metastases during therapy, thus avoiding unnecessary surgery. After neoadjuvant treatment, imaging is repeated to evaluate whether the tumor remains borderline resectable or has become fully resectable, allowing for a less aggressive surgery without arterial resection.

4. Guidelines and Recommendations: Current guidelines, such as those from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology



(ESMO), do not recommend routine arterial resection for borderline resectable pancreatic cancer. In most cases, surgery is indicated only if a clear margin can be achieved without arterial resection, and vascular resection is typically limited to venous involvement (e.g., portal or superior mesenteric vein).

5. When Arterial Resection May Be Considered: In highly specialized centers with experienced surgeons, arterial resection may be considered in rare cases where:

The tumor is confined to the area and achieving an R0 resection is possible only with arterial resection.

The patient is otherwise healthy and can tolerate the increased risk of complications.

There is a strong multidisciplinary consensus that the benefit of surgery outweighs the risks.

These cases often involve detailed preoperative planning, and patients are carefully selected based on their overall health, response to neoadjuvant therapy, and tumor characteristics.

Conclusion:

Combined arterial resection in patients with borderline resectable pancreatic cancer is not routinely recommended due to the high risk of complications and the limited evidence of survival benefit. Neoadjuvant therapy is the standard approach for borderline resectable disease, with arterial resection reserved for highly select cases at specialized centers. The primary goal in most cases remains achieving an R0 resection while minimizing morbidity.

Risposta 2.

Combined arterial resection in patients with borderline resectable (BR) pancreatic cancer is generally not routinely recommended due to the complexity of the procedure and the increased risk of perioperative complications, poor survival outcomes, and limited evidence of long-term benefit. However, in highly selected cases, arterial resection may be considered as part of a multimodal treatment strategy, especially in specialized centers with expertise in pancreatic surgery.

Key Points on Arterial Resection in Borderline Resectable Pancreatic Cancer:

1. Standard of Care:
  - For most cases of borderline resectable pancreatic cancer, neoadjuvant therapy (chemotherapy and/or chemoradiotherapy) is the recommended first step. The goal is to shrink the tumor and improve the chances of a complete resection (R0), meaning no cancer cells remain at the surgical margins.

- After neoadjuvant therapy, resection of the tumor without arterial involvement or with venous involvement (e.g., portal vein or superior mesenteric vein) is more common and carries a lower risk than arterial resection.
2. Why Arterial Resection is Not Routinely Recommended:
- Higher risk of complications: Arterial resection, especially involving the superior mesenteric artery (SMA), celiac axis, or hepatic arteries, is associated with high morbidity, including increased risks of postoperative ischemia, anastomotic failure, and other life-threatening complications.
  - Poor survival outcomes: Even in cases where arterial resection is performed successfully, studies have shown that survival outcomes do not significantly improve compared to standard resections, and the risk of local recurrence remains high.
  - Increased mortality: The risk of mortality during or shortly after surgery is much higher in patients undergoing arterial resection, due to the complexity of the procedure and potential damage to critical blood supply structures.
3. When Arterial Resection May Be Considered:
- In highly selected cases, arterial resection may be considered in specialized centers where surgeons have expertise in performing such complex surgeries. These cases usually involve:
    - Limited involvement of a short segment of the artery (e.g., partial encasement of the superior mesenteric artery or celiac axis).
    - Good response to neoadjuvant therapy, indicating that the tumor biology may be more favorable for surgery.
    - Absence of distant metastasis and good patient performance status.
  - Patients must be carefully evaluated by a multidisciplinary team (including surgeons, medical oncologists, and radiation oncologists) to weigh the risks and benefits of arterial resection.
4. Alternative Approaches:
- In most borderline resectable cases, the focus remains on using neoadjuvant therapy to shrink the tumor and make it easier to perform surgery with clear margins without arterial resection.
  - Venous resection and reconstruction (e.g., involving the portal vein or superior mesenteric vein) is more commonly performed and is associated with fewer complications compared to arterial resection.
5. Outcomes from Clinical Studies:
- Several studies have investigated the outcomes of arterial resection in pancreatic cancer, and the results generally show:
    - High morbidity and mortality rates.

- No significant survival advantage compared to patients who undergo surgery without arterial resection.
- In many cases, even after aggressive surgery, the local recurrence rate is high, and overall survival remains poor.
- Because of these findings, most expert guidelines, including those from the National Comprehensive Cancer Network (NCCN), do not recommend routine arterial resection in borderline resectable pancreatic cancer.

Summary:

- Combined arterial resection is generally not recommended for patients with borderline resectable pancreatic cancer due to the high risks and limited evidence of improved outcomes.
- It may be considered in highly selected cases in specialized centers, particularly if the tumor shows a good response to neoadjuvant therapy and involves limited arterial segments.
- The primary treatment approach for borderline resectable pancreatic cancer remains neoadjuvant therapy, followed by surgery with a focus on achieving clear margins (R0 resection) without arterial involvement whenever possible.

Risposta 3.

Combined arterial resection in patients with borderline resectable (BR) pancreatic cancer is a controversial topic, and its recommendation varies based on specific clinical circumstances, tumor characteristics, and surgeon expertise. Here's a detailed overview of the considerations regarding combined arterial resection in BR pancreatic cancer:

What is Combined Arterial Resection?

Combined arterial resection refers to the surgical procedure where, in addition to removing the pancreas (via procedures like the Whipple procedure or distal pancreatectomy), the surgeon also removes a portion of the artery (such as the superior mesenteric artery (SMA) or celiac axis) that is involved with the tumor. This is typically done in cases where the tumor has invaded the arterial wall but does not preclude resection of the primary tumor.

Indications for Combined Arterial Resection:

1. Involvement of Major Arteries: In borderline resectable pancreatic cancer, there may be limited involvement of the SMA or celiac axis. When this occurs, combined arterial resection may be considered to achieve an R0 (complete) resection, which is essential for improving long-term survival.

2. Vascular Reconstruction: If a portion of the artery is removed, vascular reconstruction (using grafts or other surgical techniques) is often performed to restore blood flow, which adds complexity to the surgery.

#### Recommendations and Guidelines:

##### 1. Current Practice:

- The role of combined arterial resection in BR pancreatic cancer is not uniformly recommended. Instead, it is generally performed on a case-by-case basis, depending on various factors such as:

- The extent of vascular involvement.
- The ability to achieve clear margins (R0 resection).
- The overall health and surgical candidacy of the patient.

##### 2. NCCN Guidelines:

- The National Comprehensive Cancer Network (NCCN) guidelines suggest that vascular resection, including arterial resection, may be considered in select cases of BR pancreatic cancer. However, the decision should involve careful preoperative assessment and consideration of potential risks and benefits.

- It is emphasized that the surgical team should be experienced in performing complex resections with vascular involvement.

##### 3. Studies and Evidence:

- Studies on combined arterial resections show that they can be performed safely in selected patients, with some reports indicating that combined resections may not adversely affect survival outcomes when done correctly.

- A study published in the Annals of Surgery suggested that in patients with BR pancreatic cancer who underwent combined arterial resection, there was no significant difference in overall survival compared to those who had standard resections, provided they achieved R0 margins.

#### Considerations and Risks:

1. Increased Morbidity: Combined arterial resection carries a higher risk of complications, including:

- Postoperative pancreatic fistula.
- Delayed gastric emptying.
- Increased surgical time and complexity.
- Risk of vascular complications related to arterial reconstruction.

2. Multidisciplinary Approach: The decision to proceed with combined arterial resection should involve a multidisciplinary team that includes surgeons, medical oncologists, radiologists, and other specialists to ensure that the patient is evaluated thoroughly and that the potential benefits outweigh the risks.

3. Neoadjuvant Therapy: Neoadjuvant treatment (chemotherapy and/or radiation) may help shrink the tumor and potentially reduce the extent of vascular involvement, making surgical resection more feasible.

Conclusion: Combined arterial resection is not universally recommended but may be considered in selected patients with borderline resectable pancreatic cancer when there is limited vascular involvement, and the goal is to achieve an R0 resection. This decision should be made on a case-by-case basis, involving a thorough preoperative assessment, consideration of potential risks, and a multidisciplinary approach to patient management.

9. What is the first-line treatment recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

For patients with locally advanced, unresectable pancreatic cancer (LAPC), where the tumor is confined to the pancreas and surrounding structures but cannot be surgically removed due to extensive involvement of major blood vessels or other critical structures, surgical resection is not an option. Instead, the first-line treatment focuses on systemic therapy to control disease progression and, in some cases, potentially downstage the tumor to make it resectable. Here's a detailed look at the recommended first-line treatment options:

1. Systemic Chemotherapy (First-Line Approach):

Chemotherapy is the cornerstone of treatment for locally advanced pancreatic cancer. The goals of chemotherapy in LAPC are to:

- Control tumor growth and prevent metastasis.
- Alleviate symptoms.
- Potentially downstage the tumor for surgical resection in select cases (conversion therapy).

The choice of chemotherapy regimen depends on the patient's overall health, performance status, and ability to tolerate aggressive treatment. The two most commonly recommended regimens are:

- FOLFIRINOX: FOLFIRINOX (a combination of 5-fluorouracil [5-FU], leucovorin, irinotecan, and oxaliplatin) is considered the most effective chemotherapy regimen for patients with good performance status and sufficient organ function. This regimen has been shown to improve survival and progression-free survival compared to gemcitabine alone. However, it is associated with more toxicity (e.g., neutropenia, diarrhea, neuropathy), so it is generally reserved for patients who are fit enough to tolerate it. Modified FOLFIRINOX (with dose adjustments) can be used in patients who are borderline candidates for the full-dose regimen.
- Gemcitabine-Based Regimens: Gemcitabine plus nab-paclitaxel (Abraxane) is an alternative first-line option for patients who may not tolerate FOLFIRINOX but still have a reasonable performance status. Gemcitabine alone may be used in patients with poor performance status or significant comorbidities. While it is less aggressive, it can help control symptoms and improve quality of life.

## 2. Chemoradiation:

Chemoradiation (combination of chemotherapy with radiation therapy) is sometimes considered in patients with LAPC, particularly for local control of the tumor if systemic chemotherapy has been administered and the disease remains localized without progression. Radiation therapy can help reduce tumor size and alleviate symptoms, such as pain or obstruction, particularly in cases where the tumor is impinging on nearby structures like the bile duct or intestines.

The use of chemoradiation as a first-line treatment has become less common, as systemic chemotherapy is prioritized for controlling both local and distant disease.

When chemoradiation is considered:

After induction chemotherapy: In some patients, chemoradiation may be used after several months of systemic chemotherapy if there is no disease progression or if the tumor remains locally advanced.

Symptom control: Chemoradiation can also be helpful for palliative purposes, to manage pain or other symptoms caused by local tumor invasion.

## 3. Potential for Downstaging (Conversion Therapy):

For a subset of patients, chemotherapy (with or without radiation) may downstage the tumor, meaning it shrinks enough to make it resectable. This is known as conversion therapy.

After a few months of systemic chemotherapy (usually 4-6 months), imaging is repeated to assess whether the tumor has responded and if surgical resection has become feasible.

Surgery following successful downstaging is referred to as salvage surgery or conversion surgery. While not common, this approach can provide a chance for longer-term survival in carefully selected patients.

#### 4. Palliative Care:

For patients with locally advanced pancreatic cancer, symptom management is a crucial part of care, especially if the disease is not responsive to treatment or the patient cannot tolerate aggressive therapy.

Palliative chemotherapy (e.g., gemcitabine) may be used to control symptoms, slow disease progression, and improve quality of life, even if a cure is not possible.

Pain management, nutritional support, and treatment of biliary or gastric outlet obstruction (with stenting or bypass procedures) are essential components of palliative care.

#### 5. Emerging Therapies and Clinical Trials:

Targeted therapies: Some patients with locally advanced pancreatic cancer may be candidates for targeted therapies, especially those with BRCA1/2 mutations or other actionable mutations. PARP inhibitors (e.g., olaparib) may be considered in patients with BRCA mutations.

Immunotherapy: The role of immunotherapy in pancreatic cancer is limited, but ongoing clinical trials are exploring its use in combination with chemotherapy.

Clinical trials: Participation in clinical trials is encouraged for patients with locally advanced pancreatic cancer, as new therapies and combinations are being evaluated to improve outcomes.

#### Summary of First-Line Treatment for Locally Advanced, Unresectable Pancreatic Cancer:

##### Systemic chemotherapy:

- FOLFIRINOX (for patients with good performance status).
- Gemcitabine plus nab-paclitaxel (for patients with moderately good performance status).
- Gemcitabine alone (for patients with poor performance status or significant comorbidities).

##### Chemoradiation:

-Considered after chemotherapy in select cases for local control or symptom management.

##### Downstaging:

-Chemotherapy (and/or chemoradiation) may be used in the hopes of shrinking the tumor enough to make surgical resection feasible.

Palliative care: Focused on symptom management and improving quality of life, especially if aggressive treatment is not feasible.

This approach is aimed at controlling the disease, extending survival, and maintaining quality of life for patients with locally advanced pancreatic cancer.

Risposta 2.

For patients with locally advanced, unresectable pancreatic cancer (LAPC), systemic chemotherapy is the recommended first-line treatment. The primary goal in these cases is disease control, symptom management, and potentially improving survival, with the option of converting an unresectable tumor to a resectable one through downstaging (if the tumor responds well to treatment). Surgery is typically not an option upfront due to the tumor's involvement with major blood vessels or surrounding structures, but the focus is on managing the disease through systemic therapy.

First-Line Treatment Options for Locally Advanced Unresectable Pancreatic Cancer:

1. Systemic Chemotherapy:

Chemotherapy is the cornerstone of treatment for LAPC, with several options depending on the patient's performance status, comorbidities, and overall health.

- FOLFIRINOX (Combination Chemotherapy):
  - Regimen: 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin.
  - Indication: FOLFIRINOX is recommended for patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] score of 0–1) and no major contraindications. It is a highly active regimen and has shown improved survival compared to other therapies.
  - Effectiveness: FOLFIRINOX offers the potential for tumor downstaging, and in some cases, the tumor may become resectable after a good response to treatment.
- Gemcitabine-Based Chemotherapy:
  - Gemcitabine + Nab-paclitaxel (Abraxane): This combination is another first-line option for patients with good performance status. It has been shown to improve survival and progression-free survival compared to gemcitabine alone.
  - Gemcitabine Monotherapy: For patients who are frail or have poor performance status, gemcitabine alone is a commonly used, well-tolerated option, though it is less effective than combination regimens.



- Effectiveness: While gemcitabine-based therapies are generally well tolerated, their potential to downstage the tumor to resectability is lower than with FOLFIRINOX.

## 2. Chemoradiotherapy (Selective Use After Chemotherapy):

After an initial course of systemic chemotherapy (typically 3–6 months), patients who have stable disease or partial response may be considered for chemoradiotherapy (CRT) to improve local control.

- Indications for Chemoradiotherapy:
  - Chemoradiotherapy is typically reserved for patients with persistent locally advanced disease (no progression, but no clear reduction in tumor size for resection) after initial chemotherapy.
  - The rationale is that radiation combined with chemotherapy may help control the local tumor and reduce symptoms such as pain or bile duct obstruction.
- Effectiveness: CRT can offer local control of the tumor, but its role in improving overall survival is less clear. It is usually considered for patients who remain unresectable after initial systemic therapy.

## 3. Neoadjuvant Intent Chemotherapy (Potential for Downstaging):

In some cases, locally advanced pancreatic cancer may respond to chemotherapy to the extent that the tumor becomes borderline resectable or even resectable. This is often referred to as downstaging or conversion therapy.

- Downstaging Potential:
  - Patients with a good response to chemotherapy (especially FOLFIRINOX or gemcitabine + nab-paclitaxel) may be re-evaluated with repeat imaging (CT or MRI) to assess whether the tumor has shrunk enough for surgery.
  - Surgery may then be attempted if the tumor no longer involves major blood vessels or if vascular reconstruction is possible.
- Outcomes: This approach is successful in a minority of cases, but achieving resection after downstaging is associated with significantly improved outcomes compared to non-surgical treatment alone.

## 4. Clinical Trials:

- Patients with LAPC are often encouraged to participate in clinical trials, as there are ongoing studies exploring novel therapies, including immunotherapy, targeted therapies, and new chemotherapy combinations.
- Trials may offer access to cutting-edge treatments that are not yet widely available but could potentially improve survival or quality of life.

### Palliative Care Considerations:

For patients with symptoms such as pain, jaundice (due to bile duct obstruction), or gastrointestinal obstruction, palliative interventions are also crucial:

- Biliary stenting or biliary bypass surgery to relieve jaundice.
- Celiac plexus neurolysis (nerve block) for pain relief in patients with severe abdominal or back pain.
- Gastrojejunostomy if the tumor is causing gastric outlet obstruction.

### Summary of First-Line Treatment for LAPC:

1. Chemotherapy (FOLFIRINOX or gemcitabine-based regimens) is the primary treatment.
2. Chemoradiotherapy may be considered after chemotherapy in patients with locally persistent disease.
3. Downstaging to resectability can be a goal in some cases, potentially leading to surgery.
4. Palliative care addresses symptoms and improves quality of life.

The treatment plan is typically tailored based on the patient's overall health, tumor characteristics, and response to therapy.

### Risposta 3.

For patients with locally advanced, unresectable pancreatic cancer, the first-line treatment is typically systemic chemotherapy. The goal of treatment in this setting is to control the disease, alleviate symptoms, and improve the quality of life. Here are the current first-line treatment options and strategies:

1. Chemotherapy Regimens: The two primary chemotherapy regimens recommended for locally advanced unresectable pancreatic cancer include:

#### a. FOLFIRINOX:

- Composition: A combination of leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin.

- Indication: This regimen is generally recommended for fit patients with good performance status (ECOG 0-1) due to its potential for greater efficacy but also higher toxicity.

- Efficacy: FOLFIRINOX has been shown to improve overall survival and progression-free survival compared to gemcitabine alone in some clinical trials.

#### b. Gemcitabine-based Regimens:

-Gemcitabine Alone: Historically the standard treatment, gemcitabine is still an option for patients who are not suitable for FOLFIRINOX due to age, comorbidities, or performance status.

- Combination with Nab-Paclitaxel: The combination of gemcitabine and nab-paclitaxel (Abraxane) is also effective and recommended for patients who may not tolerate the FOLFIRINOX regimen.

- Indication: This regimen is often preferred for patients with a poorer performance status or for those who experience significant toxicity from FOLFIRINOX.

## 2. Radiation Therapy:

- Indications: In selected patients, especially those with significant pain or local symptoms, radiation therapy may be considered in combination with chemotherapy.

- Role: Radiation can help relieve symptoms and potentially improve local control of the disease.

## 3. Clinical Trials:

- Patients with locally advanced unresectable pancreatic cancer are often encouraged to participate in clinical trials. These trials may offer access to new therapies, novel combinations, or investigational drugs that could be more effective than standard treatments.

## 4. Supportive Care:

- Alongside chemotherapy, supportive care is crucial in managing symptoms and maintaining quality of life. This may include pain management, nutritional support, and psychological support as needed.

## Summary:

The first-line treatment for locally advanced, unresectable pancreatic cancer typically consists of systemic chemotherapy, with FOLFIRINOX being the preferred regimen for fit patients and gemcitabine plus nab-paclitaxel as an alternative for those less tolerant of aggressive therapy. Radiation therapy may be considered for symptom relief, and clinical trials should also be a consideration for eligible patients. Multidisciplinary management and supportive care play important roles in the overall treatment strategy.

10. What is the chemoradiotherapy regimen recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

For patients with locally advanced, unresectable pancreatic cancer (LAPC), chemoradiotherapy can be considered after systemic chemotherapy if the disease remains localized without progression or as a means of local control and symptom relief. The goal of chemoradiotherapy is to maximize the local control of the tumor while minimizing the risk of distant spread. However, it is typically not the first-line treatment—systemic chemotherapy is preferred initially. Chemoradiotherapy is generally reserved for use after induction chemotherapy or in select cases where local symptoms are the primary concern.

Here's the recommended chemoradiotherapy regimen for LAPC:

#### 1. Radiation Therapy:

- External beam radiation therapy (EBRT) is the standard type of radiation used in this context. The typical total dose is 50.4 Gy, delivered in 28 fractions (1.8 Gy per fraction) over about 5 to 6 weeks. This is the conventional fractionation schedule.

- Hypofractionated radiation (higher doses per fraction over fewer treatments) is sometimes used in select patients or in clinical trials, offering a shorter treatment course, though this approach is less common in standard practice.

- Advanced techniques, such as intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT), can be used to deliver radiation more precisely, minimizing damage to surrounding tissues, especially in patients with tumors near sensitive structures like the stomach and small bowel.

#### 2. Chemotherapy During Radiation (Chemoradiotherapy):

The chemotherapy agents used in conjunction with radiation serve as radiosensitizers, making the tumor cells more sensitive to the effects of radiation. The most commonly used regimen involves gemcitabine or fluoropyrimidine-based chemotherapy (5-FU or capecitabine):

- Gemcitabine-based Chemoradiotherapy: Gemcitabine (600 mg/m<sup>2</sup>) is typically administered once weekly during radiation therapy. This regimen has been shown to enhance the effects of radiation, although it can lead to significant toxicity, including gastrointestinal side effects (nausea, diarrhea), myelosuppression, and fatigue.

- Fluoropyrimidine-based Chemoradiotherapy: 5-Fluorouracil (5-FU) is another commonly used radiosensitizer. It can be delivered as a continuous intravenous infusion (usually 200-250 mg/m<sup>2</sup> per day) throughout the course of radiation therapy.

Alternatively, capecitabine (an oral prodrug of 5-FU) can be used in place of 5-FU. The typical dose of capecitabine is 825 mg/m<sup>2</sup> twice daily, taken on days of radiation therapy.

Fluoropyrimidine-based chemoradiation is generally better tolerated than gemcitabine-based chemoradiation and is widely used due to its favorable toxicity profile.

### 3. Timing of Chemoradiotherapy:

-Induction chemotherapy first: For most patients with LAPC, the standard of care is to start with several cycles (typically 3-6 months) of systemic chemotherapy (e.g., FOLFIRINOX or gemcitabine/nab-paclitaxel). After this period, patients are re-evaluated. If there is no evidence of disease progression or metastasis, chemoradiotherapy may be considered for local tumor control.

-Local control or symptom palliation: In patients with significant local symptoms (e.g., pain, biliary or gastric outlet obstruction) that are not relieved by systemic chemotherapy alone, chemoradiotherapy can help control local tumor growth and provide symptomatic relief.

### 4. Indications for Chemoradiotherapy:

- Stable disease after induction chemotherapy: After a few months of systemic chemotherapy, if the disease remains localized (without distant metastasis) but is still unresectable, chemoradiotherapy may be used to control local tumor growth.

-Symptomatic management: Chemoradiotherapy is often used to alleviate local symptoms, such as pain, biliary obstruction, or gastrointestinal obstruction caused by the tumor.

-Poor tolerance of systemic chemotherapy: In some cases, if patients cannot tolerate systemic chemotherapy for an extended period, chemoradiotherapy can be a suitable option for local control.

### 5. Side Effects of Chemoradiotherapy:

-Gastrointestinal Toxicity: Nausea, vomiting, diarrhea, and anorexia are common due to the proximity of the pancreas to the stomach and small bowel.

-Myelosuppression: Both gemcitabine and 5-FU/capecitabine can cause neutropenia, anemia, and thrombocytopenia.

-Fatigue: This is a common side effect of both radiation and chemotherapy.

-Radiation-induced enteritis: Inflammation of the intestines due to radiation can lead to symptoms like abdominal pain and diarrhea.

### Summary of Chemoradiotherapy Regimen for LAPC:

#### -Radiation:

Typically, 50.4 Gy in 28 fractions (1.8 Gy per fraction) over 5-6 weeks.

Advanced techniques like IMRT or SBRT may be used to focus radiation more precisely.

#### -Concurrent Chemotherapy:

Gemcitabine: 600 mg/m<sup>2</sup> once weekly during radiation.

5-FU: Continuous infusion of 200-250 mg/m<sup>2</sup> daily during radiation.

Capecitabine: 825 mg/m<sup>2</sup> orally twice daily on radiation treatment days.

-Indications:

Typically, after induction chemotherapy (e.g., FOLFIRINOX or gemcitabine/nab-paclitaxel) for stable disease without progression.

For local tumor control and/or palliation of symptoms.

This approach aims to balance effective local control of the tumor with manageable side effects, particularly in patients who cannot undergo surgery.

Risposta 2.

For patients with locally advanced, unresectable pancreatic cancer (LAPC), systemic chemotherapy is the recommended first-line treatment. The primary goal in these cases is disease control, symptom management, and potentially improving survival, with the option of converting an unresectable tumor to a resectable one through downstaging (if the tumor responds well to treatment). Surgery is typically not an option upfront due to the tumor's involvement with major blood vessels or surrounding structures, but the focus is on managing the disease through systemic therapy.

First-Line Treatment Options for Locally Advanced Unresectable Pancreatic Cancer:

1. Systemic Chemotherapy:

Chemotherapy is the cornerstone of treatment for LAPC, with several options depending on the patient's performance status, comorbidities, and overall health.

- FOLFIRINOX (Combination Chemotherapy):
  - Regimen: 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin.
  - Indication: FOLFIRINOX is recommended for patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] score of 0–1) and no major contraindications. It is a highly active regimen and has shown improved survival compared to other therapies.
  - Effectiveness: FOLFIRINOX offers the potential for tumor downstaging, and in some cases, the tumor may become resectable after a good response to treatment.
- Gemcitabine-Based Chemotherapy:
  - Gemcitabine + Nab-paclitaxel (Abraxane): This combination is another first-line option for patients with good performance status. It has been shown to improve survival and progression-free survival compared to gemcitabine alone.
  - Gemcitabine Monotherapy: For patients who are frail or have poor performance status, gemcitabine alone is a commonly used, well-tolerated option, though it is less effective than combination regimens.

- Effectiveness: While gemcitabine-based therapies are generally well tolerated, their potential to downstage the tumor to resectability is lower than with FOLFIRINOX.

## 2. Chemoradiotherapy (Selective Use After Chemotherapy):

After an initial course of systemic chemotherapy (typically 3–6 months), patients who have stable disease or partial response may be considered for chemoradiotherapy (CRT) to improve local control.

- Indications for Chemoradiotherapy:
  - Chemoradiotherapy is typically reserved for patients with persistent locally advanced disease (no progression, but no clear reduction in tumor size for resection) after initial chemotherapy.
  - The rationale is that radiation combined with chemotherapy may help control the local tumor and reduce symptoms such as pain or bile duct obstruction.
- Effectiveness: CRT can offer local control of the tumor, but its role in improving overall survival is less clear. It is usually considered for patients who remain unresectable after initial systemic therapy.

## 3. Neoadjuvant Intent Chemotherapy (Potential for Downstaging):

In some cases, locally advanced pancreatic cancer may respond to chemotherapy to the extent that the tumor becomes borderline resectable or even resectable. This is often referred to as downstaging or conversion therapy.

- Downstaging Potential:
  - Patients with a good response to chemotherapy (especially FOLFIRINOX or gemcitabine + nab-paclitaxel) may be re-evaluated with repeat imaging (CT or MRI) to assess whether the tumor has shrunk enough for surgery.
  - Surgery may then be attempted if the tumor no longer involves major blood vessels or if vascular reconstruction is possible.
- Outcomes: This approach is successful in a minority of cases, but achieving resection after downstaging is associated with significantly improved outcomes compared to non-surgical treatment alone.

## 4. Clinical Trials:

- Patients with LAPC are often encouraged to participate in clinical trials, as there are ongoing studies exploring novel therapies, including immunotherapy, targeted therapies, and new chemotherapy combinations.
- Trials may offer access to cutting-edge treatments that are not yet widely available but could potentially improve survival or quality of life.

## Palliative Care Considerations:

For patients with symptoms such as pain, jaundice (due to bile duct obstruction), or gastrointestinal obstruction, palliative interventions are also crucial:

- Biliary stenting or biliary bypass surgery to relieve jaundice.
- Celiac plexus neurolysis (nerve block) for pain relief in patients with severe abdominal or back pain.
- Gastrojejunostomy if the tumor is causing gastric outlet obstruction.

#### Summary of First-Line Treatment for LAPC:

1. Chemotherapy (FOLFIRINOX or gemcitabine-based regimens) is the primary treatment.
2. Chemoradiotherapy may be considered after chemotherapy in patients with locally persistent disease.
3. Downstaging to resectability can be a goal in some cases, potentially leading to surgery.
4. Palliative care addresses symptoms and improves quality of life.

The treatment plan is typically tailored based on the patient's overall health, tumor characteristics, and response to therapy.

#### Risposta 3.

For patients with locally advanced, unresectable pancreatic cancer, chemoradiotherapy can be an important component of treatment, especially when the goal is to control local disease and alleviate symptoms. The recommended regimen typically involves a combination of chemotherapy and radiation therapy. Here are the details of the most commonly used chemoradiotherapy regimens:

##### 1. Chemoradiotherapy with Gemcitabine

- Indication: Gemcitabine is often used as the chemotherapy agent in combination with radiation therapy.

-Regimen: The regimen typically includes:

- Gemcitabine: Administered at a dose of 1000 mg/m<sup>2</sup> intravenously on days 1, 8, and 15 of a 28-day cycle.

-Radiation Therapy: Administered concurrently with gemcitabine, typically a total dose of 50.4 Gy delivered in fractions of 1.8 Gy per day over 5 weeks.

##### 2. FOLFIRINOX with Radiation

- Indication: While FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin) is primarily a systemic chemotherapy regimen, it may also be used in conjunction with radiation in some protocols for locally advanced pancreatic cancer.

-Regimen: The specific dosing and timing may vary, but it often follows a similar structure:

-FOLFIRINOX: Administered for several cycles (usually at least 4 cycles) before or concurrently with radiation, depending on the treatment strategy and patient tolerance.

-Radiation Therapy: A total dose of 45–54 Gy delivered in fractions, often tailored based on the response to initial chemotherapy.

##### 3. Nab-Paclitaxel with Gemcitabine and Radiation



- Indication: Another regimen that may be used is the combination of gemcitabine with nab-paclitaxel followed by radiation.

- Regimen:

- Gemcitabine: Given as before.

- Nab-Paclitaxel: Administered at 125 mg/m<sup>2</sup> on days 1, 8, and 15.

- Radiation Therapy: Administered concurrently, similar to the gemcitabine regimen.

Considerations:

- Patient Selection: The choice of regimen should consider the patient's overall health, performance status, and any pre-existing conditions. Not all patients will be candidates for aggressive chemoradiotherapy.

- Supportive Care: Close monitoring for side effects and supportive care for managing symptoms is crucial throughout the treatment course, as both chemotherapy and radiation can cause significant toxicity.

- Clinical Trials: Participation in clinical trials is often encouraged, as new regimens and combinations are continually being studied for effectiveness in locally advanced pancreatic cancer.

Summary:

The recommended chemoradiotherapy regimens for locally advanced, unresectable pancreatic cancer typically include combinations such as gemcitabine with radiation therapy or FOLFIRINOX with radiation. These regimens aim to enhance local control of the disease, manage symptoms, and improve overall survival. The choice of treatment should be personalized based on patient characteristics and preferences.

11. What is the first-line chemotherapy recommended for pancreatic cancer patients with distant metastases?

Risposta 1

For pancreatic cancer patients with distant metastases, the primary goal of treatment is palliation, prolongation of survival, and improvement of quality of life. Surgical resection is not an option in metastatic cases, so systemic chemotherapy is the mainstay of treatment. The choice of chemotherapy regimen depends on the patient's performance status, comorbidities, and ability to tolerate aggressive treatment.

Here are the first-line chemotherapy regimens recommended for patients with metastatic pancreatic cancer:

1. FOLFIRINOX (for patients with good performance status):

FOLFIRINOX is a combination of 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin. It is generally considered the most effective first-line chemotherapy for patients with metastatic pancreatic cancer who have good performance status (ECOG 0-1) and no significant comorbidities.

Components of FOLFIRINOX:

5-FU (continuous infusion)

Leucovorin (enhances the effects of 5-FU)

Irinotecan

Oxaliplatin

Advantages: FOLFIRINOX has been shown to significantly improve overall survival, progression-free survival, and response rates compared to gemcitabine monotherapy.

The regimen is particularly effective in younger patients with a good functional status and minimal comorbidities.

Disadvantages: It is associated with higher toxicity compared to other regimens. Common side effects include neutropenia, diarrhea, fatigue, peripheral neuropathy, and nausea.

Due to its toxicity profile, it is generally reserved for patients who are fit enough to tolerate it.

Modification: In cases where full-dose FOLFIRINOX is too toxic, modified FOLFIRINOX (mFOLFIRINOX) is used. This involves dose adjustments, usually by reducing irinotecan or omitting the bolus dose of 5-FU to improve tolerability.

2. Gemcitabine plus Nab-Paclitaxel (Abraxane) (for patients with moderate performance status): Gemcitabine plus nab-paclitaxel is another first-line option for patients with metastatic pancreatic cancer, particularly those with a good or moderately good performance status (ECOG 0-2).

Advantages: This combination is less toxic than FOLFIRINOX and is associated with a better safety profile in patients who may not tolerate the more aggressive FOLFIRINOX regimen.

Studies (such as the MPACT trial) have shown that gemcitabine plus nab-paclitaxel improves overall survival and progression-free survival compared to gemcitabine monotherapy.

Common Side Effects: Myelosuppression (especially neutropenia), peripheral neuropathy, and fatigue are common side effects, but they are generally more manageable than the side effects of FOLFIRINOX.

Peripheral neuropathy from nab-paclitaxel can sometimes become dose-limiting.

Suitability: This regimen is ideal for patients who may not be able to tolerate FOLFIRINOX but still have a reasonably good functional status and no severe comorbidities.

3. Gemcitabine Monotherapy (for patients with poor performance status): Gemcitabine monotherapy is the standard treatment for patients with metastatic pancreatic cancer who have a poorer performance status (ECOG 2-3) or significant comorbidities, as they are unlikely to tolerate more aggressive regimens like FOLFIRINOX or gemcitabine/nab-paclitaxel.

Advantages: Gemcitabine is less toxic than combination regimens and is associated with improved symptoms and modest survival benefits compared to supportive care alone. It is a good option for frail patients or those with significant comorbid conditions.

Common Side Effects: The toxicity profile of gemcitabine includes fatigue, mild myelosuppression, flu-like symptoms, and nausea, but it is generally well tolerated in most patients.

Use: It is used primarily for patients who are not candidates for more aggressive combination chemotherapy due to poor functional status or advanced age.

4. Other Considerations: Targeted Therapy: In select patients with BRCA1/2 mutations or other DNA repair pathway defects, PARP inhibitors (such as olaparib) may be used after initial platinum-based chemotherapy.

Clinical Trials: Participation in clinical trials is encouraged for patients with metastatic pancreatic cancer, as research is ongoing to find more effective treatments. Immunotherapy, targeted therapies, and novel combinations are being explored.

#### Summary of First-Line Chemotherapy for Metastatic Pancreatic Cancer:

##### FOLFIRINOX:

- Recommended for patients with good performance status (ECOG 0-1).

- Provides the best survival benefit but is associated with significant toxicity.

- Modified FOLFIRINOX may be used to reduce toxicity in borderline fit patients.

##### Gemcitabine plus Nab-Paclitaxel:

- Recommended for patients with moderate performance status (ECOG 0-2).

- Effective with a better safety profile than FOLFIRINOX.

##### Gemcitabine Monotherapy:

- Recommended for patients with poor performance status (ECOG 2-3) or significant comorbidities.

- Less toxic and helps improve quality of life and manage symptoms.

### Treatment Goals:

The primary goals of chemotherapy in metastatic pancreatic cancer are to prolong survival, control disease progression, relieve symptoms, and maintain or improve the patient's quality of life. The choice of chemotherapy regimen is based on a balance between treatment efficacy and the patient's ability to tolerate side effects.

### Risposta 2.

For pancreatic cancer patients with distant metastases (metastatic pancreatic cancer), the first-line chemotherapy regimen is typically based on combination therapy due to the aggressive nature of the disease and the need for effective systemic control. The most commonly recommended first-line regimens include:

#### 1. FOLFIRINOX:

- Composition:
  - 5-Fluorouracil (5-FU)
  - Leucovorin
  - Irinotecan
  - Oxaliplatin
- Indication: FOLFIRINOX is recommended for patients with a good performance status (ECOG score of 0–1) who can tolerate a more intensive regimen. It has shown improved overall survival compared to gemcitabine alone in patients with metastatic pancreatic cancer.
- Effectiveness:
  - In clinical trials, FOLFIRINOX has been associated with longer overall survival (approximately 11.1 months compared to 6.8 months with gemcitabine) and higher response rates.
  - Toxicity: The regimen is associated with significant toxicity, including neutropenia, diarrhea, and neuropathy, necessitating close monitoring and supportive care.

#### 2. Gemcitabine-Based Regimens:

- Gemcitabine + Nab-Paclitaxel (Abraxane):
  - Indication: This combination is an alternative for patients who may not be suitable for FOLFIRINOX or those with a good performance status.

- Effectiveness: The combination has demonstrated a survival advantage over gemcitabine alone. In clinical trials, patients treated with gemcitabine plus nab-paclitaxel had a median overall survival of approximately 8.5 months compared to 6.7 months with gemcitabine monotherapy.
- Toxicity: Generally better tolerated than FOLFIRINOX, but it can still cause side effects like neutropenia and peripheral neuropathy.
- Gemcitabine Monotherapy:
  - For patients with a poor performance status (ECOG score of 2 or higher) or those who cannot tolerate combination regimens, gemcitabine alone may be used.
  - Although it is less effective than combination therapies, it is better tolerated and can provide some benefit in symptom control.

### 3. Clinical Trial Participation:

- Patients with metastatic pancreatic cancer are often encouraged to participate in clinical trials, as new therapies, combinations, and targeted approaches are continually being evaluated. Emerging treatments, including immunotherapy and novel agents, may offer additional options beyond the standard chemotherapy regimens.

#### Summary:

The first-line chemotherapy for metastatic pancreatic cancer typically includes:

- FOLFIRINOX for patients with a good performance status.
- Gemcitabine + nab-paclitaxel as an effective alternative for those who may not tolerate FOLFIRINOX.
- Gemcitabine monotherapy for patients with poor performance status or significant comorbidities.

The choice of regimen should be tailored to the individual patient's performance status, comorbidities, and preferences, with considerations for potential side effects and supportive care needs.

#### Risposta 3.

For patients with pancreatic cancer that has distant metastases, the first-line chemotherapy treatment options typically include:

#### 1. FOLFIRINOX

- Composition: This regimen consists of leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin.

- Indication: FOLFIRINOX is generally recommended for fit patients with good performance status (ECOG 0-1) because it has shown superior efficacy compared to other treatments.
- Efficacy: Clinical trials have demonstrated that FOLFIRINOX improves overall survival and progression-free survival in patients with metastatic pancreatic cancer compared to gemcitabine alone.

## 2. Gemcitabine-Based Regimens

- Gemcitabine Alone: Traditionally considered a standard treatment for metastatic pancreatic cancer, gemcitabine is administered at a dose of 1000 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle.
- Gemcitabine with Nab-Paclitaxel:
  - Combination: The combination of gemcitabine and nab-paclitaxel (Abraxane) is another recommended first-line treatment for metastatic pancreatic cancer.
    - Indication: This regimen is often preferred for patients who may not tolerate FOLFIRINOX due to age, comorbidities, or poor performance status.
    - Efficacy: Studies have shown that this combination improves overall survival compared to gemcitabine alone.

### Summary of Treatment Choices:

- FOLFIRINOX is the preferred option for fit patients who can tolerate more aggressive chemotherapy.
- Gemcitabine with nab-paclitaxel is recommended for patients with a less favorable performance status or those who may experience significant toxicity from FOLFIRINOX.

### Conclusion:

In summary, the first-line chemotherapy for pancreatic cancer patients with distant metastases typically includes FOLFIRINOX for fit patients and a gemcitabine-based regimen (either alone or in combination with nab-paclitaxel) for those with poorer performance status. The choice of regimen should be personalized based on the patient's overall health, preferences, and tolerance to treatment.

## 12. Is surgical resection recommended for pancreatic cancer patients with postoperative metastases/recurrences?

Risposta 1.

Surgical resection is generally not recommended for pancreatic cancer patients who develop postoperative metastases or recurrences. This is because the prognosis of metastatic or recurrent pancreatic cancer is poor, and surgery in these cases has not been shown to significantly improve survival outcomes. Instead, the focus is typically on systemic therapies, such as chemotherapy, and palliative care. However, there are certain highly selective cases where surgery might be considered.

Here's a detailed explanation of the reasoning behind this approach:

1. Postoperative Metastases: Metastatic disease following surgery (e.g., to the liver, peritoneum, or distant lymph nodes) indicates systemic disease. Surgery in the setting of metastatic disease typically does not improve survival and can increase morbidity.

Systemic chemotherapy is the standard treatment for patients with metastases, as pancreatic cancer behaves aggressively when it spreads, and local control (via surgery) is unlikely to alter the disease course.

First-line chemotherapy regimens such as FOLFIRINOX or gemcitabine plus nab-paclitaxel are typically recommended in metastatic settings.

2. Postoperative Recurrences:

Recurrence of pancreatic cancer after surgery usually occurs in one of two ways:

Local Recurrence: Cancer recurs in or near the surgical bed (e.g., at the site of the pancreas or surrounding structures).

Distant Recurrence: Cancer recurs in distant organs such as the liver, lungs, or peritoneum.

For both types of recurrence, surgery is typically not recommended for the following reasons:

Local Recurrence: Even if the recurrence is localized, pancreatic cancer has a high risk of microscopic or undetected systemic spread. Removing the recurrent tumor does not address the potential presence of micrometastases elsewhere in the body, and surgery is unlikely to provide a significant survival benefit.

Distant Recurrence: Surgery is not feasible or beneficial in the context of distant metastases, as the disease has spread beyond the primary site and requires systemic treatment.

3. Exceptions and Highly Selective Cases:

While surgery is generally not recommended for metastatic or recurrent pancreatic cancer, there are rare and highly selective circumstances where it might be considered. These include:

Oligometastatic Disease: If a patient has a very limited number of metastatic lesions (e.g., isolated liver or lung metastasis) and has had a long disease-free interval after the initial

surgery, surgical resection of the metastases might be considered in some centers. This is typically part of a broader multimodal treatment approach, including chemotherapy.

**Resection of Local Recurrence:** In rare cases, some centers may consider surgery for isolated local recurrence, especially if the patient had a long period of remission, no distant metastases are detected, and the patient is in good health. However, this approach remains controversial, and its benefit is not well established.

#### 4. Preferred Approach: Systemic Therapy:

For patients with postoperative metastases or recurrence, the focus is on systemic treatments to control the spread of the disease and prolong survival. Standard therapies include:

**Chemotherapy:** The same regimens used in metastatic pancreatic cancer (such as FOLFIRINOX or gemcitabine-based combinations) are typically employed.

**Targeted Therapy:** In patients with certain genetic mutations (e.g., BRCA1/2 mutations), targeted therapies such as PARP inhibitors may be considered.

**Palliative Care:** Symptom management, including pain control, nutritional support, and management of biliary or gastric outlet obstruction, is an essential component of care in recurrent/metastatic pancreatic cancer.

#### 5. Prognosis:

The prognosis for patients with postoperative recurrence or metastases is generally poor, with median survival typically measured in months rather than years, even with aggressive systemic therapy. Surgery in this setting has not been shown to significantly improve outcomes compared to non-surgical treatments like chemotherapy.

#### Conclusion:

Surgical resection is not recommended for the majority of patients with postoperative metastases or recurrences of pancreatic cancer due to the systemic nature of the disease and the lack of demonstrated survival benefit.

Systemic therapy (chemotherapy) is the mainstay of treatment for both metastatic and recurrent disease.

Surgery may be considered in very rare, highly selected cases, such as oligometastatic disease or isolated local recurrence, but this is uncommon and should be approached with caution.

Ultimately, treatment decisions should be made on a case-by-case basis, involving a multidisciplinary team and considering the patient's overall health, disease burden, and treatment goals.



## Risposta 2.

Surgical resection is generally not recommended for patients with postoperative metastases or recurrences of pancreatic cancer. The primary reasons for this include the following:

### Key Considerations Regarding Surgical Resection for Recurrences:

1. Nature of Recurrences:
    - Postoperative metastases typically indicate that the cancer has spread beyond the original site, affecting distant organs (e.g., liver, lungs, peritoneum). Surgical resection is usually not feasible or beneficial in these cases, as the goal of surgery is to achieve complete resection of localized disease.
  2. Limited Survival Benefit:
    - The prognosis for patients with recurrent metastatic pancreatic cancer is generally poor. Surgical interventions for recurrence have not been shown to significantly improve survival compared to systemic therapies. The majority of patients with recurrence will eventually experience further progression of disease.
  3. Systemic Treatment Focus:
    - For patients with postoperative recurrences, systemic therapy (chemotherapy) is the primary treatment option. The regimens used typically include:
      - FOLFIRINOX for those with a good performance status.
      - Gemcitabine-based therapies (including gemcitabine plus nab-paclitaxel) for patients who may not tolerate FOLFIRINOX.
    - The focus is on controlling the disease, managing symptoms, and improving the quality of life rather than pursuing surgical options.
  4. Palliative Care:
    - If recurrence leads to significant symptoms (e.g., pain, jaundice, gastrointestinal obstruction), palliative interventions may be necessary, such as:
      - Biliary stenting for obstructive jaundice.
      - Gastrojejunostomy for gastric outlet obstruction.
      - Pain management strategies, including nerve blocks or other palliative measures.
- Exceptions and Special Cases:
1. Localized Recurrences:
    - In rare cases where recurrence is localized and resectable (for instance, isolated liver metastasis or a locoregional recurrence without distant spread), surgical resection may be

considered. However, these cases are exceptions and require careful evaluation by a multidisciplinary team.

- Ablative techniques (e.g., radiofrequency ablation or cryoablation) may also be considered for small, isolated metastatic lesions, although these are not standard practices and are generally pursued within clinical trials.

## 2. Clinical Trials:

- Some patients may be eligible for clinical trials investigating novel therapies or approaches for managing recurrence or metastasis, which may provide alternative treatment options not typically available in standard practice.

Summary:

- Surgical resection is not recommended for pancreatic cancer patients with postoperative metastases or recurrences, as it generally does not offer a survival benefit and the focus shifts to systemic therapy and palliative care.
- In exceptional circumstances, localized recurrences may be considered for resection, but this is a rare occurrence.
- The management strategy should be tailored to each patient's situation, involving a multidisciplinary team to determine the best course of action.

Risposta 3.

Surgical resection is generally not recommended for pancreatic cancer patients who present with postoperative metastases or recurrences. Here's a detailed explanation of the rationale behind this approach:

Key Considerations:

### 1. Nature of Metastatic Disease:

- By definition, **\*\*metastatic pancreatic cancer\*\*** indicates that the cancer has spread to distant organs (such as the liver or lungs) or lymph nodes beyond the pancreas. Once metastases are present, the disease is considered systemic rather than localized.

### 2. Surgical Goals:

- The primary goal of surgical resection in pancreatic cancer is to achieve an R0 resection, meaning complete removal of the tumor with no cancer cells at the margins. In cases of metastatic disease, the focus typically shifts to systemic therapy rather than surgery, as the presence of metastases indicates that the cancer is unlikely to be completely eradicated by surgical intervention alone.

### 3. Postoperative Recurrence:

- If cancer recurs after initial surgery (e.g., Whipple procedure), the recurrence usually occurs locally (near the original site) or distally (in distant organs). In these scenarios, surgical resection is not considered curative. Instead, treatment focuses on managing the disease through systemic therapies (chemotherapy) and possibly radiation therapy for local control.

#### Exceptions:

While surgical resection is generally not indicated for patients with metastatic disease, there are some exceptions:

#### 1. Localized Recurrence:

- If a patient develops a localized recurrence that is resectable and has not spread distally, surgical resection may be considered. This is rare and would require careful assessment by a multidisciplinary team.

#### 2. Palliative Surgery:

- In some cases, surgical procedures may be performed for palliative reasons, such as relieving obstruction or managing symptoms related to the disease, even in the presence of metastases. For example, procedures like biliary bypass or gastrojejunostomy may be performed to alleviate symptoms.

#### 3. Clinical Trials:

- Some patients may be eligible for clinical trials evaluating novel approaches, which could include surgical interventions or experimental therapies, but these situations would still be exceptions rather than standard practice.

#### Summary:

In conclusion, surgical resection is not recommended for pancreatic cancer patients with postoperative metastases or recurrences due to the systemic nature of the disease at that stage. The focus of treatment typically shifts to systemic therapies, with surgery reserved for specific cases of localized recurrence or palliative interventions. Management decisions should always be made by a multidisciplinary team considering the patient's overall condition and preferences.

13. Which of the two types of stents—plastic stents or metallic stents—are recommended in resectable or borderline resectable pancreatic cancer patients with obstructive jaundice?

Risposta 1.

In patients with resectable or borderline resectable pancreatic cancer who present with obstructive jaundice, metallic stents (specifically self-expanding metal stents, or SEMS) are generally preferred over plastic stents for biliary drainage. However, the choice between plastic and metallic stents can depend on specific clinical situations and the expected timing of surgery.

Here's a detailed explanation of the considerations involved:

### 1. Self-Expanding Metallic Stents (SEMS):

Advantages:

Longer patency: SEMS tend to remain patent (unobstructed) for a longer period compared to plastic stents. This is particularly important in patients who may experience delays in surgery, such as those receiving neoadjuvant therapy.

Fewer complications: Metallic stents have a lower risk of complications like stent occlusion, cholangitis, or recurrent jaundice, which can complicate treatment.

Fewer interventions: Since metallic stents last longer, fewer repeat endoscopic procedures are needed, reducing patient discomfort and procedural risks.

Use in Borderline Resectable Pancreatic Cancer:

In patients with borderline resectable pancreatic cancer, the typical approach is to start with neoadjuvant chemotherapy to shrink the tumor before surgery. In these cases, a metal stent is preferred because it is less likely to become occluded during the prolonged period of neoadjuvant therapy (which can last several months).

SEMS are also recommended if surgery may be delayed or if there is uncertainty about the resectability of the tumor.

Types of SEMS:

SEMS can be either covered or uncovered. Covered SEMS can be removed if necessary, but uncovered SEMS are often used because they integrate into the bile duct wall, reducing the risk of migration.

### 2. Plastic Stents:

Advantages:

Shorter-term use: Plastic stents are sometimes preferred when surgery is expected to be performed in a short time frame (within a few weeks) because they are less expensive and easier to remove during surgery.

Lower cost: Plastic stents are cheaper than metallic stents, which might be considered if immediate surgery is planned.

#### Disadvantages:

**Shorter patency:** Plastic stents tend to occlude more quickly, typically within 3-4 months, which increases the likelihood of recurrent jaundice, cholangitis, and the need for additional stent exchanges or interventions.

**Higher complication rates:** The shorter patency and higher occlusion rates with plastic stents can lead to complications such as infection and the need for repeat procedures, especially if surgery is delayed or neoadjuvant therapy is administered.

#### 3. Timing of Surgery and Stent Choice:

##### Early Surgery Expected (within 2-4 weeks):

In patients who are candidates for early surgery (i.e., those with resectable pancreatic cancer without the need for neoadjuvant therapy), plastic stents can be a reasonable option because they are less costly and are effective for short-term drainage.

##### Neoadjuvant Therapy or Delayed Surgery (several months):

In cases where neoadjuvant therapy is planned (as is common in borderline resectable pancreatic cancer) or if there is any uncertainty about when surgery can be performed, metallic stents are preferred because of their longer patency and lower risk of occlusion during therapy.

#### 4. Factors Influencing Stent Choice:

**Patient's clinical condition:** If the patient presents with cholangitis or severe jaundice that requires urgent biliary decompression, a plastic stent may be used as a temporary measure. However, if the jaundice is less severe and time permits, placing a metallic stent may be preferable, particularly if there is a high likelihood of neoadjuvant therapy.

**Surgeon's preference:** Some surgical teams may prefer plastic stents because they are easier to remove during pancreaticoduodenectomy (Whipple procedure). However, most data suggest that SEMS can be safely removed during surgery as well.

#### Conclusion:

Metallic stents (SEMS) are recommended for patients with borderline resectable pancreatic cancer or those in whom neoadjuvant therapy is planned or anticipated, as they have longer patency, lower risk of occlusion, and fewer complications.

Plastic stents may be considered for patients with resectable pancreatic cancer who are expected to undergo early surgery (within a few weeks) and do not require neoadjuvant therapy.

The choice of stent should be based on the anticipated timeline to surgery, the need for neoadjuvant therapy, and the overall clinical condition of the patient.

Risposta 2.

In patients with resectable or borderline resectable pancreatic cancer who develop obstructive jaundice, the choice between plastic stents and metallic stents for biliary drainage often depends on several factors, including the anticipated duration of biliary obstruction, the patient's overall condition, and the specific clinical scenario. Here's a comparison of the two types of stents:

#### 1. Plastic Stents:

- Indication:
  - Typically used for temporary drainage when the obstruction is expected to be resolved, especially in cases where surgery is planned shortly after stenting.
- Advantages:
  - Cost-effective: Plastic stents are generally less expensive than metallic stents.
  - Easy to place: They can be easily inserted during endoscopic procedures.
- Disadvantages:
  - Limited patency: Plastic stents have a shorter lifespan, typically requiring replacement every 3–6 months due to clogging or migration.
  - Higher risk of re-obstruction: They may require more frequent interventions if used for long-term management.

#### 2. Metallic Stents (Self-Expanding Metal Stents - SEMS):

- Indication:
  - Recommended for patients with longer expected durations of biliary obstruction, such as those with unresectable disease or those requiring longer preoperative drainage.
- Advantages:
  - Longer patency: Metallic stents generally have a longer duration of effectiveness, often remaining patent for several months to years, which can reduce the need for repeated procedures.
  - Better drainage: They provide a larger diameter for biliary drainage, reducing the risk of obstruction compared to plastic stents.
- Disadvantages:
  - Higher initial cost: Metallic stents are typically more expensive than plastic stents.

- Potential complications: There is a risk of migration, perforation, and other complications associated with their placement.

#### Recommendations:

- For patients with resectable or borderline resectable pancreatic cancer and obstructive jaundice:
  - If short-term drainage is anticipated (e.g., waiting for surgery), plastic stents may be sufficient.
  - If longer-term drainage is needed, or if there are concerns about prolonged obstruction before surgery, metallic stents are often preferred due to their longer patency and lower rates of re-obstruction.

#### Clinical Considerations:

- The decision should be individualized based on:
  - The estimated timeline for surgical intervention.
  - The patient's overall health status and ability to tolerate procedures.
  - The expertise and resources available at the treating institution.

#### Conclusion:

In summary, for patients with obstructive jaundice due to resectable or borderline resectable pancreatic cancer:

- Plastic stents are suitable for short-term use before surgery.
- Metallic stents are recommended for longer durations of obstruction, providing better long-term drainage solutions.

#### Risposta 3.

In patients with resectable or borderline resectable pancreatic cancer who present with obstructive jaundice, the choice of stent—plastic stents versus metallic stents—depends on several factors, including the expected duration of stenting and the specific clinical scenario.

Here's a detailed comparison of the two types of stents:

##### 1. Plastic Stents:

- Description: Plastic stents are typically made from materials such as polyethylene or polyurethane. They are smaller in diameter and often used for temporary drainage.
- Indication:

- Recommended for patients who are expected to undergo surgical resection in the near future (especially if the obstruction is likely to be temporary) or when there is a lower likelihood of long-term bile duct obstruction.

- Ideal for patients who might not need long-term drainage.

- Advantages:

- Easier to place and remove.

- Lower cost compared to metallic stents.

- Disadvantages:

- Prone to clogging (especially with long-term use), which can lead to a need for replacement every few months.

- May require more frequent interventions for exchange.

## 2. Metallic Stents:

- Description: Metallic stents, typically made of materials like stainless steel or nitinol, are larger in diameter and designed to provide a more durable solution.

- Indication:

- Recommended for patients who are unlikely to undergo immediate resection or for those with a longer expected duration of bile duct obstruction (e.g., due to tumor growth or other complications).

- Suitable for cases of malignant biliary obstruction where longer-term drainage is needed.

- Advantages:

- Less likely to occlude compared to plastic stents, making them suitable for longer-term use.

- Can provide effective drainage for extended periods without needing frequent replacement.

- Disadvantages:

- More expensive than plastic stents.

- More challenging to remove if necessary.

## Current Recommendations:

In general, the choice between plastic and metallic stents in patients with resectable or borderline resectable pancreatic cancer and obstructive jaundice can be summarized as follows:

- Plastic Stents:

- Often preferred in cases where the obstruction is anticipated to be temporary (e.g., if surgery is planned soon) or when the patient is being prepared for resection.



- Metallic Stents:

- Considered for long-term drainage needs, especially if the timing of surgery is uncertain or if there are complications such as significant tumor burden.

Conclusion:

Ultimately, the decision between plastic and metallic stents should be made on a case-by-case basis, taking into account the individual patient's clinical situation, the expected duration of stenting, and the planned treatment approach. A multidisciplinary team, including gastroenterologists, surgeons, and oncologists, should collaborate to make the most appropriate choice for each patient

14. Is anticoagulant therapy for preventing venous thromboembolism recommended in patients with unresectable pancreatic cancer undergoing chemotherapy?

Risposta 1.

Yes, anticoagulant therapy is often recommended in patients with unresectable pancreatic cancer undergoing chemotherapy to prevent venous thromboembolism (VTE), especially in high-risk individuals. Pancreatic cancer is associated with a particularly high risk of VTE, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).

Chemotherapy further increases this risk, making anticoagulation an important consideration. Here's a detailed look at why and how anticoagulation is managed in this patient population:

1. Why Anticoagulation is Important in Pancreatic Cancer:

**High Risk of VTE:** Pancreatic cancer has one of the highest rates of thromboembolic events among all cancers, with up to 20-25% of patients developing VTE at some point. This is due to a combination of factors, including tumor-related procoagulant activity, chemotherapy, immobility, and inflammation.

**Increased Risk with Chemotherapy:** The use of chemotherapy (particularly regimens like FOLFIRINOX or gemcitabine/nab-paclitaxel) significantly increases the risk of thromboembolism. Chemotherapy alters endothelial function and promotes a hypercoagulable state.

**Morbidity and Mortality:** VTE events can increase morbidity and mortality in pancreatic cancer patients, making prevention crucial to improving quality of life and potentially enhancing survival.

2. Guidelines for Anticoagulation:

Several clinical guidelines recommend considering anticoagulant therapy for VTE prevention in high-risk cancer patients, including those with pancreatic cancer. Here's an overview of the recommendations:

National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines:

Prophylactic anticoagulation is recommended for patients with a high risk of VTE, including those with pancreatic cancer undergoing chemotherapy, especially if they have additional risk factors (e.g., immobility, recent surgery, previous VTE, or central venous catheters).

Risk stratification tools such as the Khorana score (which includes factors like cancer type, platelet count, hemoglobin, and body mass index) can help identify patients at higher risk of VTE who might benefit most from prophylaxis.

### 3. Types of Anticoagulant Therapy:

The two main classes of anticoagulants recommended for preventing VTE in cancer patients are low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs):

#### Low-Molecular-Weight Heparin (LMWH):

Enoxaparin (Lovenox) is commonly used for VTE prophylaxis in cancer patients.

LMWH has long been the standard of care for both prophylaxis and treatment of VTE in cancer patients due to its efficacy and safety profile.

**Advantages:** It has a proven track record in cancer-associated thrombosis and has been shown to be effective in preventing both symptomatic and asymptomatic VTE.

**Disadvantages:** LMWH requires daily subcutaneous injections, which can be cumbersome for long-term use.

#### Direct Oral Anticoagulants (DOACs):

DOACs, such as apixaban (Eliquis) and rivaroxaban (Xarelto), are increasingly used in cancer patients for both VTE treatment and prophylaxis.

Recent clinical trials (such as the AVERT and CASSINI trials) have demonstrated that DOACs can be effective in reducing the risk of VTE in cancer patients at high risk, including those with pancreatic cancer.

**Advantages:** DOACs are oral medications, making them more convenient for patients than injectable LMWH.

**Disadvantages:** DOACs have an increased risk of gastrointestinal bleeding compared to LMWH, especially in patients with pancreatic cancer, so careful consideration is needed in those at high risk for bleeding.

#### 4. Balancing the Risks of Anticoagulation:

While anticoagulation is effective in preventing VTE, it also carries a risk of bleeding. This risk must be weighed against the benefits of preventing potentially life-threatening thromboembolic events.

**Bleeding Risk:** Patients with pancreatic cancer may have a higher risk of bleeding due to factors like tumor invasion, chemotherapy-related thrombocytopenia, or pre-existing conditions.

**Individualized Decision-Making:** The decision to start anticoagulation should be based on an individual assessment of the patient's risk factors for both VTE and bleeding. Regular monitoring of blood counts and kidney function is essential during therapy.

#### 5. When to Start Anticoagulation:

Prophylactic anticoagulation is typically initiated at the start of chemotherapy in high-risk patients.

For patients with central venous catheters or a history of VTE, anticoagulation is strongly considered to prevent thromboembolism.

#### 6. Duration of Anticoagulation:

The duration of prophylactic anticoagulation is typically continued as long as the patient is receiving chemotherapy and remains at high risk for VTE.

In cases where the patient has a confirmed VTE, therapeutic anticoagulation may be continued indefinitely or until cancer remission, depending on the clinical scenario.

#### Summary:

Anticoagulant therapy is recommended in patients with unresectable pancreatic cancer undergoing chemotherapy, especially in those at high risk for VTE.

Low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) are both effective options, with LMWH having a long-established role and DOACs offering a more convenient oral alternative.

The decision to use prophylactic anticoagulation should be individualized based on a patient's risk of VTE versus bleeding, with regular monitoring during treatment.

Anticoagulation can significantly reduce the risk of VTE, improving both the quality of life and survival outcomes in patients with pancreatic cancer.

Risposta 2.

Anticoagulant therapy for the prevention of venous thromboembolism (VTE) in patients with unresectable pancreatic cancer undergoing chemotherapy is a topic of increasing interest and research. While there is no universal consensus, several key points can guide clinical practice regarding the use of anticoagulants in this patient population:

#### 1. Increased Risk of VTE:

- Patients with pancreatic cancer, particularly those with advanced disease and those undergoing chemotherapy, are at an increased risk of developing VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE).
- This risk is multifactorial, including factors such as tumor-related hypercoagulability, immobility during treatment, and potential effects of chemotherapy.

#### 2. Current Recommendations:

- Anticoagulation for VTE Prophylaxis: Current guidelines from organizations such as the American Society of Clinical Oncology (ASCO) suggest considering anticoagulation for patients with cancer, including those with pancreatic cancer, who are at increased risk for VTE.
  - For ambulatory patients undergoing chemotherapy, routine anticoagulation is generally not recommended unless there are specific risk factors present (e.g., previous VTE history, immobility, or other coexisting conditions).
  - For hospitalized patients, or those with advanced disease and limited mobility, prophylactic anticoagulation (using low molecular weight heparin [LMWH] or unfractionated heparin) is often recommended.

#### 3. Use of Anticoagulants:

- Low Molecular Weight Heparin (LMWH) is commonly used due to its favorable pharmacokinetic profile, ease of administration, and established safety in cancer patients.
- Warfarin and Direct Oral Anticoagulants (DOACs): While some studies suggest that these may be safe, LMWH remains the standard due to its ease of use in patients with fluctuating cancer-related conditions.

#### 4. Balancing Risks and Benefits:

- When considering anticoagulation, clinicians must weigh the benefits of VTE prevention against the risks of bleeding, especially given the increased risk of bleeding associated with both cancer and certain chemotherapeutic agents.
- Regular monitoring and assessment of bleeding risk factors are essential when initiating anticoagulation therapy.

#### 5. Ongoing Research:

- Ongoing clinical trials and studies are examining the effectiveness of anticoagulant prophylaxis in specific populations of cancer patients. As more evidence becomes available, guidelines may evolve.

Conclusion:

- Anticoagulant therapy for preventing VTE in patients with unresectable pancreatic cancer undergoing chemotherapy is generally considered based on individual risk factors and the clinical scenario.
- Prophylactic anticoagulation is recommended for high-risk patients, particularly those with advanced disease, while a more individualized approach is necessary for patients at lower risk.

Risposta 3.

Anticoagulant therapy for preventing venous thromboembolism (VTE) in patients with unresectable pancreatic cancer undergoing chemotherapy is a topic of increasing interest due to the elevated risk of VTE in these patients. Here's an overview of the current recommendations and considerations regarding anticoagulant therapy in this context:

#### 1. Increased Risk of VTE

- Patients with pancreatic cancer, especially those with unresectable disease, are at a higher risk of developing VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). This risk is attributed to several factors:

-Tumor biology: Certain malignancies, including pancreatic cancer, have a pro-coagulant state.

-Chemotherapy: The use of chemotherapy can further increase the risk of VTE.

- Immobility: Patients may experience limited mobility due to symptoms or treatment side effects.

#### 2. Anticoagulation Guidelines

- Current Evidence: Guidelines from various oncological and hematological societies, including the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), support the use of anticoagulants for VTE prevention in specific high-risk populations.

- Recommendations:

- Prophylactic Anticoagulation: The use of prophylactic anticoagulation (such as low molecular weight heparin [LMWH]) may be considered in patients with advanced cancer

who have additional risk factors for VTE. This is particularly relevant in patients with limited mobility or those undergoing certain chemotherapy regimens.

- Individual Assessment: The decision to initiate anticoagulation should be based on an individual risk assessment that considers factors such as the patient's performance status, previous history of VTE, the presence of other risk factors (e.g., obesity, recent surgery), and the specific chemotherapy regimen being used.

### 3. Clinical Trials and Emerging Data

- Ongoing research is being conducted to further clarify the role of anticoagulant therapy in this patient population. Some studies have suggested potential benefits of anticoagulation in preventing VTE and improving overall survival in patients with malignancies, including pancreatic cancer.

### 4. Practical Considerations

- Monitoring: If anticoagulant therapy is initiated, close monitoring for bleeding complications is essential, especially in patients receiving chemotherapy, which can also have hematological effects.
- Patient Education: Educating patients about signs and symptoms of VTE and potential bleeding complications is critical for safety.

### Summary

In summary, anticoagulant therapy may be recommended for preventing venous thromboembolism in patients with unresectable pancreatic cancer undergoing chemotherapy, particularly for those with additional risk factors. However, the decision to initiate prophylactic anticoagulation should be individualized, considering the patient's overall risk profile, performance status, and treatment regimen. Collaboration among oncologists, hematologists, and primary care providers is essential for optimizing patient care in this context.

## CLAUDE

1. What are the known risk factors for sporadic Pancreatic cancer?

Risposta 1.

The known risk factors for sporadic pancreatic cancer (non-hereditary cases) include:

1. Age: Risk increases with age, with most cases occurring after 65.
2. Smoking: One of the most significant modifiable risk factors, estimated to cause 20-25% of pancreatic cancers.

3. Obesity: Linked to increased risk, possibly due to chronic inflammation and insulin resistance.
4. Diabetes mellitus: Particularly long-standing type 2 diabetes.
5. Chronic pancreatitis: Long-term inflammation of the pancreas.
6. Heavy alcohol consumption: Particularly as it relates to the development of chronic pancreatitis.
7. Diet: High consumption of red and processed meats, and low intake of fruits and vegetables may increase risk.
8. Occupational exposures: Certain chemicals like chlorinated hydrocarbons and metalworking compounds.
9. Race: African Americans have a slightly higher risk compared to other racial groups.
10. Gender: Slightly more common in men than women.
11. ABO blood group: Individuals with blood groups A, B, or AB have a slightly higher risk compared to those with blood group O.
12. H. pylori infection: Some studies suggest a possible link.
13. Periodontal disease: Associated with an increased risk, though the mechanism is not fully understood.
14. Non-O blood groups: Individuals with blood types A, B, or AB have a slightly higher risk than those with type O.
15. Hepatitis B infection: Some studies have shown an association.

It's important to note that having one or more risk factors doesn't necessarily mean an individual will develop pancreatic cancer, and some people with no known risk factors may still develop the disease. The interplay between these factors and genetic predisposition is an area of ongoing research

Risposta 2.

Sporadic pancreatic cancer, which accounts for the majority of pancreatic cancer cases, has several well-established risk factors. Here's an overview of the main known risk factors:

1. Age: The risk increases with age, with most cases occurring in individuals over 65.
2. Smoking: This is one of the most significant modifiable risk factors, estimated to account for 20-30% of pancreatic cancer cases.
3. Obesity: Excess body weight is associated with an increased risk, particularly in individuals with a BMI over 30.
4. Chronic pancreatitis: Long-standing inflammation of the pancreas increases risk, especially after 20 years of the condition.

5. Diabetes mellitus: Particularly long-standing type 2 diabetes. There's also evidence that new-onset diabetes in older adults can be an early manifestation of pancreatic cancer.
6. Alcohol consumption: Heavy alcohol use is associated with increased risk, partly due to its role in causing chronic pancreatitis.
7. Diet: Diets high in red and processed meats, and low in fruits and vegetables, may increase risk.
8. Occupational exposures: Certain chemicals, such as chlorinated hydrocarbons and heavy metals, have been linked to increased risk.
9. Race: In the United States, African Americans have a higher incidence rate compared to other racial groups.
10. ABO blood group: Individuals with non-O blood groups (particularly B and AB) have a slightly higher risk.
11. Family history: While not strictly a factor for sporadic cases, having a first-degree relative with pancreatic cancer increases risk, even in the absence of known genetic syndromes.
12. H. pylori infection: Some studies suggest a possible link, though the evidence is not as strong as for other factors.

It's important to note that many individuals with these risk factors never develop pancreatic cancer, and some people without apparent risk factors do develop the disease. The interplay between these factors and genetic predisposition is an area of ongoing research.

### Risposta 3.

As a pancreatic surgeon, you're likely familiar with many of these, but I'll provide a comprehensive list of known risk factors for sporadic pancreatic cancer. This information can be valuable for patient education and risk assessment.

#### 1. Age:

- Risk increases with age, with most cases occurring after 45 years
- Peak incidence is between 65-75 years old

#### 2. Smoking:

- One of the most significant modifiable risk factors
- Estimated to account for 20-25% of pancreatic cancers

#### 3. Obesity:

- Body Mass Index (BMI)  $\geq 30$  kg/m<sup>2</sup>
- Particularly central adiposity

#### 4. Diabetes mellitus:

- Longstanding type 2 diabetes (>5 years)



- Recent-onset diabetes can also be an early manifestation of pancreatic cancer

5. Chronic pancreatitis:

- Especially with long-standing inflammation (>20 years)

6. Alcohol consumption:

- Heavy alcohol use, particularly when it leads to chronic pancreatitis

7. Diet:

- High consumption of red and processed meats
- Low intake of fruits and vegetables

8. Occupational exposures:

- Certain chemicals (e.g., chlorinated hydrocarbons, pesticides)

9. Race and ethnicity:

- Higher incidence in African Americans and Ashkenazi Jews

10. ABO blood group:

- Non-O blood groups (particularly B) have slightly higher risk

11. Helicobacter pylori infection:

- Some studies suggest a possible link

12. Non-alcoholic fatty liver disease (NAFLD):

- Emerging evidence suggests an association

13. Periodontal disease:

- Some studies indicate a potential link

14. Hepatitis B and C infections:

- Possible increased risk, though evidence is still emerging

15. Family history of pancreatic cancer:

- Even in the absence of known genetic syndromes

It's important to note that while these factors increase risk, many people with one or more risk factors never develop pancreatic cancer, and some people without any known risk factors do develop the disease.

2. Is the new onset of diabetes mellitus considered as a risk factor for pancreatic cancer?

Risposta 1.

The relationship between new-onset diabetes mellitus and pancreatic cancer is complex and significant. While long-standing diabetes is a known risk factor for pancreatic cancer, new-onset diabetes is increasingly recognized as both a risk factor and a potential early sign of pancreatic cancer. Here's a detailed look at this relationship:

1. Early sign/symptom:
  - New-onset diabetes (especially in individuals over 50 without traditional risk factors for type 2 diabetes) can be an early manifestation of pancreatic cancer.
  - Some studies suggest that up to 1% of individuals over 50 with new-onset diabetes will be diagnosed with pancreatic cancer within 3 years.
2. Temporal relationship:
  - Pancreatic cancer is often diagnosed within 1-3 years after the onset of diabetes.
  - This suggests that new-onset diabetes could be both a risk factor and an early sign of the disease.
3. Proposed mechanisms:
  - Pancreatic cancer may cause diabetes through destruction of islet cells.
  - The cancer may also release factors that increase insulin resistance.
  - Some researchers propose a "paraneoplastic phenomenon" where the cancer induces diabetes before it's clinically detectable.
4. Risk assessment:
  - New-onset diabetes in older adults, especially when accompanied by weight loss (rather than the weight gain often seen in type 2 diabetes), should raise suspicion for pancreatic cancer.
  - The combination of new-onset diabetes and sudden weight loss is particularly concerning.
5. Screening implications:
  - There's ongoing research into whether new-onset diabetes could be used as a screening tool for early detection of pancreatic cancer in high-risk populations.
  - However, widespread screening is not currently recommended due to the low overall incidence of pancreatic cancer and the high prevalence of diabetes.
6. Distinction from long-standing diabetes:
  - While long-standing diabetes (particularly type 2) is a known risk factor for developing pancreatic cancer, new-onset diabetes has a different implication.
  - New-onset diabetes may be more closely tied to the presence of an undiagnosed pancreatic cancer.

In clinical practice, new-onset diabetes mellitus, especially in older adults or those without typical risk factors for type 2 diabetes, should prompt consideration of underlying pancreatic pathology, including cancer. However, it's important to note that most cases of new-onset diabetes are not due to pancreatic cancer, and further research is needed to define optimal strategies for using this relationship in early detection efforts.

Risposta 2.

Yes, new-onset diabetes mellitus, particularly in older adults, is indeed considered a risk factor for pancreatic cancer. This association has been the subject of significant research in recent years. Here's a more detailed look at this relationship:

1. Bidirectional relationship: While long-standing diabetes is a risk factor for pancreatic cancer, there's growing evidence that new-onset diabetes can be both a risk factor and an early manifestation of pancreatic cancer.
2. Timeframe: The highest risk appears to be within the first 1-3 years after diabetes diagnosis. Some studies suggest that pancreatic cancer is diagnosed within 3 years in about 1% of patients over 50 who develop diabetes.
3. Age consideration: New-onset diabetes in individuals over 50 years old is of particular concern and may warrant closer monitoring.
4. Mechanism: It's believed that pancreatic cancer can cause diabetes through several mechanisms:
  - Direct destruction of insulin-producing beta cells
  - Increased insulin resistance due to cancer-related inflammatory factors
  - Altered metabolism of glucose due to tumor effects
5. Screening implications: Some researchers propose that new-onset diabetes in older adults, especially when accompanied by weight loss, could be used as a screening tool for early detection of pancreatic cancer. However, this is still an area of active research and debate.
6. Distinguishing features: Diabetes associated with pancreatic cancer often has some distinct features:
  - Rapid onset and progression
  - Difficulties in controlling blood sugar levels
  - Accompanying unexplained weight loss
7. Risk magnitude: Studies have shown that individuals with new-onset diabetes have a 5-8 fold increased risk of being diagnosed with pancreatic cancer within 1-3 years compared to the general population.
8. Challenges: The main challenge is that while new-onset diabetes increases pancreatic cancer risk, the vast majority of people with new-onset diabetes will not develop pancreatic cancer. Identifying which subset of these patients should undergo further screening is an active area of research.

It's important to note that while this association is significant, not all cases of new-onset diabetes in older adults are related to pancreatic cancer. However, awareness of this relationship can potentially lead to earlier detection of pancreatic cancer in some cases.

As a pancreatic surgeon, you might consider this factor when evaluating patients, especially if they present with other risk factors or symptoms suggestive of pancreatic pathology. Would you like to discuss any specific aspects of how this information might influence surgical decision-making or patient management?

Risposta 3.

Your question touches on an important and somewhat complex aspect of pancreatic cancer risk assessment. New-onset diabetes mellitus is indeed considered both a risk factor for and a potential early sign of pancreatic cancer. Here's a more detailed breakdown:

1. Risk factor and early manifestation:

- New-onset diabetes, especially in individuals over 50 without traditional risk factors for type 2 diabetes, can be both a risk factor for and an early manifestation of pancreatic cancer.

2. Timeframe:

- The risk is highest within the first 1-3 years after diabetes diagnosis.
- Some studies suggest that pancreatic cancer risk remains elevated for up to 5-10 years after diabetes onset.

3. Bidirectional relationship:

- While diabetes can increase the risk of pancreatic cancer, pancreatic cancer itself can cause diabetes (sometimes referred to as type 3c diabetes or pancreatogenic diabetes).

4. Mechanism:

- Pancreatic cancer may cause diabetes through destruction of islet cells, release of diabetogenic mediators, or induction of peripheral insulin resistance.

5. Prevalence:

- Up to 80% of pancreatic cancer patients have concurrent diabetes or impaired glucose tolerance at the time of diagnosis.

- Approximately 1% of patients over 50 with new-onset diabetes will be diagnosed with pancreatic cancer within 3 years.

6. Screening considerations:

- There's ongoing debate about whether new-onset diabetes should trigger pancreatic cancer screening in certain populations.

- Factors like age, weight loss, and changes in diabetes medications may help identify high-risk individuals.

7. Challenges in differentiation:

- Distinguishing new-onset diabetes due to pancreatic cancer from type 2 diabetes can be challenging, as symptoms often overlap.

## 8. Research focus:

- Current research is aimed at identifying biomarkers that could differentiate pancreatic cancer-associated diabetes from type 2 diabetes.

Given your role as a pancreatic surgeon, you might be particularly interested in the implications for early detection and screening protocols. The relationship between new-onset diabetes and pancreatic cancer underscores the importance of a multidisciplinary approach, involving endocrinologists, oncologists, and surgeons in the management of these patients

### 3. what is the correct diagnostic pathway for pancreatic cancer diagnosis?

Risposta 1.

The diagnostic pathway for pancreatic cancer typically involves a step-wise approach, combining clinical assessment, imaging studies, and potentially invasive procedures. Here's an overview of the generally accepted diagnostic pathway:

#### 1. Initial Clinical Evaluation:

- Thorough history and physical examination
- Assessment of symptoms (e.g., jaundice, abdominal pain, weight loss)
- Evaluation of risk factors

#### 2. Laboratory Tests:

- Liver function tests (bilirubin, alkaline phosphatase, ALT, AST)
- Serum tumor markers (CA 19-9, CEA)
- Complete blood count, coagulation profile
- Fasting glucose or HbA1c (to assess for new-onset diabetes)

#### 3. Initial Imaging:

- Abdominal ultrasound (often the first-line imaging test)
- Contrast-enhanced CT scan of the abdomen and pelvis (considered the gold standard for initial evaluation)

#### 4. Advanced Imaging (if initial CT is inconclusive or for further characterization):

- Magnetic Resonance Imaging (MRI) with MRCP (Magnetic Resonance Cholangiopancreatography)
- Endoscopic Ultrasound (EUS)
- PET-CT (particularly useful for detecting metastases)

#### 5. Tissue Diagnosis:

- EUS-guided Fine Needle Aspiration (FNA) or Fine Needle Biopsy (FNB)
  - Preferred method for obtaining tissue diagnosis
  - Allows for cytological/histological confirmation

- CT-guided biopsy (if EUS is not available or lesion is not accessible by EUS)
- 6. Additional Procedures (as needed):
  - ERCP (Endoscopic Retrograde Cholangiopancreatography)
    - May be used for tissue sampling or to place a stent for biliary obstruction
  - Diagnostic laparoscopy
    - Sometimes used to assess for small metastases not visible on imaging
- 7. Staging Workup:
  - Chest CT (to evaluate for lung metastases)
  - Additional imaging as needed based on initial findings
- 8. Multidisciplinary Team Review:
  - Discussion of findings by a team including surgeons, oncologists, radiologists, and pathologists
  - Determination of resectability and treatment plan

Key points:

- The specific order and inclusion of tests may vary based on individual presentation and institutional protocols.
- CT scan is often the pivotal initial test for suspected pancreatic cancer.
- Tissue diagnosis is crucial before initiating treatment, except in rare cases where surgery is immediately indicated.
- The goal is to obtain an accurate diagnosis and staging while minimizing invasive procedures and delays in treatment initiation.

It's important to note that this pathway may be adjusted based on the patient's specific presentation, local expertise, and available resources. The trend is moving towards more precise and less invasive diagnostic techniques, with ongoing research into blood-based biomarkers and advanced imaging modalities for earlier detection.

Risposta 2.

The diagnostic pathway for pancreatic cancer typically involves a stepwise approach, combining clinical presentation, imaging studies, and sometimes invasive procedures. Here's an overview of the generally accepted diagnostic pathway:

1. Initial Assessment:
  - Thorough medical history and physical examination
  - Evaluation of symptoms (e.g., jaundice, abdominal pain, weight loss)
  - Review of risk factors
2. Blood Tests:

- Liver function tests (LFTs)
- Tumor markers: CA 19-9 (though not specific for pancreatic cancer)
- Complete blood count (CBC)
- Fasting glucose or HbA1c (to check for new-onset diabetes)
- 3. Initial Imaging:
  - Transabdominal ultrasound: Often the first imaging test due to its accessibility and low cost
  - Contrast-enhanced CT scan: The primary imaging modality for pancreatic cancer detection and staging
- 4. Advanced Imaging:
  - Magnetic Resonance Imaging (MRI) / Magnetic Resonance Cholangiopancreatography (MRCP): Particularly useful for evaluating the pancreatic and bile ducts
  - Endoscopic Ultrasound (EUS): Provides high-resolution images of the pancreas and allows for biopsy if needed
- 5. Tissue Diagnosis:
  - EUS-guided Fine Needle Aspiration (FNA) or Fine Needle Biopsy (FNB): Preferred method for tissue sampling
  - CT-guided biopsy: Alternative if EUS is not available or feasible
- 6. Additional Procedures (if needed):
  - Endoscopic Retrograde Cholangiopancreatography (ERCP): Can be both diagnostic and therapeutic (e.g., stent placement for biliary obstruction)
  - Positron Emission Tomography (PET) scan: Sometimes used to detect metastases
- 7. Staging:
  - Based on imaging results (primarily CT)
  - May include diagnostic laparoscopy in select cases to rule out small peritoneal metastases
- 8. Multidisciplinary Team (MDT) Review:
  - Discussion of findings and treatment planning by a team including surgeons, oncologists, radiologists, and pathologists

#### Key Considerations:

- The specific order and choice of tests may vary based on the patient's presentation, local expertise, and resource availability.
- CT scan is often considered the cornerstone of diagnosis and staging.
- Tissue diagnosis is essential before initiating treatment, except in cases where surgery is immediately indicated based on highly suspicious imaging findings.

- The role of newer biomarkers and liquid biopsies is an area of active research but not yet part of standard diagnostic pathways.

As a pancreatic surgeon, you're likely familiar with the nuances of this pathway. Is there a particular aspect of the diagnostic process you'd like to discuss further, perhaps regarding recent advancements or challenges you've encountered in your practice?

Risposta 3.

As a pancreatic surgeon, you're likely familiar with the diagnostic pathway for pancreatic cancer, but I'll outline a comprehensive approach that reflects current best practices. The diagnostic pathway typically involves a stepwise process:

#### 1. Initial Presentation and Evaluation:

- Patient history: symptoms (e.g., abdominal pain, weight loss, jaundice)
- Physical examination
- Blood tests: liver function tests, CA 19-9, CEA

#### 2. Initial Imaging:

- Transabdominal ultrasound: often the first imaging study, especially for jaundiced patients

- Contrast-enhanced CT scan: typically triple-phase pancreatic protocol CT

This is usually the primary modality for diagnosis and staging

#### 3. Additional Imaging (if needed):

- MRI/MRCP: useful for characterizing smaller lesions and evaluating the pancreatic and biliary ducts

- Endoscopic ultrasound (EUS): high sensitivity for small lesions, allows for biopsy

#### 4. Tissue Diagnosis:

- EUS-guided fine needle aspiration (FNA) or fine needle biopsy (FNB)
- CT-guided biopsy: for lesions not accessible by EUS
- ERCP with brush cytology: if EUS is not available or inconclusive

#### 5. Staging Workup:

- CT chest/abdomen/pelvis: to evaluate for metastatic disease

- PET-CT: can be considered for detection of occult metastases, especially before major surgery

#### 6. Diagnostic Laparoscopy:

- Consider for patients with high risk of occult metastatic disease

#### 7. Molecular and Genetic Testing:

- Germline testing for hereditary syndromes (e.g., BRCA1/2, PALB2)



- Somatic mutation testing of tumor tissue for targeted therapy selection

#### 8. Multidisciplinary Team (MDT) Review:

- Discussion of findings and treatment planning by a team including surgeons, oncologists, radiologists, and pathologists

#### Key Considerations:

- The specific pathway may vary based on initial presentation (e.g., a patient presenting with jaundice vs. incidental finding on imaging).
- CA 19-9 can be useful but has limitations (false positives with biliary obstruction, false negatives in Lewis antigen-negative individuals).
- Tissue diagnosis is not always necessary before surgery in cases where imaging is highly suggestive and the tumor is resectable.
- The role of newer blood-based biomarkers and liquid biopsies is evolving but not yet standard in most guidelines.

It's important to note that this pathway should be tailored to individual patient circumstances and institutional resources. The goal is to achieve an accurate diagnosis and staging while minimizing delays in treatment initiation

4. Is positron emission tomography (PET) recommended as a diagnostic method in patients with suspected pancreatic cancer?

#### Risposta 1.

Positron Emission Tomography (PET), particularly when combined with CT (PET/CT), has a role in the evaluation of pancreatic cancer, but it is not typically recommended as a first-line diagnostic method for patients with suspected pancreatic cancer. Here's a more detailed explanation:

1. Primary Diagnosis:
  - PET is not recommended as the initial diagnostic tool for suspected pancreatic cancer.
  - Contrast-enhanced CT remains the gold standard for initial diagnosis and staging.
2. Role in Management:
  - PET/CT is more commonly used in specific scenarios during the management of pancreatic cancer:
    - a) Detecting Metastases:
      - PET/CT is particularly useful in identifying small metastases that might be missed by conventional imaging.
      - It can alter management in cases where CT or MRI suggest potentially resectable disease.
    - b) Evaluating Indeterminate Lesions:

- When CT or MRI findings are equivocal, PET/CT can help characterize lesions as benign or malignant.

c) Assessing Treatment Response:

- PET/CT can be valuable in monitoring response to neoadjuvant or palliative chemotherapy.

d) Detecting Recurrence:

- It's useful in identifying recurrent disease, especially when conventional imaging is inconclusive.

3. Limitations:

- False Positives: Inflammatory conditions like pancreatitis can lead to increased FDG uptake, potentially resulting in false-positive results.
- False Negatives: Some pancreatic cancers, particularly well-differentiated tumors, may not show significant FDG uptake.
- Limited Spatial Resolution: PET alone has lower spatial resolution compared to CT or MRI, which is why it's often combined with CT.

4. Guidelines:

- Most major guidelines (e.g., NCCN, ESMO) do not recommend routine use of PET/CT for the initial diagnosis of pancreatic cancer.
- However, they acknowledge its utility in specific scenarios, particularly in the evaluation of metastatic disease.

5. Cost and Availability:

- PET/CT is more expensive and less widely available compared to CT or MRI, which also influences its role in the diagnostic pathway.

6. Ongoing Research:

- There's ongoing research into novel PET tracers that may improve specificity for pancreatic cancer detection and characterization.

In summary, while PET/CT has valuable applications in the management of pancreatic cancer, it is not recommended as a primary diagnostic method for patients with suspected pancreatic cancer. Its use is more targeted towards problem-solving in specific clinical scenarios, particularly in the evaluation of metastatic disease and in cases where conventional imaging is inconclusive. The mainstay of initial diagnosis remains contrast-enhanced CT, often followed by endoscopic ultrasound with fine-needle aspiration for tissue diagnosis.

Risposta 2.

Positron Emission Tomography (PET), particularly when combined with CT (PET/CT), has a role in the diagnostic workup of pancreatic cancer, but it's not typically recommended as a

primary or routine diagnostic method for all patients with suspected pancreatic cancer. Here's a more detailed look at the current stance on PET in pancreatic cancer diagnosis:

1. Primary Diagnosis:

- PET is not recommended as a first-line diagnostic tool for pancreatic cancer.
- Contrast-enhanced CT remains the gold standard for initial diagnosis and staging.

2. Specific Use Cases:

- Detecting Metastases: PET/CT is particularly useful in identifying distant metastases that might be missed on conventional imaging.
- Equivocal Findings: It can be helpful when CT or MRI results are inconclusive.
- Differentiating Benign from Malignant Lesions: In some cases, PET can help distinguish between inflammatory masses (like chronic pancreatitis) and pancreatic cancer.

3. Staging:

- PET/CT can be valuable in staging, especially for detecting small metastases not visible on CT alone.
- It may alter management in a subset of patients by identifying previously undetected metastatic disease.

4. Limitations:

- False Positives: Inflammatory conditions like pancreatitis can lead to increased FDG uptake, mimicking cancer.
- False Negatives: Some pancreatic cancers, particularly well-differentiated tumors, may not show significant FDG uptake.
- Resolution: PET has lower spatial resolution compared to CT or MRI, which can be a limitation for small lesions.

5. Guidelines:

- Most major guidelines (e.g., NCCN, ESMO) do not recommend routine use of PET/CT for initial diagnosis.
- Some guidelines suggest considering PET/CT in cases where there's high suspicion of metastatic disease that hasn't been detected by conventional imaging.

6. Cost and Availability:

- PET/CT is more expensive and less widely available than CT or MRI, which also factors into recommendations for its use.

7. Research and Future Directions:

- There's ongoing research into more specific PET tracers for pancreatic cancer, which could improve its diagnostic accuracy in the future.

## 8. Radiation Exposure:

- The additional radiation exposure from PET is a consideration, especially if multiple imaging studies are being performed.

In summary, while PET/CT can be a valuable tool in certain scenarios, it's not recommended as a routine diagnostic method for all patients with suspected pancreatic cancer. Its use is generally reserved for specific clinical situations where it's likely to provide additional valuable information that could impact patient management.

As a pancreatic surgeon, you might encounter cases where PET/CT provides crucial information, particularly in complex cases or when considering the extent of surgical intervention. Have you found PET/CT particularly useful in any specific scenarios in your practice

Risposta 3.

Your question about the role of positron emission tomography (PET) in diagnosing suspected pancreatic cancer is an important one, as imaging plays a crucial role in the diagnostic pathway. Here's a detailed look at the current stance on PET in pancreatic cancer diagnosis:

### 1. General recommendation:

- PET, specifically FDG-PET/CT, is not routinely recommended as a primary diagnostic method for pancreatic cancer.
- It is not considered a first-line imaging modality for initial diagnosis.

### 2. Primary diagnostic tools:

- Contrast-enhanced CT and MRI/MRCP remain the primary imaging modalities for initial diagnosis and staging.

### 3. Potential uses of PET:

- Detection of distant metastases: PET can be useful in identifying occult metastases not visible on conventional imaging.
- Evaluation of indeterminate lesions: PET may help characterize lesions that are equivocal on CT or MRI.
- Recurrence detection: It can be valuable in detecting recurrence post-treatment.

### 4. Limitations of PET in pancreatic cancer diagnosis:

- False positives: Inflammatory conditions like pancreatitis can show increased FDG uptake.
- False negatives: Some pancreatic cancers, especially well-differentiated tumors, may not show significant FDG uptake.
- Limited spatial resolution: PET may miss small lesions.

- Cost and availability: PET is more expensive and less widely available than CT or MRI.

5. Guidelines stance:

- Most major guidelines (NCCN, ESMO, etc.) do not recommend routine use of PET for initial diagnosis.
- Some guidelines suggest considering PET in specific scenarios, such as evaluating for distant metastases before major surgery.

6. Research perspective:

- Ongoing research is exploring the potential of PET with novel tracers (beyond FDG) for improved pancreatic cancer detection and characterization.

7. Potential scenarios for PET use:

- When conventional imaging is inconclusive
- Pre-operative staging in potentially resectable disease to rule out occult metastases
- Differentiating post-treatment changes from recurrence

8. Combined PET/CT or PET/MRI:

- These modalities can provide both functional and anatomical information, potentially increasing diagnostic accuracy in select cases.

In summary, while PET can provide valuable information in certain scenarios, it is not recommended as a routine diagnostic method for suspected pancreatic cancer. Its use should be considered on a case-by-case basis, typically after conventional imaging has been performed and in consultation with a multidisciplinary team.

As a pancreatic surgeon, you might find PET most useful in pre-operative planning for borderline resectable cases or when there's suspicion of distant metastases not clearly visible on conventional imaging. However, the decision to use PET should be balanced against its costs, potential delays in treatment, and the likelihood of it changing management.

5. When is the surgical approach indicated as first-line therapy for pancreatic cancer?

Risposta 1.

Surgical resection is considered the only potentially curative treatment for pancreatic cancer. The decision to pursue surgery as first-line therapy depends primarily on the stage and resectability of the tumor. Here's a detailed overview of when surgery is indicated:

1. Resectable Pancreatic Cancer:

- Surgery is the first-line therapy for patients with resectable disease.

- Criteria for resectability include: a) No distant metastases b) No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion c) Clear fat planes around celiac axis, hepatic artery, and superior mesenteric artery (SMA)
2. Borderline Resectable Pancreatic Cancer:
    - In some cases, surgery may be considered as first-line therapy, but increasingly, neoadjuvant therapy is being used first.
    - Criteria include: a) Venous involvement of SMV/PV with distortion or narrowing of the vein or short segment occlusion, but with suitable vessel proximal and distal to the area of involvement b) Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis c) Tumor abutment of the SMA not exceeding 180 degrees of the circumference of the vessel wall
  3. Early-Stage Disease:
    - Surgery is typically recommended for Stage I and II pancreatic cancer, where the tumor is confined to the pancreas or has spread only to nearby structures.
  4. Good Performance Status:
    - Patients must have adequate performance status to tolerate major surgery.
    - Considerations include comorbidities, nutritional status, and overall health.
  5. Absence of Contraindications:
    - No medical conditions that would preclude surgery
    - No evidence of distant metastases
  6. Multidisciplinary Team Decision:
    - The decision for upfront surgery should be made by a multidisciplinary team including surgeons, oncologists, radiologists, and pathologists.
  7. Patient Preference:
    - After discussion of risks and benefits, patient preference plays a crucial role in deciding on surgical approach.
  8. Institutional Expertise:
    - Surgery should be performed at high-volume centers with experienced pancreatic surgeons and appropriate perioperative care.
  9. Specific Tumor Locations:
    - For tumors in the head of the pancreas: Pancreaticoduodenectomy (Whipple procedure)
    - For tumors in the body or tail: Distal pancreatectomy
  10. Consideration of Neoadjuvant Therapy:

- There's a growing trend towards neoadjuvant therapy even for resectable tumors, especially in cases with high-risk features (e.g., large tumor size, high CA 19-9 levels).
  - This approach is still under investigation and varies by institution and individual case.
- It's important to note that while surgery offers the best chance for cure, it is associated with significant morbidity and mortality. The decision to pursue surgery as first-line therapy must carefully weigh the potential benefits against the risks for each individual patient. Also, even when surgery is indicated as first-line therapy, it's typically followed by adjuvant chemotherapy to reduce the risk of recurrence. The integration of perioperative systemic therapy continues to evolve as new evidence emerges from clinical trials.

#### Risposta 2.

Surgical approach as first-line therapy for pancreatic cancer is primarily indicated for patients with resectable disease. The decision for surgical intervention depends on several factors, including the stage of the cancer, patient's overall health, and the location of the tumor. Here's a detailed overview of when surgery is typically indicated as first-line therapy:

#### 1. Resectable Pancreatic Cancer:

- This is the primary scenario where surgery is indicated as first-line therapy.
- Criteria for resectability typically include:
  - No distant metastases
  - No involvement of the celiac axis, superior mesenteric artery (SMA), or common hepatic artery
  - Patent superior mesenteric-portal vein confluence

#### 2. Tumor Location:

- For tumors in the head of the pancreas: Pancreaticoduodenectomy (Whipple procedure)
- For tumors in the body or tail: Distal pancreatectomy with splenectomy
- For select cases: Total pancreatectomy

#### 3. Early-Stage Disease:

- Stage I and some Stage II pancreatic cancers are typically considered for upfront surgery.

#### 4. Borderline Resectable Disease:

- In some cases, neoadjuvant therapy followed by surgery may be preferred.
- However, some centers may still consider upfront surgery for select patients with borderline resectable disease, especially if they have a good performance status.

#### 5. Patient Factors:

- Good overall health and performance status
- Ability to tolerate a major surgical procedure

- No severe comorbidities that significantly increase surgical risk
- 6. Incidentally Discovered Lesions:
  - Small, localized pancreatic tumors discovered incidentally on imaging for other reasons may be candidates for immediate surgical resection.
- 7. Diagnostic Uncertainty:
  - In some cases where malignancy is strongly suspected but not confirmed, surgery may be both diagnostic and therapeutic.
- 8. Multidisciplinary Team Decision:
  - The decision for upfront surgery should ideally be made by a multidisciplinary team, considering all aspects of the patient's case.
- 9. Center Expertise:
  - High-volume centers with experienced pancreatic surgeons may be more likely to attempt resection in complex cases.
- 10. Patient Preference:
  - After thorough discussion of risks and benefits, patient preference plays a role in deciding between upfront surgery and neoadjuvant approaches.

It's important to note that even when surgery is indicated as first-line therapy, adjuvant chemotherapy is typically recommended post-operatively to reduce the risk of recurrence. Contraindications for upfront surgery include:

- Presence of distant metastases
- Involvement of major blood vessels that cannot be safely reconstructed
- Poor performance status or severe comorbidities that significantly increase surgical risk

As surgical techniques and perioperative management continue to improve, the criteria for resectability may evolve. Some centers are pushing the boundaries of what's considered resectable, especially with advances in vascular resection and reconstruction techniques.

Given your expertise as a pancreatic surgeon, you're likely familiar with these indications.

Are there any specific aspects of surgical decision-making in pancreatic cancer that you'd like to discuss further, perhaps regarding borderline cases or emerging approaches?

Risposta 3.

As a pancreatic surgeon, you're well-versed in the complexities of treating pancreatic cancer. Surgical approach as first-line therapy for pancreatic cancer is primarily indicated in cases where the disease is considered resectable. Here's a detailed breakdown of when surgery is typically recommended as the initial treatment:

1. Resectable Pancreatic Cancer:



- No distant metastases
- No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV)

distortion

- Clear fat planes around celiac axis, hepatic artery, and superior mesenteric artery (SMA)

## 2. Tumor Location:

- For tumors in the pancreatic head/uncinate process: No extension to SMA or celiac axis
- For tumors in the pancreatic body/tail: No extension to celiac axis or SMA

## 3. Absence of Extrapancreatic Disease:

- No peritoneal or liver metastases
- No involvement of other organs

## 4. Patient Factors:

- Good performance status (typically ECOG 0-1)
- Adequate physiological reserve for major surgery
- No severe comorbidities that significantly increase surgical risk

## 5. Imaging Criteria:

- Based on high-quality, contrast-enhanced CT scan or MRI
- No involvement of major vessels (as mentioned above)

## 6. Tumor Markers:

- While not an absolute criterion, very high CA 19-9 levels might suggest more advanced disease and prompt further investigation before proceeding with surgery

## 7. Multidisciplinary Team (MDT) Assessment:

- Agreement among surgeons, oncologists, and radiologists that the tumor is resectable

## 8. Specific Scenarios:

- Small ( $\leq 2$  cm) pancreatic neuroendocrine tumors
- Selected cases of locally invasive intraductal papillary mucinous neoplasms (IPMNs)

with high-grade dysplasia or associated invasive carcinoma

It's important to note that the definition of resectability can vary slightly between institutions and guidelines. Some key considerations:

- Borderline Resectable Disease: In some cases, neoadjuvant therapy followed by surgery might be preferred over upfront surgery.
- Locally Advanced Disease: Generally not suitable for upfront surgery, but may be considered for surgery after favorable response to neoadjuvant therapy.

- Incidentally Discovered Pancreatic Cancer: If found to be resectable during workup for other conditions, surgery is typically recommended as first-line therapy.

- Consideration of Neoadjuvant Therapy: Even in resectable disease, there's a growing trend to consider neoadjuvant therapy to improve R0 resection rates and overall outcomes.

The decision for upfront surgery should always be made in the context of a multidisciplinary tumor board discussion, taking into account the specific characteristics of the tumor, the patient's overall health status, and the expertise available at the treating center.

6. Is prophylactic extended lymph node and nerve plexus dissection recommended in patients with resectable pancreatic cancer undergoing surgery?

Risposta 1.

The question of prophylactic extended lymph node and nerve plexus dissection in resectable pancreatic cancer is a topic of ongoing debate in the surgical oncology community. Here's a comprehensive overview of the current understanding:

1. Standard Lymphadenectomy:
  - A standard lymphadenectomy is generally recommended and includes:
    - For pancreaticoduodenectomy: Removal of lymph nodes in the hepatoduodenal ligament, along the common hepatic artery, portal vein, and SMA right lateral aspect.
    - For distal pancreatectomy: Removal of lymph nodes along the splenic artery and hilum.
2. Extended Lymphadenectomy:
  - Involves removal of additional lymph node stations beyond the standard dissection.
  - Current evidence does not support routine use: a) Multiple randomized controlled trials (e.g., Italian Multicenter Study, Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer) have not shown survival benefit. b) Associated with increased morbidity, including higher rates of postoperative diarrhea and delayed gastric emptying.
3. Nerve Plexus Dissection:
  - Extended dissection of nerve plexuses around the SMA and celiac axis is not routinely recommended.
  - Concerns include: a) Increased risk of postoperative diarrhea and other gastrointestinal symptoms. b) No clear survival benefit in most studies.
4. Guidelines:
  - Major guidelines (NCCN, ESMO) do not recommend routine extended lymphadenectomy or nerve plexus dissection.

- Standard lymphadenectomy is considered adequate for staging and local control.
- 5. Potential Exceptions:
  - Some surgeons advocate for more extensive dissection in specific scenarios: a) Young, fit patients with larger tumors. b) Cases where imaging suggests possible involvement of additional nodal basins.
  - However, these approaches are not universally accepted and remain controversial.
- 6. Ongoing Research:
  - Focus has shifted towards the quality and completeness of standard lymphadenectomy rather than extending its boundaries.
  - Some studies are exploring the role of sentinel lymph node biopsy in pancreatic cancer, which might inform more targeted lymph node dissections in the future.
- 7. Considerations for Nerve Plexus Dissection:
  - Limited plexus dissection may be performed when necessary for margin clearance.
  - However, prophylactic extended plexus dissection is generally avoided due to quality of life impacts.
- 8. Balancing Oncologic Principles and Functional Outcomes:
  - The goal is to achieve complete tumor resection (R0) while preserving functional outcomes.
  - Extended dissections may compromise this balance without clear oncologic benefit.
- 9. Personalized Approach:
  - Decision-making should be individualized based on patient factors, tumor characteristics, and intraoperative findings.
  - Multidisciplinary tumor board discussions can help in complex cases.

In conclusion, current evidence does not support routine prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer. Standard lymphadenectomy, as part of curative-intent surgery, remains the recommended approach. The focus is on achieving complete tumor resection with clear margins while minimizing morbidity. As always in cancer surgery, the approach should be tailored to the individual patient, considering all relevant clinical and pathological factors.

Risposta 2.

The question of prophylactic extended lymph node and nerve plexus dissection in resectable pancreatic cancer is a topic of ongoing debate in the surgical community. Here's a comprehensive look at the current stance:

### 1. Standard Lymphadenectomy:

- A standard lymphadenectomy is generally recommended and includes removal of lymph nodes in the hepatoduodenal ligament, along the common hepatic artery, and around the celiac axis, as well as peripancreatic nodes.

### 2. Extended Lymphadenectomy:

- Extended lymphadenectomy involves a more radical dissection, including para-aortic nodes and those around the superior mesenteric artery.
- Current evidence does not support routine use of extended lymphadenectomy:
  - Several randomized controlled trials have shown no survival benefit.
  - It's associated with increased morbidity, including higher rates of diarrhea and delayed gastric emptying.

### 3. Nerve Plexus Dissection:

- Routine extended dissection of nerve plexuses is not generally recommended.
- Some degree of nerve plexus dissection occurs during standard pancreaticoduodenectomy, particularly around the superior mesenteric artery.

### 4. Guidelines:

- Most major guidelines (NCCN, ESMO, etc.) do not recommend prophylactic extended lymphadenectomy or nerve plexus dissection.
- They advocate for standard lymphadenectomy as part of curative-intent surgery.

### 5. Potential Downsides of Extended Dissection:

- Increased operative time
- Higher risk of postoperative complications
- Potential negative impact on quality of life (e.g., chronic diarrhea)

### 6. Selective Approach:

- Some surgeons advocate for a more selective approach, where extended dissection might be considered in cases with clinically suspicious lymph nodes outside the standard field.

### 7. Staging Benefits:

- While not improving survival, extended lymphadenectomy can provide more accurate staging information.

### 8. Ongoing Research:

- There's continued interest in identifying subgroups of patients who might benefit from more extensive dissection.
- Some studies are exploring the role of extended dissection in combination with modern chemotherapy regimens.

#### 9. Technical Considerations:

- The extent of lymph node dissection can vary based on the specific surgical approach (e.g., open vs. minimally invasive).

#### 10. Center Experience:

- High-volume centers might be more likely to perform extended dissections in select cases, based on individual patient factors and tumor characteristics.

#### 11. Future Directions:

- Emerging techniques like sentinel lymph node mapping in pancreatic cancer might help tailor the extent of lymphadenectomy in the future.

In summary, while standard lymphadenectomy is a crucial part of pancreatic cancer surgery, current evidence does not support routine prophylactic extended lymph node and nerve plexus dissection. The focus has shifted towards achieving an adequate oncological resection while minimizing morbidity.

As a pancreatic surgeon, you may have encountered cases where you've had to weigh the potential benefits of extended dissection against the risks. Have you observed any trends or had any experiences in your practice that have influenced your approach to lymphadenectomy in pancreatic cancer surgery?

Risposta 3.

This is an excellent question that touches on an ongoing debate in pancreatic cancer surgery. The role of extended lymphadenectomy and nerve plexus dissection in pancreatic cancer surgery has been a subject of considerable research and discussion. Here's a detailed overview:

#### Extended Lymph Node Dissection:

##### 1. Current Recommendations:

- Most major guidelines, including those from NCCN and ESMO, do not recommend routine prophylactic extended lymphadenectomy.
- Standard lymphadenectomy is generally considered sufficient.

##### 2. Evidence:

- Several randomized controlled trials have failed to show a survival benefit for extended lymphadenectomy.
- Notable studies include the Japanese Study Group of Pancreatic Cancer (JSPAC-1) trial and the Italian Multicenter trial.

##### 3. Potential Drawbacks:

- Increased operative time
- Higher risk of postoperative complications, particularly pancreatic fistula and delayed gastric emptying

- Potential negative impact on quality of life

#### 4. Lymph Node Yield:

- A minimum of 15 lymph nodes examined is generally recommended for adequate staging.
- This can usually be achieved with standard lymphadenectomy.

#### Extended Nerve Plexus Dissection:

##### 1. Current Stance:

- Routine prophylactic extended nerve plexus dissection is not widely recommended.

##### 2. Evidence:

- Studies have shown mixed results, with some suggesting improved R0 resection rates but others showing no survival benefit.
- The ESPAC-1 trial did not demonstrate a survival advantage for extended retroperitoneal soft tissue dissection.

##### 3. Considerations:

- May be considered in cases where there's suspicion of perineural invasion on preoperative imaging.
- Can lead to significant postoperative diarrhea and quality of life issues.

##### 4. Technique Variations:

- Some centers perform limited plexus dissection around the superior mesenteric artery as part of a standard procedure.

#### Key Points:

1. Individualization: The extent of lymphadenectomy and nerve plexus dissection should be tailored to the individual patient and tumor characteristics.
2. R0 Resection: The primary goal should be achieving an R0 resection, which may necessitate limited extension of dissection in some cases.
3. Staging: Adequate lymph node sampling for accurate staging can usually be achieved with standard lymphadenectomy.
4. Morbidity: The potential oncological benefits of extended dissection must be weighed against the increased risk of postoperative complications.

5. Expertise: These procedures should be performed in high-volume centers with experienced surgeons.

6. Ongoing Research: Some studies are exploring the role of selective extended dissection based on preoperative imaging or intraoperative findings.

In summary, while extended lymph node and nerve plexus dissection can be performed safely in experienced hands, current evidence does not support its routine prophylactic use in resectable pancreatic cancer. The standard approach focuses on achieving R0 resection with adequate lymph node sampling for staging, while minimizing postoperative morbidity.

7. What is the definition of borderline resectable pancreatic cancer?

Risposta 1.

The concept of borderline resectable pancreatic cancer (BRPC) represents a category between clearly resectable and unresectable locally advanced pancreatic cancer. This classification is important for treatment planning, as these patients may benefit from neoadjuvant therapy before considering surgery. The definition of BRPC has evolved over time, but current consensus is largely based on the degree of vascular involvement. Here's a detailed breakdown of the definition:

1. National Comprehensive Cancer Network (NCCN) Criteria: The NCCN guidelines provide one of the most widely used definitions:
  - a) Venous involvement:
    - Tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) of  $>180$  degrees or  $\leq 180$  degrees with irregularity of the vein contour or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement, allowing for safe resection and reconstruction.
  - b) Arterial involvement:
    - Tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for safe resection and reconstruction.
    - Tumor contact with the superior mesenteric artery (SMA) of  $\leq 180$  degrees.
    - Tumor contact with the celiac artery of  $\leq 180$  degrees.
2. Intergroup Criteria (Alliance A021101): This definition is used in many clinical trials:
  - Tumor abutment ( $\leq 180$  degree or  $\leq 50\%$  of the vessel circumference) of the SMA or celiac axis.

- Short-segment encasement (>180 degree or >50% of the vessel circumference) of the common hepatic artery, typically at the gastroduodenal artery origin.
  - Tumor-vein interface (SMV/PV): (a) abutment with or without impingement and narrowing; (b) encasement with or without occlusion but with suitable vessel proximal and distal, allowing for safe reconstruction.
3. International Association of Pancreatology (IAP) Consensus: The IAP proposed a "biological" definition that includes:
    - Radiological criteria similar to NCCN.
    - CA 19-9 level >500 U/mL.
    - Regional lymph node metastasis.
  4. Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT) Consensus: Their definition aligns closely with the NCCN criteria.
  5. MD Anderson Cancer Center Criteria: They include "borderline resectable type A" (arterial involvement) and "type B" (suspicion of metastases).

#### Key Points:

- The core concept across all definitions is the degree of vascular involvement that makes immediate resection challenging but not impossible.
- The definitions aim to identify patients who might benefit from neoadjuvant therapy to increase the chances of R0 resection.
- There's an increasing trend to consider biological factors (like CA 19-9 levels) and conditional factors (patient performance status) in addition to anatomical criteria.
- The exact measurements and degrees of involvement may vary slightly between different guidelines, but the general principles remain consistent.
- These definitions are used to guide treatment decisions, often leading to neoadjuvant therapy followed by reassessment for potential resection.

It's important to note that the management of BRPC continues to evolve, and multidisciplinary tumor board discussions are crucial for making treatment decisions in these complex cases. The definition may be refined further as more data becomes available from ongoing clinical trials and research.

Risposta 2.



The concept of borderline resectable pancreatic cancer (BRPC) represents a category between clearly resectable and unresectable disease. The definition has evolved over time, but current consensus generally aligns with the following criteria:

1. Anatomical Criteria: According to the National Comprehensive Cancer Network (NCCN) and other major guidelines, BRPC is typically defined by the following vascular involvement:
  - a) Venous involvement:
    - Tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) of  $>180$  degrees without vein contour irregularity
    - Tumor contact of  $\leq 180$  degrees with vein contour irregularity or thrombosis, but allowing suitable vessel proximal and distal to the site of involvement for safe resection and reconstruction
  - b) Arterial involvement:
    - Tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation
    - Tumor contact with the superior mesenteric artery (SMA) of  $\leq 180$  degrees
    - Tumor contact with the celiac axis of  $\leq 180$  degrees
2. No Distant Metastases:
  - Absence of distant metastatic disease is crucial for the BRPC classification
3. Biological and Conditional Factors: Some institutions also consider:
  - CA 19-9 levels
  - Regional lymph node status
  - Patient performance status and comorbidities
4. Resectability Potential:
  - There should be a high likelihood of achieving a margin-negative (R0) resection with current surgical techniques
5. Radiological Assessment:
  - High-quality, contrast-enhanced CT imaging is crucial for accurate staging and determination of BRPC status
  - Some centers also utilize endoscopic ultrasound (EUS) for additional assessment
6. Multidisciplinary Evaluation:
  - The determination of BRPC often involves review by a multidisciplinary team including surgeons, radiologists, and oncologists
7. Treatment Approach:

- BRPC is often managed with neoadjuvant therapy (chemotherapy with or without radiation) followed by reassessment for surgery

- The goal is to increase the chances of R0 resection and improve overall outcomes

#### 8. Institutional Variability:

- Some high-volume centers may have more aggressive definitions of borderline resectability based on their surgical expertise and outcomes

#### 9. Evolving Concept:

- The definition continues to evolve with advancements in imaging, surgical techniques, and neoadjuvant therapies

It's important to note that the management of BRPC is an area of active research and debate in the pancreatic cancer community. The approach can vary between institutions, with some adopting more aggressive surgical strategies and others favoring extended neoadjuvant treatment.

As a pancreatic surgeon, you're likely familiar with the nuances of assessing borderline resectability. Have you encountered any particular challenges in defining or managing BRPC cases in your practice? Are there specific aspects of the definition or management approach you find particularly important or controversial?

Risposta 3.

The definition of borderline resectable pancreatic cancer (BRPC) is an important concept in pancreatic surgery, as it helps guide treatment decisions and surgical planning. While there's some variation in exact criteria between different guidelines and institutions, I'll provide you with the generally accepted definition based on the most recent consensus:

Borderline resectable pancreatic cancer typically refers to tumors that are at the anatomic interface between resectable and locally advanced unresectable disease. The definition primarily focuses on the relationship of the tumor to key vascular structures. Here's a breakdown:

#### 1. National Comprehensive Cancer Network (NCCN) Criteria:

##### a) Venous involvement:

- Tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) of  $>180$  degrees without vein contour irregularity, or
- Tumor contact of  $\leq 180$  degrees with vein contour irregularity or thrombosis but with suitable vessel proximal and distal to the site of involvement, allowing for safe resection and reconstruction.

b) Arterial involvement:

- Tumor contact with the common hepatic artery (CHA) without extension to the celiac axis or hepatic artery bifurcation, allowing for safe resection and reconstruction.
- Tumor contact with the superior mesenteric artery (SMA) of  $\leq 180$  degrees.
- Tumor contact with the celiac axis of  $\leq 180$  degrees.

2. International Study Group of Pancreatic Surgery (ISGPS) Criteria:

Similar to NCCN, with some additional specifications:

- Involvement of SMV/PV with occlusion  $> 180$  degrees, abutment of SMA  $< 180$  degrees.
- Encasement of gastroduodenal artery up to hepatic artery, without involvement of the celiac axis.

3. Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT) Consensus:

Largely aligns with NCCN criteria, emphasizing the importance of multidisciplinary assessment.

4. Biological Factors:

Some institutions also consider biological factors in defining BRPC:

- CA 19-9 levels  $> 1000$  U/mL
- Regional lymph node involvement
- These factors may indicate more aggressive disease biology

5. Radiological Assessment:

- High-quality, contrast-enhanced CT or MRI is crucial for accurate determination of resectability status.
- Specific protocols (e.g., pancreatic protocol CT) are recommended for optimal visualization.

6. Institutional Variation:

- Some high-volume centers may have more aggressive criteria for resectability based on their surgical expertise and outcomes.

Key Implications of BRPC Classification:

1. Treatment Approach: BRPC often indicates a need for neoadjuvant therapy before considering surgery.
2. Surgical Planning: May require vascular resection and reconstruction techniques.
3. Multidisciplinary Management: Requires close collaboration between surgeons, medical oncologists, and radiation oncologists.

4. Prognosis: Generally, has a prognosis intermediate between resectable and locally advanced disease.

It's important to note that the management of BRPC continues to evolve, with ongoing research into optimal neoadjuvant regimens and surgical techniques. The classification of a tumor as borderline resectable should always prompt a thorough multidisciplinary discussion to determine the best treatment strategy for each individual patient.

8. Is combined arterial resection recommended in patients with BR pancreatic cancer?

Risposta 1.

The question of combined arterial resection in patients with borderline resectable (BR) pancreatic cancer is complex and controversial. Here's a comprehensive overview of the current understanding:

1. General Approach:

- Historically, arterial involvement was considered a contraindication to resection due to increased morbidity and mortality.
- However, advances in surgical techniques and perioperative care have led to reconsideration of this approach in select cases.

2. Current Recommendations:

- Most major guidelines (NCCN, ESMO) do not routinely recommend planned arterial resection for BR pancreatic cancer.
- It's generally considered on a case-by-case basis in highly selected patients at high-volume centers with extensive experience.

3. Potential Benefits:

- May allow for R0 resection in cases that would otherwise be unresectable.
- Some studies have shown long-term survival in select patients undergoing arterial resection.

4. Concerns and Risks:

- Higher perioperative morbidity and mortality compared to standard resection.
- Increased risk of complications such as hepatic ischemia, biliary fistula, and pancreatic fistula.
- Potential for prolonged operative time and increased blood loss.

5. Types of Arterial Resection:

- Common hepatic artery resection is more frequently performed and generally better tolerated.

- Superior mesenteric artery (SMA) resection is more controversial and associated with higher risks.
- Celiac axis resection (Appleby procedure) may be considered in select cases of body/tail tumors.

#### 6. Role of Neoadjuvant Therapy:

- There's an increasing trend to use neoadjuvant therapy in BR pancreatic cancer.
- This approach may downstage tumors, potentially avoiding the need for arterial resection.
- If arterial involvement persists after neoadjuvant therapy, the prognosis is generally poor, and arterial resection is less likely to be beneficial.

#### 7. Patient Selection:

- Crucial factors include: a) Patient's overall health and fitness for extended surgery b) Extent of arterial involvement c) Absence of other metastatic disease d) Response to neoadjuvant therapy (if given) e) Surgeon and institutional experience

#### 8. Outcomes:

- Studies show mixed results, with some reporting similar survival to standard resections in highly selected patients.
- However, many studies show poorer long-term outcomes compared to patients not requiring arterial resection.

#### 9. Expert Consensus:

- The 2017 International Study Group on Pancreatic Surgery (ISGPS) consensus statement suggests that arterial resection should not be performed routinely and should be reserved for highly selected patients.

#### 10. Emerging Approaches:

- Some centers are exploring innovative techniques like irreversible electroporation (IRE) or intraoperative radiation therapy (IORT) as alternatives to arterial resection in managing arterial involvement.

#### 11. Multidisciplinary Approach:

- Decisions regarding arterial resection should involve multidisciplinary tumor board discussions, including surgeons, oncologists, radiologists, and pathologists.

In conclusion, while combined arterial resection is not routinely recommended for patients with BR pancreatic cancer, it may be considered in highly selected cases at experienced high-volume centers. The decision should be made on an individual basis, taking into account the extent of disease, patient factors, and institutional expertise. The trend is moving towards using neoadjuvant therapy to potentially downstage tumors and reassess resectability, rather

than planning upfront arterial resections. As always in complex oncologic surgery, the potential benefits must be carefully weighed against the risks, and shared decision-making with the patient is crucial.

Risposta 2.

The question of combined arterial resection in patients with borderline resectable (BR) pancreatic cancer is complex and controversial. Here's a comprehensive overview of the current stance on this issue:

1. General Recommendation:

- Combined arterial resection is not routinely recommended for BR pancreatic cancer in most guidelines.
- It's generally considered a high-risk procedure with increased morbidity and mortality.

2. Specific Scenarios:

- In highly selected cases, arterial resection might be considered, particularly:
  - After neoadjuvant therapy with good response
  - In high-volume centers with extensive experience
  - For patients with excellent performance status

3. Types of Arterial Involvement:

- Celiac axis resection (Appleby procedure) is more commonly performed than superior mesenteric artery (SMA) resection.
- Hepatic artery resection and reconstruction is sometimes feasible.

4. Outcomes:

- Studies have shown mixed results:
  - Some report increased perioperative morbidity and mortality
  - Others suggest comparable long-term outcomes in highly selected patients

5. Neoadjuvant Therapy:

- Many centers prefer neoadjuvant therapy for BR pancreatic cancer to:
  - Potentially downstage the tumor
  - Select patients with favorable tumor biology
  - Potentially avoid the need for arterial resection

6. Technical Considerations:

- Arterial resection and reconstruction require advanced surgical skills and resources.
- The specific technique depends on the extent and location of involvement.

7. Patient Selection:

- Careful patient selection is crucial, considering:

- Overall health and comorbidities
- Extent of vascular involvement
- Response to neoadjuvant therapy
- Potential for achieving R0 resection

#### 8. Institutional Experience:

- Outcomes tend to be better in high-volume centers with experienced teams.
- Some specialized centers report more favorable outcomes with arterial resection.

#### 9. Risk-Benefit Analysis:

- The potential for cure must be weighed against the increased risks of the procedure.
- Quality of life considerations are important in decision-making.

#### 10. Alternative Approaches:

- Some centers explore alternatives like irreversible electroporation (IRE) for tumors involving major arteries.

#### 11. Ongoing Research:

- Several studies are ongoing to better define the role of arterial resection in BR pancreatic cancer.
- There's interest in identifying subgroups that might benefit most from this approach.

#### 12. Multidisciplinary Decision:

- The decision to perform arterial resection should involve a multidisciplinary team discussion.

In summary, while combined arterial resection is not routinely recommended for BR pancreatic cancer, it may be considered in highly selected cases, particularly after neoadjuvant therapy and in experienced centers. The decision should be individualized based on patient factors, tumor characteristics, and institutional expertise.

As a pancreatic surgeon, you're likely familiar with the complexities of these cases. Have you had experience with arterial resections in BR pancreatic cancer? What factors do you find most crucial in decision-making for these challenging cases?

Risposta 3.

The question of arterial resection in borderline resectable (BR) pancreatic cancer is complex and somewhat controversial. Here's a detailed overview of the current stance on combined arterial resection in BR pancreatic cancer:

#### 1. General Recommendation:

- Arterial resection is not routinely recommended in BR pancreatic cancer.
- Most guidelines and expert opinions suggest avoiding planned arterial resection if possible.

## 2. Current Practice:

- Arterial resection is performed in selected cases at high-volume centers with extensive experience.

- It's more commonly considered after neoadjuvant therapy in cases with good response.

## 3. Outcomes:

- Historically, arterial resection has been associated with higher morbidity and mortality compared to standard resections.

- Some recent studies from high-volume centers show improved outcomes, but results are still generally inferior to standard resections.

## 4. Specific Arteries:

- Hepatic artery resection is more commonly performed than superior mesenteric artery (SMA) or celiac axis resection.

- Celiac axis resection (Appleby procedure) may be considered in select body/tail tumors.

## 5. Neoadjuvant Therapy:

- Neoadjuvant therapy is strongly recommended for BR pancreatic cancer, especially if arterial involvement is suspected.

- Good response to neoadjuvant therapy may increase the chances of R0 resection without arterial resection.

## 6. Decision Factors:

- Extent of arterial involvement
- Patient's overall health and fitness for extensive surgery
- Tumor biology and response to neoadjuvant therapy
- Surgical expertise and institutional experience

## 7. Potential Benefits:

- May allow R0 resection in otherwise unresectable cases
- Potentially improved long-term survival in carefully selected patients

## 8. Risks and Challenges:

- Higher perioperative morbidity and mortality
- Increased risk of pancreatic fistula and other complications
- Technical complexity of vascular reconstruction
- Potential for compromised blood supply to organs (e.g., liver in hepatic artery resection)

## 9. Expert Consensus:

- Most expert panels suggest that if significant arterial resection is anticipated preoperatively, patients should be treated with neoadjuvant therapy first.



- Arterial resection should be considered only if R0 resection is achievable and only in highly selected patients.

#### 10. Ongoing Research:

- Several studies are investigating the role of more aggressive surgical approaches in conjunction with modern neoadjuvant regimens.

- Some centers are exploring novel techniques like irreversible electroporation (IRE) as an adjunct to arterial resection.

In summary, while combined arterial resection is not broadly recommended in BR pancreatic cancer, it may be considered in highly selected cases at experienced centers. The decision should be made on a case-by-case basis after thorough multidisciplinary discussion, considering factors such as the extent of involvement, response to neoadjuvant therapy, patient fitness, and the likelihood of achieving R0 resection.

As a pancreatic surgeon, you're likely aware that this is an area of ongoing debate and research. The approach to arterial resection often depends on institutional experience and philosophy, with some high-volume centers being more aggressive than others

9. What is the first-line treatment recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

For patients with locally advanced, unresectable pancreatic cancer, the first-line treatment approach has evolved. Here's a comprehensive overview:

1. Standard First-Line Treatment:
  - Systemic chemotherapy is the primary first-line treatment
  - Currently, FOLFIRINOX or gemcitabine plus nab-paclitaxel (Abraxane) are the two most recommended regimens
2. FOLFIRINOX Regimen:
  - Considered the standard of care for fit patients (ECOG performance status 0-1)
  - Combination of: a) Fluorouracil (5-FU) b) Irinotecan c) Oxaliplatin
  - Higher response rates and longer progression-free survival
  - More toxic, requiring careful patient selection
3. Gemcitabine plus nab-paclitaxel:
  - Alternative first-line option
  - Better tolerated compared to FOLFIRINOX
  - Recommended for patients with slightly lower performance status
  - Showed improved overall survival in clinical trials

4. Additional Considerations:

- Treatment selection based on: a) Patient's performance status b) Comorbidities c) Nutritional status d) Patient preferences e) Molecular profiling results

5. Emerging Approaches:

- Incorporation of targeted therapies
- Immunotherapy combinations under investigation
- Precision medicine approaches based on molecular profiling

6. Goals of Treatment:

- Improve overall survival
- Control local and systemic disease
- Maintain quality of life
- Manage symptoms

7. Palliative Care:

- Integrated with systemic treatment
- Management of pain, nutritional support, and symptom control

The choice between FOLFIRINOX and gemcitabine/nab-paclitaxel depends on individual patient factors and should be made through shared decision-making with a multidisciplinary team.

Risposta 2.

For patients with locally advanced, unresectable pancreatic cancer, the first-line treatment typically involves a combination chemotherapy regimen. Currently, the most recommended first-line approach is:

FOLFIRINOX (a combination of four chemotherapy drugs):

- 5-Fluorouracil (5-FU)
- Leucovorin (folinic acid)
- Irinotecan
- Oxaliplatin

Alternatively, for patients who may not tolerate the more intensive FOLFIRINOX regimen, another first-line option is:

- Gemcitabine plus nab-paclitaxel (Abraxane)

The choice between these two regimens depends on several factors:

1. Patient's performance status
2. Age
3. Comorbidities

4. Potential side effect tolerance
5. Overall health condition

FOLFIRINOX has shown improved overall survival compared to gemcitabine alone in multiple clinical studies, but it is also associated with more significant toxicity. Therefore, the treatment selection is personalized based on the individual patient's specific circumstances. Oncologists will typically conduct a thorough assessment to determine the most appropriate first-line treatment strategy for each patient with locally advanced, unresectable pancreatic cancer.

Risposta 3.

For patients with locally advanced, unresectable pancreatic cancer, the first-line treatment approach has evolved significantly in recent years. Here's a comprehensive overview:

1. Standard First-Line Treatment:

- FOLFIRINOX or modified FOLFIRINOX
- Or gemcitabine plus nab-paclitaxel (Abraxane)

2. FOLFIRINOX Regimen:

- Combination of:
  - \* Folinic acid (leucovorin)
  - \* Fluorouracil (5-FU)
  - \* Irinotecan
  - \* Oxaliplatin
- Advantages:
  - \* Improved overall survival compared to gemcitabine alone
  - \* Better response rates
- Considerations:
  - \* More toxic
  - \* Requires careful patient selection
  - \* Often used in patients with good performance status (ECOG 0-1)

3. Gemcitabine plus nab-paclitaxel:

- Alternative first-line option
- Less toxic than FOLFIRINOX
- May be preferred for patients with:
  - \* Slightly lower performance status

- \* More significant comorbidities
- \* Concerns about FOLFIRINOX toxicity

#### 4. Treatment Goals:

- Local disease control
- Symptom management
- Potential conversion to resectability
- Prolonging survival

#### 5. Additional Considerations:

- Molecular profiling for potential targeted therapies
- BRCA and other genetic mutations may influence treatment choice
- Consideration of clinical trials

#### 6. Supportive Care:

- Pain management
- Nutritional support
- Management of potential complications

#### 7. Emerging Approaches:

- Investigational combination therapies
- Immunotherapy approaches
- Targeted molecular therapies

#### 8. Decision-Making Factors:

- Patient's performance status
- Comorbidities
- Molecular profile
- Patient preferences
- Potential for clinical trial participation

#### Key Points:

- No single approach fits all patients
- Multidisciplinary team assessment is crucial
- Treatment should be individualized
- Regular monitoring and potential treatment modification

10. What is the chemoradiotherapy regimen recommended for patients with locally advanced, unresectable pancreatic cancer?

## Risposta 1.

For patients with locally advanced, unresectable pancreatic cancer, the recommended chemoradiotherapy approach involves several key considerations:

1. Standard Chemoradiotherapy Approach:
  - Concurrent chemoradiation with radiosensitizing chemotherapy
  - Typically using one of two primary regimens:
2. Gemcitabine-Based Chemoradiation:
  - Gemcitabine as the radiosensitizing agent
  - Radiation dose: 50.4 Gy in 28 fractions
  - Concurrent low-dose gemcitabine (typically 300 mg/m<sup>2</sup> weekly)
  - Considered the more traditional approach
3. FOLFIRINOX-Based Approach:
  - Emerging alternative for fit patients
  - Typically modified FOLFIRINOX
  - Lower intensity compared to full-dose systemic FOLFIRINOX
  - Radiation dose similar to gemcitabine-based approach
4. Radiation Technique:
  - Intensity-Modulated Radiation Therapy (IMRT) preferred
  - Allows for more precise targeting
  - Reduces toxicity to surrounding critical structures
5. Patient Selection Criteria:
  - Good performance status (ECOG 0-1)
  - Adequate organ function
  - No significant weight loss
  - No contraindications to radiation or chemotherapy
6. Treatment Goals:
  - Local disease control
  - Potential downstaging
  - Symptom management
  - Improved local progression-free survival
7. Important Considerations:
  - Careful patient selection
  - Multidisciplinary approach

- Close monitoring for toxicity
- Potential for conversion to borderline resectable status

#### 8. Emerging Alternatives:

- Stereotactic body radiotherapy (SBRT)
- Combination with immunotherapy under investigation
- Molecular profiling to guide treatment

#### Limitations:

- No standard of care definitively proven superior
- Treatment must be individualized
- Significant toxicity potential
- Limited overall survival benefit

Recommendation: Chemoradiotherapy should be considered for carefully selected patients with locally advanced, unresectable pancreatic cancer, typically using either gemcitabine-based or modified FOLFIRINOX-based concurrent chemoradiation, with a radiation dose of approximately 50.4 Gy in 28 fractions.

#### Risposta 2.

For patients with locally advanced, unresectable pancreatic cancer, the standard chemoradiotherapy regimen is:

#### Gemcitabine-based chemoradiation:

- Gemcitabine as the radiosensitizing chemotherapy agent
- Radiation therapy typically delivered at 50.4-54 Gy in 28-30 fractions
- Concurrent administration of gemcitabine during radiation

#### Alternative options include:

##### 1. 5-Fluorouracil (5-FU) based chemoradiation

- Can be administered as a continuous infusion during radiation
- Similar radiation dosing to gemcitabine protocol

#### Key considerations:

- Chemoradiotherapy aims to control local disease progression
- Treatment is typically given before or after systemic chemotherapy
- Patient selection depends on performance status, tumor characteristics, and overall health

Recent studies have also explored more modern approaches:

- FOLFIRINOX-based chemoradiation

- Combination of newer targeted agents with radiation

The specific regimen is determined by a multidisciplinary oncology team, taking into account individual patient factors and current clinical guidelines

Risposta 3.

For patients with locally advanced, unresectable pancreatic cancer, chemoradiotherapy is an important treatment modality. Here's a comprehensive overview of the recommended regimen:

1. Standard Chemoradiotherapy Approach:

- Concurrent chemotherapy and radiation therapy
- Typically using gemcitabine-based regimens

2. Recommended Regimens:

a) Gemcitabine-based Chemoradiotherapy:

- Concurrent gemcitabine with radiation therapy
- Typical dosing:
  - \* Gemcitabine: 1000 mg/m<sup>2</sup> weekly during radiation
  - \* Radiation: 50-54 Gy in 25-30 fractions

b) Alternative Regimen:

- 5-Fluorouracil (5-FU) with radiation
- Typical dosing:
  - \* Continuous 5-FU infusion during radiation
  - \* Radiation: 50-54 Gy in 25-30 fractions

3. Radiation Technique:

- Intensity-modulated radiation therapy (IMRT) preferred
- Allows for more precise targeting
- Reduces toxicity to surrounding tissues

4. Treatment Considerations:

- Performance status (ECOG 0-1)
- Absence of significant weight loss
- Minimal comorbidities
- Adequate organ function

5. Goals of Chemoradiotherapy:

- Local disease control

- Symptom management
- Potential conversion to resectability
- Improving overall survival

#### 6. Potential Sequencing:

- Often preceded by initial systemic chemotherapy (e.g., FOLFIRINOX)
- May be followed by additional systemic therapy

#### 7. Limitations:

- Not suitable for all patients
- Potential for significant toxicity
- Limited evidence of substantial survival benefit compared to systemic therapy alone

#### 8. Emerging Approaches:

- Stereotactic body radiation therapy (SBRT)
- Combination with immunotherapy
- Molecular-targeted approaches

#### 9. Patient Selection Criteria:

- No distant metastases
- No significant weight loss
- Good performance status
- Adequate organ function

#### 10. Potential Toxicities:

- Acute: Gastrointestinal toxicity, fatigue
- Late: Potential long-term digestive and metabolic complications

#### Important Considerations:

- Individualized approach is crucial
- Multidisciplinary team assessment recommended
- Regular monitoring during treatment
- Potential for clinical trial participation

#### 11. What is the first-line chemotherapy recommended for pancreatic cancer patients with distant metastases?

##### Risposta 1.

For pancreatic cancer patients with distant metastases, the first-line chemotherapy recommendations are as follows:

##### 1. First-Line Options:



- FOLFIRINOX
- Gemcitabine plus nab-paclitaxel (Abraxane)
- Choice depends on patient factors and performance status
- 2. FOLFIRINOX Regimen:
  - Recommended for fit patients (ECOG performance status 0-1)
  - Combination of: a) Fluorouracil (5-FU) b) Irinotecan c) Oxaliplatin
  - Demonstrated superior overall survival
  - Higher response rates
  - More intensive, more toxic
  - Median overall survival: ~11.1 months
- 3. Gemcitabine plus nab-paclitaxel:
  - Alternative first-line option
  - Better tolerated
  - Good option for patients with slightly lower performance status
  - Median overall survival: ~8.5 months
  - Less toxic compared to FOLFIRINOX
- 4. Patient Selection Criteria:
  - FOLFIRINOX: Younger patients, good performance status
  - Gemcitabine/nab-paclitaxel: Slightly older patients, some comorbidities
- 5. Additional Considerations:
  - Molecular profiling
  - Patient preferences
  - Comorbidities
  - Nutritional status
  - Patient's ability to tolerate intensive chemotherapy
- 6. Performance Status Assessment:
  - ECOG 0-1: Candidates for more intensive regimens
  - ECOG 2: May require reduced-intensity approaches
  - ECOG >2: Best supportive care
- 7. Emerging Approaches:
  - Combination with targeted therapies
  - Immunotherapy investigations
  - Precision medicine strategies

The selection between FOLFIRINOX and gemcitabine/nab-paclitaxel should be personalized based on individual patient characteristics and made through shared decision-making with a multidisciplinary oncology team.

Risposta 2.

For pancreatic cancer patients with distant metastases, the first-line chemotherapy recommendations are:

1. FOLFIRINOX (preferred for fit patients):
  - 5-Fluorouracil
  - Leucovorin
  - Irinotecan
  - Oxaliplatin
2. Gemcitabine plus nab-paclitaxel (Abraxane):
  - Standard alternative for patients who cannot tolerate FOLFIRINOX
  - More manageable toxicity profile
3. Gemcitabine alone:
  - Considered for patients with poor performance status
  - Less intensive option with lower response rates

Selection criteria depends on:

- Patient's performance status (ECOG)
- Age
- Comorbidities
- Organ function
- Patient's ability to tolerate aggressive chemotherapy

Additional considerations:

- FOLFIRINOX shows superior overall survival
- Gemcitabine/nab-paclitaxel offers improved response rates
- Molecular profiling and biomarker testing can further guide treatment selection

The choice is individualized based on comprehensive patient assessment and goals of care.

Risposta 3.

For patients with metastatic pancreatic cancer, the first-line chemotherapy recommendations are as follows:

1. Preferred First-Line Regimens:

a) FOLFIRINOX (modified)

- Primary recommended option for fit patients
- Combination of:
  - \* Folinic acid (leucovorin)
  - \* Fluorouracil (5-FU)
  - \* Irinotecan
  - \* Oxaliplatin
- Recommended for patients with:
  - \* Good performance status (ECOG 0-1)
  - \* No significant comorbidities
  - \* Age <75 years
  - \* Adequate organ function

b) Gemcitabine plus nab-paclitaxel (Abraxane)

- Alternative first-line option
- Preferred for patients with:
  - \* Slightly lower performance status
  - \* More significant comorbidities
  - \* Concerns about FOLFIRINOX toxicity

2. Patient Selection Considerations:

- Performance status
- Age
- Comorbidities
- Organ function
- Patient preferences

3. Molecular Profiling Considerations:

- BRCA mutations
- Other genetic alterations
- Potential targeted therapy options

4. Treatment Goals:

- Prolonging survival
- Symptom management
- Maintaining quality of life

5. Emerging Approaches:

- Immunotherapy combinations

- Targeted molecular therapies
- Precision medicine approaches

#### 6. Monitoring and Management:

- Regular assessment of treatment response
- Management of treatment-related toxicities
- Potential dose modifications

#### 7. Second-Line Considerations:

- Subsequent treatment depends on:
  - \* First-line therapy used
  - \* Patient's response
  - \* Performance status
  - \* Molecular profile

Recommendations are based on current clinical guidelines and recent clinical trials, emphasizing an individualized approach to treatment.

#### 12. Is surgical resection recommended for pancreatic cancer patients with postoperative metastases/recurrences?

Risposta 1.

For pancreatic cancer patients with postoperative metastases or recurrences, surgical resection is generally not recommended as a standard approach. Here's a detailed explanation:

##### 1. Current Standard of Care:

- Surgical resection is not recommended for most patients with postoperative metastases/recurrences
- Systemic therapy is the primary treatment approach
- Palliative interventions may be considered for symptom management

##### 2. Reasons Against Surgical Resection:

- Poor prognosis
- High morbidity and mortality associated with repeated surgeries
- Limited survival benefit
- Potential compromise of quality of life

##### 3. Management Approach:

- Systemic chemotherapy (FOLFIRINOX or gemcitabine/nab-paclitaxel)

- Palliative care
- Symptom management
- Potential clinical trial participation
- 4. Potential Exceptional Circumstances:
  - Very rare, highly selected cases might consider: a) Isolated, oligometastatic recurrence b) Long disease-free interval (>12 months) c) Good performance status d) Limited metastatic burden e) Multidisciplinary tumor board recommendation
- 5. Palliative Interventions:
  - Biliary or gastric bypass if obstructive symptoms
  - Pain management
  - Nutritional support
  - Stent placement if necessary
- 6. Emerging Approaches:
  - Molecular profiling
  - Targeted therapies
  - Immunotherapy investigations
  - Precision medicine strategies

The consensus is that surgical resection is not recommended for most patients with postoperative metastases or recurrences. Treatment should focus on systemic therapy, palliative care, and maintaining quality of life.

Risposta 2.

For pancreatic cancer patients with postoperative metastases or recurrences, surgical resection is generally NOT recommended. The standard approach is:

Key Management Principles:

1. Systemic chemotherapy is the primary treatment
2. Surgical re-intervention is typically not advised due to:
  - Poor prognosis
  - Limited survival benefit
  - High surgical risks
  - Potential complications

Recommended Treatment Approach:

- Systemic chemotherapy (FOLFIRINOX or gemcitabine-based)
- Palliative care
- Potential clinical trial enrollment

- Molecular profiling to guide targeted therapies
- Consideration of maintenance therapy

Exceptions/Considerations:

- Very rare cases of isolated, oligometastatic recurrence
- Patients with excellent performance status
- Limited, surgically accessible metastatic lesions
- Multidisciplinary team recommendation

Prognostic Factors:

- Time to recurrence
- Location of metastases
- Performance status
- Response to initial treatment

The primary goal shifts from curative intent to prolonging survival and maintaining quality of life through systemic treatments and supportive care.

Risposta 3.

For pancreatic cancer patients with postoperative metastases or recurrences, surgical resection is generally not recommended as a standard approach. Here's a detailed breakdown:

1. Standard Recommendation:

- Surgical resection is NOT routinely recommended for postoperative metastases/recurrences

- Primary management is systemic therapy

2. Rationale Against Surgical Resection:

- Poor overall prognosis
- High risk of additional metastatic spread
- Limited survival benefit
- Significant surgical morbidity

3. Management Approach:

- Systemic chemotherapy
- Palliative care
- Symptom management
- Potential clinical trial participation

4. Highly Selective Scenarios Where Surgery Might Be Considered:

- Oligometastatic disease (very limited metastases)
- Excellent response to initial treatment
- No evidence of widespread metastatic disease
- Patient with excellent performance status
- Multidisciplinary team recommendation
- Potentially curative intent

#### 5. Metastasis Sites Affecting Decision:

- Liver metastases: Generally less favorable for surgical intervention
- Isolated lung metastases: Occasional consideration for metastasectomy
- Local recurrence: Rare potential for surgical intervention

#### 6. Treatment Priorities:

- Systemic therapy
- Quality of life preservation
- Symptom control
- Potential clinical trial enrollment

13. Which of the two types of stents—plastic stents or metallic stents—are recommended in resectable or borderline resectable pancreatic cancer patients with obstructive jaundice?

Risposta 1.

For resectable or borderline resectable pancreatic cancer patients with obstructive jaundice, the recommendation is as follows:

#### 1. Metallic Stents: Preferred Option:

- o Self-expanding metallic stents (SEMS)
- o Recommended for most patients
- o Advantages: a) Longer patency duration b) Lower re-intervention rates c) Larger diameter d) Better quality of life

#### 2. Specific Recommendations:

- o Fully covered or partially covered SEMS
- o Recommended in patients awaiting surgery
- o Easier removal compared to uncovered metallic stents

#### 3. Timing of Stent Placement:

- o Before neoadjuvant therapy
- o Typically placed via ERCP

- Minimally invasive approach

#### 4. Plastic Stents:

- Less preferred
- Limited use in specific scenarios
- Shorter patency duration
- Higher re-intervention rates

#### 5. Considerations for Stent Selection:

- Patient's expected survival
- Time to definitive surgical intervention
- Potential need for future interventions

The current standard recommendation is to use self-expanding metallic stents (SEMS) for resectable or borderline resectable pancreatic cancer patients with obstructive jaundice.

Risposta 2.

In patients with resectable or borderline resectable pancreatic cancer and obstructive jaundice, metallic stents are generally recommended over plastic stents. Here's a detailed breakdown:

Metallic Stents (Preferred):

##### 1. Advantages:

- Longer patency duration
- Reduced need for repeated interventions
- Lower risk of cholangitis
- Less frequent stent occlusion
- Better quality of life
- Lower overall healthcare costs

##### 2. Types:

- Fully covered metallic stents
- Partially covered metallic stents

Plastic Stents (Less Preferred):

##### 1. Limitations:

- Shorter patency duration
- Higher risk of stent occlusion
- More frequent interventional procedures
- Increased risk of cholangitis



- Higher healthcare costs due to repeated interventions

Recommendations:

- Self-expandable metallic stents (SEMS) are preferred
- Should be placed prior to surgical resection
- Aim to relieve biliary obstruction and improve patient's nutritional status
- Timing of stent placement should be coordinated with surgical planning

The choice depends on individual patient factors, but metallic stents are generally considered the standard of care in this clinical scenario

Risposta 3.

For patients with resectable or borderline resectable pancreatic cancer and obstructive jaundice, the current recommendation is:

1. Metallic Stents (Preferred Option):

- Recommended over plastic stents
- Specifically, fully covered self-expandable metallic stents (SEMS)

2. Advantages of Metallic Stents:

- Longer patency duration
- Lower risk of obstruction
- Fewer interventions required
- Reduced biliary complications
- Better quality of life

3. Specific Considerations:

- Fully covered metallic stents preferred
- Reduces the risk of tumor ingrowth
- Easier to remove before surgery

4. Plastic Stents:

- Less recommended
- Higher rates of:
  - \* Stent occlusion
  - \* Cholangitis
  - \* Need for repeated interventions

5. Timing of Stent Placement:

- Before neoadjuvant therapy

- Minimally invasive approach
- Typically via ERCP or percutaneous transhepatic cholangiography

#### 6. Removal Strategy:

- Metallic stents can be easily removed before surgical resection
- Timing coordinated with surgical and oncological treatment plan

### 14. Is anticoagulant therapy for preventing venous thromboembolism recommended in patients with unresectable pancreatic cancer undergoing chemotherapy?

Risposta 1.

For patients with unresectable pancreatic cancer undergoing chemotherapy, thromboprophylaxis is strongly recommended due to the high risk of venous thromboembolism (VTE). Here's a comprehensive overview:

#### 1. Recommendation Status:

- Anticoagulant thromboprophylaxis is recommended
- Pancreatic cancer patients have one of the highest risks of VTE among cancer patients

#### 2. Risk Factors:

- Advanced cancer stage
- Chemotherapy
- Hospitalization
- Surgery
- Immobility
- Patient-specific comorbidities

#### 3. Recommended Approach:

- Low molecular weight heparin (LMWH) preferred
- Specifically, dalteparin or enoxaparin
- Preferred over direct oral anticoagulants (DOACs)

#### 4. Dosing Considerations:

- Prophylactic dosing in ambulatory patients
- Adjusted dosing may be considered in high-risk patients
- Individualized approach based on patient factors

#### 5. Duration of Therapy:

- Typically continued throughout active chemotherapy
- May be extended based on individual risk assessment

#### 6. Benefits:

- Reduces VTE risk
- Potential survival benefit
- Improves quality of life
- Prevents treatment interruptions

7. Monitoring:

- Regular assessment of bleeding risk
- Platelet count monitoring
- Renal function evaluation

The current standard recommendation is to use low molecular weight heparin for thromboprophylaxis in unresectable pancreatic cancer patients undergoing chemotherapy

Risposta 2.

For patients with unresectable pancreatic cancer undergoing chemotherapy, low molecular weight heparin (LMWH) is recommended for preventing venous thromboembolism (VTE).

Here are the key details:

Recommended Approach:

- Low molecular weight heparin (LMWH) is preferred over other anticoagulants
- Prophylactic or therapeutic doses based on individual risk assessment

Rationale:

- Pancreatic cancer patients have a high risk of VTE
- Cancer itself increases thrombotic risk
- Chemotherapy further increases thrombotic complications
- LMWH has shown:

1. Reduced VTE incidence
2. Potential survival benefits
3. Lower bleeding complications compared to warfarin

Specific Recommendations:

- Dalteparin or enoxaparin are commonly used LMWH agents
- Individualized dosing based on:
  1. Patient's body weight
  2. Renal function
  3. Platelet count
  4. Bleeding risk
  5. Concurrent medications

Considerations:

- Routine VTE risk assessment recommended
- Regular monitoring of coagulation parameters
- Potential survival advantage beyond VTE prevention

The decision should be made through shared decision-making between the oncologist and patient, considering individual risk factors and potential benefits

Risposta 3.

For patients with unresectable pancreatic cancer undergoing chemotherapy, anticoagulant therapy for venous thromboembolism (VTE) prevention is recommended. Here's a comprehensive overview:

1. Recommendation:

- Prophylactic anticoagulation is recommended
- Particularly for patients with advanced pancreatic cancer receiving chemotherapy

2. Rationale:

- Pancreatic cancer patients have:
  - \* High risk of VTE
  - \* Increased procoagulant state
  - \* Chemotherapy further increases thrombotic risk

3. Recommended Anticoagulants:

- Low molecular weight heparin (LMWH)
  - \* Preferred option
  - \* Examples: Enoxaparin, Dalteparin
- Direct oral anticoagulants (DOACs) may be considered in selected patients

4. Risk Stratification:

- Factors increasing VTE risk:
  - \* Advanced stage cancer
  - \* Metastatic disease
  - \* Hospitalization
  - \* Immobility
  - \* Chemotherapy
  - \* Prior VTE history

5. Dosing Considerations:

- Prophylactic or intermediate-dose LMWH
- Individualized based on patient's:
  - \* Renal function
  - \* Platelet count
  - \* Bleeding risk
  - \* Overall clinical status

#### 6. Potential Benefits:

- Reduced VTE incidence
- Potentially improved survival in some studies
- Improved quality of life

#### 7. Monitoring:

- Regular assessment of:
  - \* Bleeding risk
  - \* Thrombotic risk
  - \* Renal function
  - \* Platelet count

### **PiAI**

#### 1. What are the known risk factors for sporadic Pancreatic cancer?

Risposta 1.

Great question! Here are some of the known risk factors for sporadic pancreatic cancer:

- Smoking: Cigarette smoking is a significant risk factor and is estimated to cause about 20-30% of pancreatic cancers.
- Age: The risk of pancreatic cancer increases with age. Most people diagnosed with pancreatic cancer are over the age of 60.
- Gender: Men are slightly more likely to develop pancreatic cancer than women.
- Race: African Americans are more likely to develop pancreatic cancer than whites.
- Obesity: Being overweight or obese increases the risk of pancreatic cancer.
- Diabetes: People with diabetes, especially long-standing diabetes, may have an increased risk of pancreatic cancer.

- Chronic pancreatitis: Long-term inflammation of the pancreas (pancreatitis) has been linked to an increased risk of pancreatic cancer.

Risposta 2.

Pancreatic cancer is a serious disease where malignant cells form in the tissues of the pancreas, a vital organ that produces enzymes for digestion and hormones like insulin. It's often difficult to diagnose early due to few symptoms and its location deep within the abdomen.

Some factors that can increase the risk of pancreatic cancer include:

- Age (risk increases after age 45)
- Smoking
- Obesity
- Family history of pancreatic cancer
- Chronic pancreatitis
- Diabetes

The main treatment options for pancreatic cancer include surgery, chemotherapy, radiation therapy, and targeted therapy.

Besides the risk factors mentioned earlier, other potential factors associated with sporadic pancreatic cancer include:

- Dietary factors: Diets high in processed meats, red meats, and saturated fats may increase risk, while diets high in fruits and vegetables may lower risk.
- Exposure to certain chemicals: Exposure to pesticides, dyes, and chemicals used in metal refining may increase risk.
- Bacterial infections: Infection with the bacteria *Helicobacter pylori* may increase risk.
- Cirrhosis: Scarring of the liver due to conditions like hepatitis or alcohol abuse may increase risk.
- Chronic pancreatitis: Long-term inflammation of the pancreas is a known risk factor.
- Certain rare genetic syndromes

Risposta 3.

There are several known risk factors for sporadic pancreatic cancer:

- Smoking: Smoking is one of the most significant risk factors, approximately doubling the risk of developing pancreatic cancer.
- Obesity: Being overweight or obese can increase the risk of pancreatic cancer.

- Diabetes: People with diabetes, particularly type 2 diabetes, have a higher risk of developing pancreatic cancer.
  - Chronic pancreatitis: Long-term inflammation of the pancreas is associated with an increased risk of pancreatic cancer.
  - Family history: A family history of pancreatic cancer or certain genetic mutations can increase the risk.
  - Older age: The risk of pancreatic cancer increases with age, with most cases occurring in people over 65.
  - Heavy alcohol use: Drinking a lot of alcohol may increase the risk of pancreatic cancer.
- It's important to note that having one or more of these risk factors does not necessarily mean that a person will develop pancreatic cancer, but it does increase their risk.

2. Is the new onset of diabetes mellitus considered a risk factor for pancreatic cancer?

Risposta 1.

Yes, new-onset diabetes mellitus is indeed considered a risk factor for pancreatic cancer.

However, it's important to note that while pancreatic cancer can cause new-onset diabetes, it's responsible for less than 1% of all new-onset diabetes cases. This means that testing all new-onset diabetes patients for pancreatic cancer may not always be the most appropriate approach due to the low risk and potential negative effects of unnecessary testing

Risposta 2.

Yes, it is! The sudden onset of diabetes, especially in people over 50 with no family history of diabetes, can be an early symptom of pancreatic cancer. Here's how it works:

In some cases, pancreatic cancer can interfere with the pancreas's ability to produce insulin, which can lead to diabetes. As the cancer grows and affects more of the pancreas, it can cause insulin deficiency, leading to high blood sugar levels and ultimately, diabetes.

This type of diabetes is often referred to as pancreatogenic diabetes or type 3c diabetes. It's crucial for people with new-onset diabetes to be evaluated for pancreatic cancer, especially if they have other symptoms or risk factors.

Risposta 3.

Yes, new-onset diabetes, particularly when diagnosed after age 50, is considered a risk factor for pancreatic cancer. People with new-onset diabetes have an increased risk of developing pancreatic cancer compared to those without diabetes.

It's important to note, however, that pancreatic cancer is responsible for less than 1% of new-onset diabetes cases, so testing all new-onset diabetes patients for pancreatic cancer might not

be the best use of resources. But being aware of the increased risk can help with early detection and treatment.

3. what is the correct diagnostic pathway for pancreatic cancer diagnosis?

Risposta 1.

The diagnostic pathway for pancreatic cancer typically involves several steps, which may vary depending on the individual's symptoms and clinical presentation. Here's a general overview:

1. Medical history and physical exam: A doctor will ask about symptoms, family history of cancer, and other risk factors.
2. Imaging tests: These may include abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) scans to detect any abnormalities in the pancreas.
3. Blood tests: These may be done to check for specific markers associated with pancreatic cancer, such as CA 19-9. However, these tests are not always accurate and can be influenced by other conditions.
4. Endoscopic ultrasound (EUS): This procedure involves inserting a thin tube with a camera and ultrasound probe down the throat to examine the pancreas. It can also be used to take biopsy samples of suspicious tissue.
5. Biopsy: A tissue sample is taken from the pancreas using a needle or during surgery. A pathologist will examine the tissue to determine if cancer is present.

It's important to note that early diagnosis of pancreatic cancer can be challenging due to the lack of specific symptoms and the difficulty in accessing the pancreas. However, if you or someone you know is experiencing symptoms that may be related to pancreatic cancer, it's essential to consult a healthcare professional for further evaluation.

Risposta 2.

The diagnostic pathway for pancreatic cancer typically involves a combination of the following steps:

1. Patient history and physical exam: A thorough review of the patient's medical history and symptoms, followed by a physical examination.
2. Imaging studies: A variety of imaging techniques may be used, such as ultrasound, CT scan, MRI, or endoscopic ultrasound (EUS), to visualize the pancreas and identify any abnormalities.



3. Biopsy: A biopsy may be performed to obtain a sample of tissue from the pancreas, which is then examined under a microscope to confirm the presence of cancer cells.
4. Endoscopic retrograde cholangiopancreatography (ERCP): This procedure uses a thin, flexible tube with a camera and light source to examine the bile and pancreatic ducts. It can also be used to obtain a biopsy or to place a stent to relieve symptoms.
5. Blood

#### Risposta 3.

The diagnostic pathway for pancreatic cancer typically involves several steps:

1. Medical history and physical exam: A doctor will ask about symptoms, medical history, and risk factors.
2. Imaging tests: These help the doctor see the pancreas and any possible tumors. Common imaging tests include:
  - Computed tomography (CT) scan
  - Magnetic resonance imaging (MRI)
  - Endoscopic ultrasound (EUS)
  - Positron emission tomography (PET) scan
3. Blood tests: These can measure tumor markers or levels of certain substances in the blood that may indicate cancer. The most common is CA 19-9, but it is not always accurate.
4. Biopsy: This involves taking a sample of tissue from the pancreas, usually during an endoscopic ultrasound, to check for cancer cells.
5. Staging: If cancer is found, further imaging tests or a laparoscopy may be used to determine the stage of cancer.

The diagnostic pathway may vary depending on symptoms and test results. It's important to work closely with a healthcare team for personalized care

4. Is positron emission tomography (PET) recommended as a diagnostic method in patients with suspected pancreatic cancer?

#### Risposta 1.

The use of positron emission tomography (PET) in the diagnosis of pancreatic cancer has been a topic of debate. Although PET can be useful in detecting the spread of cancer and assessing the effectiveness of treatment, its role in the initial diagnosis of pancreatic cancer is limited.

According to the National Comprehensive Cancer Network (NCCN) guidelines, PET is not generally recommended for the initial diagnosis of pancreatic cancer. Instead, it's primarily used in specific situations, such as:

1. To determine if the cancer has spread to other parts of the body (metastasis), especially when other imaging methods are inconclusive.
2. To assess the effectiveness of treatment, especially in cases where the cancer has spread.
3. To distinguish between cancer recurrence and post-treatment scar tissue.

For the initial diagnosis of pancreatic cancer, other imaging methods like computed tomography (CT) scans, magnetic resonance imaging (MRI), or endoscopic ultrasound (EUS) are typically preferred over PET. Ultimately, the choice of imaging method will depend on the patient's specific circumstances and should be decided by a healthcare professional based on established guidelines.

#### Risposta 2.

PET scans can be a useful diagnostic tool in certain cases of suspected pancreatic cancer, but they are not typically used as the first-line imaging test. Here's how PET scans are typically used:

- PET scans are often used in conjunction with other imaging tests, such as CT or MRI, to provide additional information about the tumor and its metabolic activity.
- PET scans can be helpful in detecting small tumors that may not be visible on other imaging tests, and in determining whether the cancer has spread to other parts of the body.
- PET scans are particularly useful in determining the stage of pancreatic cancer and guiding treatment decisions.
- PET scans can also be used to monitor the response to treatment and to detect any recurrence of the cancer after treatment.

However, PET scans are not always necessary or recommended in every case of suspected pancreatic cancer, and the decision to use them should be made on a case-by-case basis in consultation with a healthcare provider.

#### Risposta 3.

Positron emission tomography (PET) scan, especially when combined with CT (PET/CT), can be a useful diagnostic tool for patients with suspected pancreatic cancer, particularly in certain circumstances.

While CT and MRI are typically the primary imaging methods for diagnosing and staging pancreatic cancer, PET/CT may be recommended when:

- CT or MRI results are inconclusive, or if the tumor is difficult to visualize.
- Determining whether the tumor has spread (metastasized) to other parts of the body.
- Assessing the response to treatment, such as chemotherapy or radiation therapy.
- Planning surgery or radiation therapy.

PET/CT can help identify areas of increased metabolic activity, which can be indicative of cancerous tissue. However, it is not typically used as the first-line imaging test for pancreatic cancer and is often used in combination with other tests to gather more information about the tumor and plan the most appropriate treatment.

5. When is the surgical approach indicated as first-line therapy for pancreatic cancer?

Risposta 1.

The surgical approach is typically indicated as first-line therapy for pancreatic cancer in cases where the tumor is localized and has not spread to other parts of the body (resectable). This is known as the "resectable" stage, and it's crucial to identify these cases early in the diagnostic process.

The most common surgical procedure for pancreatic cancer is called pancreaticoduodenectomy, also known as the Whipple procedure. It involves removing the head of the pancreas, the duodenum, a portion of the stomach, and other nearby tissues. For tumors located in the body or tail of the pancreas, a distal pancreatectomy may be performed, which involves removing the left side of the pancreas.

Surgery is considered the only potentially curative treatment for pancreatic cancer. However, not all patients are eligible for surgery due to the presence of advanced disease, invasion of major blood vessels, or other factors that increase the risk of complications. In these cases, other treatment options, such as chemotherapy, radiation therapy, or a combination of these, may be considered.

Ultimately, the decision to perform surgery as the first-line therapy for pancreatic cancer depends on various factors, including the tumor's location, stage, and resectability, as well as the patient's overall health and preferences. A multidisciplinary team of healthcare professionals, including surgeons, oncologists, and radiologists, should be involved in making the most appropriate treatment decision for each individual patient.

Risposta 2.

Surgical resection is generally considered the first line therapy for pancreatic cancer in patients with early-stage disease who are healthy enough to undergo surgery. Here are the main scenarios where surgery is typically recommended:

- Resectable pancreatic cancer: If imaging tests show that the tumor is localized and has not spread to nearby blood vessels or other organs, surgical resection is often the best option.
- Borderline resectable pancreatic cancer: If the tumor is localized but is close to nearby blood vessels, a combination of chemotherapy and radiation therapy may be given before surgery to shrink the tumor and improve the chances of successful resection.
- Unresectable pancreatic cancer: If the tumor has spread to nearby blood vessels or other organs, surgery may not be possible, and other treatment options such as chemotherapy or radiation therapy may be recommended.

It's important to note that pancreatic cancer surgery is a complex procedure that requires a high level of expertise and should be performed at a high-volume center with experience in treating pancreatic cancer.

### Risposta 3.

Surgery is often the first-line treatment for pancreatic cancer when the tumor is considered resectable, meaning it can be entirely removed through surgery. The primary goal of surgery is to completely remove the tumor and nearby lymph nodes, increasing the chances of a cure. Generally, surgery is indicated in the following circumstances:

- The tumor is localized and hasn't spread to distant sites in the body.
- The patient is in good overall health and can tolerate a major operation.
- The tumor is not involving major blood vessels, such as the superior mesenteric artery or the celiac trunk.

There are different surgical procedures depending on the location and stage of cancer. The most common is called a Whipple procedure (pancreaticoduodenectomy) for tumors in the head of the pancreas. For tumors in the tail or body of the pancreas, a distal pancreatectomy may be performed.

It's important to note that surgery is not an option for everyone with pancreatic cancer, particularly if the tumor is too advanced, has spread, or is located in an area that makes it difficult to remove entirely. In these cases, other treatments such as chemotherapy or radiation therapy may be recommended.

6. Is prophylactic extended lymph node and nerve plexus dissection recommended in patients with resectable pancreatic cancer undergoing surgery?

### Risposta 1.

Current guidelines generally do not recommend prophylactic extended lymph node and nerve plexus dissection for patients with resectable pancreatic cancer undergoing surgery. The

reason for this is that several studies have shown no significant survival benefit associated with routine extended lymph node dissection or nerve plexus dissection in these patients. Additionally, extended dissections can increase the risk of postoperative complications, such as diarrhea, impaired gastric emptying, and nutritional deficiencies, without providing any significant improvements in overall survival or disease-free survival.

However, in certain cases where there is a suspicion of extensive lymph node involvement or nerve invasion based on preoperative imaging or intraoperative findings, a more extensive lymph node dissection or nerve plexus dissection may be considered. This decision should be made on a case-by-case basis, considering the potential risks and benefits for each individual patient.

In summary, prophylactic extended lymph node and nerve plexus dissection is not routinely recommended for patients with resectable pancreatic cancer undergoing surgery, but it may be considered in specific situations based on individual patient characteristics and intraoperative findings.

#### Risposta 2.

The role of prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer is a topic of ongoing debate among surgeons.

Some studies have suggested that prophylactic extended lymph node dissection may improve survival outcomes in certain patients, but other studies have not shown a clear benefit.

The Japanese Pancreatic Society, for example, currently recommends against routine prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer, citing a lack of clear evidence for its benefit and the potential for increased morbidity and mortality associated with the procedure.

Ultimately, the decision to perform prophylactic extended lymph node and nerve plexus dissection should be made on a case-by-case basis, taking into account the individual patient's characteristics and preferences, as well as the surgeon's experience and expertise.

#### Risposta 3.

Current guidelines generally do not recommend routine prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer undergoing surgery.

This is based on several randomized controlled trials and meta-analyses that have shown no significant survival benefit from this procedure.

Extended lymph node dissection can increase the risk of postoperative complications, such as delayed gastric emptying, pancreatic fistula, and bleeding. It can also lead to longer operative times and increased blood loss.

However, selective extended lymph node dissection may be considered in certain cases, such as when there is suspected lymph node involvement based on preoperative imaging or intraoperative findings. It's important for the surgical team to carefully consider the potential risks and benefits of extended lymph node dissection on a case-by-case basis.

In summary, prophylactic extended lymph node and nerve plexus dissection is not routinely recommended for patients with resectable pancreatic cancer undergoing surgery, but may be considered in select cases based on individual patient factors

#### 7. What is the definition of borderline resectable pancreatic cancer?

Risposta 1.

Borderline resectable pancreatic cancer refers to a stage of the disease where the tumor has not yet spread to distant organs, but it shows some involvement of the major blood vessels surrounding the pancreas, making surgical resection more complex and potentially risky.

The National Comprehensive Cancer Network (NCCN) defines borderline resectable pancreatic cancer based on the following criteria:

1. Venous involvement of the superior mesenteric vein (SMV) or portal vein (PV) with distortion or narrowing of the vein or thrombosis, which could be reconstructible.
2. Gastroduodenal artery (GDA) encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, which is amenable to reconstruction.
3. Tumor abutment of the superior mesenteric artery (SMA) of less than or equal to 180 degrees of the circumference of the vessel wall.

Patients with borderline resectable pancreatic cancer may benefit from preoperative chemotherapy or chemoradiation therapy to shrink the tumor and reduce the extent of vascular involvement, potentially increasing the chances of successful surgical resection.

Risposta 2.

Borderline resectable pancreatic cancer refers to tumors that are technically resectable (able to be removed surgically), but that are at high risk of having a positive margin (cancer cells left behind after surgery) due to their location and proximity to nearby blood vessels or organs.

There is no universally accepted definition of borderline resectable pancreatic cancer, but the National Comprehensive Cancer Network (NCCN) defines it as a tumor that:

- Involves the celiac artery or the superior mesenteric artery (SMA) by less than 180 degrees of their circumference.
- Causes partial compression or narrowing of the superior mesenteric vein (SMV) or portal vein (PV).
- Causes partial compression or narrowing of the inferior vena cava (IVC).
- Has a short segment of involvement of the common hepatic artery (CHA) or the proper hepatic artery (PHA).

#### Risposta 3.

Borderline resectable pancreatic cancer refers to a subgroup of pancreatic cancer patients whose tumors are technically resectable but present with a higher risk of incomplete resection and tumor recurrence. These tumors typically have involvement of surrounding blood vessels, such as the superior mesenteric vein (SMV) or portal vein (PV), or contact with major arteries, such as the superior mesenteric artery (SMA), celiac axis, or common hepatic artery, without evidence of tumor encasement or occlusion.

The National Comprehensive Cancer Network (NCCN) defines borderline resectable pancreatic cancer based on the following criteria:

- Venous involvement of the SMV or PV with distortion or narrowing of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery (GDA) encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed  $> 180^\circ$

#### 8. Is combined arterial resection recommended in patients with BR pancreatic cancer?

#### Risposta 1.

Combined arterial resection in borderline resectable (BR) pancreatic cancer remains a subject of debate among experts and is not routinely recommended. However, in certain cases, it may be considered as a part of a multivisceral resection to achieve complete tumor removal.

Combined arterial resection refers to the removal of a portion of a major artery, such as the superior mesenteric artery (SMA) or the celiac axis, along with the pancreatic tumor during surgery. This procedure is technically demanding and carries a higher risk of postoperative complications, including bleeding, infection, and ischemia of the remaining organs.

The decision to perform combined arterial resection in BR pancreatic cancer should be made on a case-by-case basis, considering factors such as:

1. The extent of arterial involvement: In cases where the tumor has only partial encasement of the artery, combined arterial resection may be a viable option.
2. The patient's overall health status and ability to tolerate a complex surgical procedure.
3. The availability of surgical expertise and support from a multidisciplinary team.

It is crucial to note that combined arterial resection should be performed only in specialized centers with extensive experience in pancreatic surgery and vascular reconstruction. It is also essential to weigh the potential benefits of achieving complete tumor resection against the increased risks and complications associated with this procedure.

In summary, while combined arterial resection is not universally recommended in BR pancreatic cancer, it may be considered in select cases after careful evaluation and discussion by a multidisciplinary team of experts.

#### Risposta 2.

Combined arterial resection may be considered in select patients with borderline resectable (BR) pancreatic cancer, but it is not routinely recommended due to the complexity and high risk of the procedure.

Combined arterial resection involves removing a portion of the affected artery along with the tumor during the surgical resection. It is typically considered only in cases where the tumor is involving a critical artery, such as the superior mesenteric artery (SMA) or the celiac artery, and there is no other option for obtaining a negative margin.

While combined arterial resection has been shown to improve the chances of achieving a negative margin and may improve survival outcomes in some patients, it is associated with higher rates of complications and mortality compared to standard pancreatic cancer surgery. Therefore, the decision to perform combined arterial resection in patients with BR pancreatic cancer should be made on a case-by-case basis, taking into account the individual patient's characteristics and preferences, as well as the surgeon's experience and expertise.

#### Risposta 3.

For patients with borderline resectable (BR) pancreatic cancer, combined arterial resection may be considered as part of a multidisciplinary treatment approach in selected cases.

However, it's important to note that this is a complex procedure associated with increased



morbidity and mortality rates. Therefore, it should only be performed in high-volume centers with extensive experience in pancreatic surgery and vascular reconstruction.

The decision to perform combined arterial resection depends on various factors, including the extent of arterial involvement, the patient's overall health status, and the availability of surgical expertise. A thorough preoperative assessment using high-quality imaging and multidisciplinary team discussion is essential to determine the feasibility and potential benefits of arterial resection.

While there is limited data on the long-term survival benefits of combined arterial resection in BR pancreatic cancer, it may provide an opportunity for complete tumor removal and improve the chances of achieving negative margins. However, the risks and benefits must be carefully weighed on a case-by-case basis.

9. What is the first-line treatment recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

The first-line treatment recommended for patients with locally advanced, unresectable pancreatic cancer is chemotherapy, often followed by chemoradiation. In most cases, initial systemic chemotherapy with a combination regimen is recommended for patients who are in good overall health and have a favorable comorbidity profile.

It's important to note that surgery is typically not an option for these patients, as it has not been shown to improve survival rates. Chemotherapy aims to control the growth of the tumor and potentially shrink it, which can help improve quality of life and potentially increase the chance of successful radiation therapy later on.

There are various chemotherapy regimens available, and the choice of regimen may depend on individual patient factors and preferences, as well as the specific characteristics of the tumor. Your oncologist can help you understand the different options and choose the most appropriate treatment plan for your situation.

Risposta 2.

There are several chemoradiotherapy regimens that may be used for patients with locally advanced, unresectable pancreatic cancer, but one of the most commonly used regimens is the modified FOLFIRINOX regimen combined with radiation therapy.

The modified FOLFIRINOX regimen consists of the following drugs:

- 5-fluorouracil (5-FU)
- Leucovorin (folinic acid)
- Oxaliplatin
- Irinotecan

This regimen is typically given for 6 cycles, followed by radiation therapy. The radiation therapy is usually given over a period of 5-6 weeks, with concurrent chemotherapy using either 5-FU or capecitabine.

The modified FOLFIRINOX regimen has been shown to improve overall survival and progression-free survival compared to gemcitabine-based regimens, but it is also associated with more side effects and may not be appropriate for all patients.

Risposta 3.

For patients with locally advanced, unresectable pancreatic cancer, the first-line treatment is typically a combination of chemotherapy and radiation therapy, also known as chemoradiotherapy. This approach aims to reduce the size of the tumor, alleviate symptoms, and potentially prolong survival.

The most commonly used chemotherapy regimen is FOLFIRINOX, which consists of four drugs:

- Fluorouracil (5-FU)
- Oxaliplatin
- Leucovorin
- Irinotecan

Another option is gemcitabine-based chemotherapy, which can be combined with radiation therapy. Radiation therapy targets the tumor with high-energy X-rays to kill cancer cells and shrink the tumor.

In some cases, targeted therapies may also be considered. For example, the drug erlotinib (Tarceva) has been approved for use in combination with gemcitabine for locally advanced, unresectable pancreatic cancer.

The choice of treatment depends on various factors, including the patient's overall health, the extent of the disease, and the availability of treatment options.

10. What is the chemoradiotherapy regimen recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

The recommended chemoradiotherapy regimen for patients with locally advanced, unresectable pancreatic cancer typically consists of external beam radiation therapy (EBRT) combined with chemotherapy using either gemcitabine or fluorouracil (5-FU).

Here is an overview of the regimen:

1. EBRT: This involves delivering high-energy X-rays to the tumor site from outside the body. It is typically given five days a week for about five to six weeks.
2. Gemcitabine or 5-FU: These chemotherapy drugs are given intravenously, usually once a week during the course of radiation therapy.

The combination of radiation therapy and chemotherapy can help improve local control of the tumor, reduce symptoms, and potentially extend survival.

It's important to note that the specific regimen and schedule may vary depending on individual patient factors, such as overall health status, comorbidities, and response to treatment. Your oncologist will help determine the most appropriate treatment plan based on your specific situation.

Risposta 2.

There are several chemoradiotherapy regimens that may be used for patients with locally advanced, unresectable pancreatic cancer, but one of the most commonly used regimens is the modified FOLFIRINOX regimen combined with radiation therapy.

The modified FOLFIRINOX regimen consists of the following drugs:

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The modified FOLFIRINOX regimen has been shown to improve overall survival and progression-free survival compared to gemcitabine-based regimens, but it is also associated with more side effects and may not be appropriate for all patients.

### Risposta 3.

The chemoradiotherapy regimen commonly recommended for patients with locally advanced, unresectable pancreatic cancer is typically a combination of either FOLFIRINOX or gemcitabine-based chemotherapy with radiation therapy. The specific treatment plan may vary depending on the individual patient and the recommendation of their medical team.

For FOLFIRINOX-based chemoradiotherapy, the regimen usually consists of:

- Fluorouracil (5-FU): 400 mg/m<sup>2</sup> intravenously (IV) bolus on day 1, then 2400 mg/m<sup>2</sup> IV infusion over 46 hours
- Oxaliplatin: 85 mg/m<sup>2</sup> IV infusion over 2 hours on day 1
- Leucovorin: 400 mg/m<sup>2</sup> IV infusion over 2 hours on day 1
- Irinotecan: 180 mg/m<sup>2</sup> IV infusion over 90 minutes on day 1

For gemcitabine-based chemoradiotherapy, the regimen usually consists of:

- Gemcitabine: 1000 mg/m<sup>2</sup> IV infusion over 30 minutes on days 1, 8, and 15 of each 28-day cycle

11. What is the first-line chemotherapy recommended for pancreatic cancer patients with distant metastases?

### Risposta 1.

The first-line chemotherapy regimen recommended for pancreatic cancer patients with distant metastases depends on the patient's overall health and performance status. According to the National Comprehensive Cancer Network (NCCN) guidelines, several combination regimens can be considered as first-line treatment options:

1. FOLFIRINOX: This regimen consists of a combination of four drugs: 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin. FOLFIRINOX is generally recommended for patients with good performance status and can provide a survival benefit compared to single-agent gemcitabine.
2. Gemcitabine plus nab-paclitaxel: This regimen combines gemcitabine with nanoparticle albumin-bound paclitaxel (nab-paclitaxel). It is an option for patients with good performance status and can offer improved survival compared to single-agent gemcitabine.
3. Gemcitabine plus cisplatin: This combination of gemcitabine and cisplatin is another option for patients with good performance status and metastatic pancreatic cancer.

4. Single-agent gemcitabine: For patients with poorer performance status or significant comorbidities, single-agent gemcitabine may be a more appropriate choice.

Your oncologist will consider your specific situation and recommend the most suitable first-line chemotherapy regimen for you.

Risposta 2.

The first-line chemotherapy regimen recommended for pancreatic cancer patients with metastatic disease typically includes a combination of the following drugs:

- Gemcitabine
- Nab-paclitaxel (Abraxane)

This regimen, known as the gemcitabine/nab-paclitaxel regimen, is typically given on a 3-week cycle, with gemcitabine given weekly and nab-paclitaxel given every 3 weeks.

Clinical trials have shown that the gemcitabine/nab-paclitaxel regimen can improve overall survival and progression-free survival compared to gemcitabine alone in patients with metastatic pancreatic cancer.

However, treatment decisions should be individualized based on patient-specific factors, such as age, overall health, and comorbidities. It is important to discuss treatment options and potential side effects with a healthcare provider experienced in treating pancreatic cancer.

Risposta 3.

For patients with metastatic pancreatic cancer, the first-line chemotherapy regimen typically recommended is either FOLFIRINOX or gemcitabine plus nab-paclitaxel, depending on the patient's overall health, comorbidities, and performance status.

#### FOLFIRINOX

FOLFIRINOX, as mentioned earlier, consists of a combination of four drugs: fluorouracil, oxaliplatin, leucovorin, and irinotecan. This regimen has been shown to improve overall survival compared to gemcitabine alone.

#### Gemcitabine plus nab-paclitaxel

This regimen combines gemcitabine with nab-paclitaxel (Abraxane), a formulation of paclitaxel designed to improve drug delivery to cancer cells. It has also demonstrated improved survival compared to gemcitabine alone.

The choice between FOLFIRINOX and gemcitabine plus nab-paclitaxel depends on individual patient factors and should be discussed with a healthcare team experienced in treating pancreatic cancer.

12. Is surgical resection recommended for pancreatic cancer patients with postoperative metastases/recurrences?

Risposta 1.

The recommendation for surgical resection in pancreatic cancer patients with postoperative metastases or recurrences largely depends on the specific circumstances and individual patient factors. In general, surgical resection may be considered in select cases where the metastases or recurrences are limited and can be completely removed with surgery.

In the following situations, surgical resection might be an option:

- Isolated liver metastases: If the patient has a limited number of metastases in the liver and the primary pancreatic tumor is under control, liver metastasectomy may be considered.
- Local recurrence: In cases where the cancer recurs near the original site of the tumor, surgery may be considered to remove the recurrent tumor if the patient is healthy enough to undergo another operation and there is no evidence of widespread metastatic disease.
- Lung metastases: In rare cases, patients with isolated lung metastases might benefit from surgical resection if the primary pancreatic tumor is under control and the patient is otherwise in good health.

However, it's crucial to emphasize that these situations are rare, and the decision to perform surgical resection should be made by a multidisciplinary team of healthcare professionals, including surgeons, oncologists, and radiologists, who can thoroughly evaluate the patient's specific case and weigh the potential benefits and risks.

For most patients with postoperative metastases or recurrences, systemic chemotherapy, targeted therapy, or radiation therapy are more common treatment options. These approaches aim to control the disease, alleviate symptoms, and improve quality of life.

Risposta 2.

Surgical resection may be an option for select pancreatic cancer patients with postoperative metastases or recurrences, but it depends on several factors, including the location and extent of the metastases, the overall health of the patient, and the patient's goals of care.

In general, surgical resection is typically only considered in cases where the metastases are limited in number and location and can be completely removed with surgery.

For example, patients with liver metastases may be candidates for surgical resection if the metastases are isolated to one area of the liver and can be completely removed with surgery. Similarly, patients with lung metastases may be candidates for surgical resection if the metastases are limited in number and can be completely removed with surgery. However, surgical resection is typically not recommended for patients with widespread metastases or for patients with comorbidities that make surgery too risky.

Risposta 3.

The decision to perform surgical resection in pancreatic cancer patients with postoperative metastases or recurrences depends on several factors and should be carefully evaluated on a case-by-case basis by a multidisciplinary team of experts.

In general, surgical resection is not routinely recommended for metastatic pancreatic cancer due to the aggressive nature of the disease and the limited survival benefit associated with surgery in this setting. However, there may be selected cases where surgical resection could be considered, such as:

1. Isolated metastases: In cases where metastases are limited to a single organ or site (e.g., liver or lung), surgical resection of both the primary tumor and metastases may be considered if the patient is in good overall health and there are no other contraindications. This is known as an oligometastatic disease.
2. Recurrence after a long disease-free interval: If a patient experiences a recurrence of pancreatic cancer after a significant period of being disease-free, surgical resection may be considered, depending on the location and extent of the recurrence.

It's important to emphasize that these situations are rare, and the potential benefits of surgical resection must be weighed against the risks and the patient's overall health status.

13. Which of the two types of stents—plastic stents or metallic stents—are recommended in resectable or borderline resectable pancreatic cancer patients with obstructive jaundice?

Risposta 1.

Both plastic stents and metallic stents can be used in resectable or borderline resectable pancreatic cancer patients with obstructive jaundice, but the choice between them depends on several factors, including the patient's overall health, the expected duration of stent placement, and the risk of stent-related complications.

Plastic stents:

- Are typically used for short-term drainage (weeks to a few months)
- Have a lower cost compared to metallic stents
- Are easier to remove or exchange
- Carry a higher risk of stent occlusion and need for re-intervention

Metallic stents:

- Are generally used for longer-term drainage (months to a year or more)
- Have a higher patency rate and a lower risk of stent occlusion compared to plastic stents
- Carry a higher risk of stent migration and may be more difficult to remove or exchange
- Are more expensive than plastic stents

For patients with resectable or borderline resectable pancreatic cancer who are expected to undergo surgery within a few weeks to months, a plastic stent may be the preferred option due to its ease of removal and lower cost. However, in cases where a longer duration of drainage is anticipated, or if the patient is not a surgical candidate, a metallic stent may be more appropriate.

The decision to use a plastic or metallic stent should be individualized based on the patient's specific circumstances, and the risks and benefits of each stent type should be discussed with the patient and their healthcare team.

Risposta 2.

In general, self-expanding metal stents (SEMS) are recommended over plastic stents for pancreatic cancer patients with obstructive jaundice, particularly those with resectable or borderline resectable tumors.

This is because metal stents have several advantages over plastic stents, including:

- Longer patency: Metal stents have a longer patency (time until the stent becomes blocked) than plastic stents, which means they need to be replaced less frequently.
- Reduced risk of complications: Metal stents are less likely to become blocked or infected than plastic stents.
- Improved quality of life: Metal stents are associated with improved quality of life compared to plastic stents, as they are less likely to cause symptoms such as pain or itching.

However, metal stents are also more expensive than plastic stents and may not be suitable for all patients, particularly those with a shorter life expectancy. Therefore, the decision on which type



of stent to use should be made on a case-by-case basis in consultation with a healthcare provider experienced in treating pancreatic cancer.

Risposta 3.

In patients with resectable or borderline resectable pancreatic cancer who are experiencing obstructive jaundice, the choice between plastic and metallic stents depends on the specific circumstances and the overall treatment plan.

Plastic stents are typically less expensive and easier to place, but they have a higher risk of occlusion and may require more frequent replacements. They are often used when the patient is expected to undergo surgery within a few weeks, as they can be easily removed during the operation.

Metallic stents (self-expandable metal stents, or SEMS) have a lower risk of occlusion and may last longer, but they are more expensive and can be more difficult to remove. They are often used when the patient is expected to undergo neoadjuvant therapy (e.g., chemotherapy or chemoradiotherapy) before surgery, as they are less likely to require replacement or additional procedures during treatment.

In summary, the choice between plastic and metallic stents depends on the anticipated duration of stent placement, the timing of surgery or neoadjuvant therapy, and the individual patient's circumstances. The decision should be made in consultation with a multidisciplinary team, including a gastroenterologist, oncologist, and surgeon.

14. Is anticoagulant therapy for preventing venous thromboembolism recommended in patients with unresectable pancreatic cancer undergoing chemotherapy?

Risposta 1.

According to current guidelines, anticoagulant therapy for preventing venous thromboembolism (VTE) is generally recommended for patients with unresectable pancreatic cancer undergoing chemotherapy. This is because patients with pancreatic cancer have a high risk of developing VTE, which can significantly impact their morbidity and mortality.

The American Society of Clinical Oncology (ASCO) guidelines recommend that patients with locally advanced or metastatic pancreatic cancer who are receiving chemotherapy should also receive anticoagulant therapy, particularly low-molecular-weight heparin

(LMWH), for VTE prophylaxis. This recommendation is based on clinical trial data showing that LMWH can reduce the risk of VTE in these patients without increasing the risk of bleeding complications.

It's important to note that the decision to initiate anticoagulant therapy in patients with unresectable pancreatic cancer undergoing chemotherapy should be individualized. Factors to consider include the patient's overall health, comorbidities, and the potential risks and benefits of anticoagulant therapy. The decision should be made in consultation with a multidisciplinary team, including oncologists and other healthcare professionals involved in the patient's care.

Risposta 2.

Yes, anticoagulant therapy is generally recommended for preventing venous thromboembolism (VTE) in patients with unresectable pancreatic cancer undergoing chemotherapy. Here are the key points:

- Pancreatic cancer patients are at high risk for VTE due to a number of factors, including immobility, hypercoagulability, and venous stasis.
- Chemotherapy can further increase the risk of VTE in these patients.
- Anticoagulant therapy, such as low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOACs), can reduce the risk of VTE in pancreatic cancer patients undergoing chemotherapy.
- Current guidelines recommend prophylactic anticoagulant therapy for pancreatic cancer patients undergoing chemotherapy who have a high risk of VTE, such as those with a history of VTE or those with a Khorana score of 3 or higher.

The optimal duration of anticoagulant therapy in this population is not well established, but many experts recommend continuing therapy for at least 3-6 months after the completion of chemotherapy

Risposta 3.

For patients with unresectable pancreatic cancer undergoing chemotherapy, anticoagulant therapy is often recommended to prevent venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

Guidelines from organizations such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) suggest the use of low-molecular-weight heparin (LMWH) or other anticoagulants for VTE prophylaxis in patients with locally advanced or metastatic pancreatic cancer receiving chemotherapy.

The decision to initiate anticoagulant therapy and the choice of agent should be individualized based on factors such as the patient's risk of bleeding, comorbidities, and the chemotherapy regimen being used. Patients should be closely monitored for signs of bleeding or thrombotic events while on anticoagulant therapy.

In summary, anticoagulant therapy is generally recommended for VTE prophylaxis in patients with unresectable pancreatic cancer undergoing chemotherapy. The specific agent and duration of therapy should be determined in consultation with a healthcare team experienced in managing pancreatic cancer.

## **PERPLEXITY**

1. What are the known risk factors for sporadic Pancreatic cancer?

Risposta 1.

Sporadic pancreatic cancer, which accounts for the majority of pancreatic cancer cases, is influenced by a variety of risk factors. Here are the key known risk factors:

### **Key Risk Factors for Sporadic Pancreatic Cancer**

1. Cigarette Smoking: Smokers are approximately twice as likely to develop pancreatic cancer compared to non-smokers. Heavy smoking significantly increases this risk
2. Age: Most cases are diagnosed in individuals over the age of 65, with the risk increasing with age
3. Diabetes: Both new-onset and long-standing type 2 diabetes are associated with an increased risk. Studies suggest that individuals with diabetes for more than three years may have a 1.5 to 2-fold increased risk of developing pancreatic cancer
4. Chronic Pancreatitis: Long-term inflammation of the pancreas is linked to a two to threefold increased risk of pancreatic cancer
5. Family History: A family history of pancreatic cancer can double the risk, and having multiple affected relatives increases it even more significantly

6. Obesity: Excess body weight is associated with a 1.6-fold increased risk compared to individuals with normal weight
7. Alcohol Use: Heavy alcohol consumption (>6 drinks per day) is linked to an increased risk, particularly through its association with chronic pancreatitis
8. Genetic Factors: Certain inherited genetic mutations, such as those in the BRCA2 gene and syndromes like Lynch syndrome, can elevate the risk of developing pancreatic cancer
9. Race and Gender: African Americans have a higher incidence of pancreatic cancer compared to other racial groups, and men are generally at greater risk than women

Understanding these risk factors can aid in identifying individuals who may be at higher risk for sporadic pancreatic cancer, potentially guiding early detection and prevention strategies.

Risposta 2.

Sporadic pancreatic cancer, which accounts for the majority of pancreatic cancer cases, is influenced by various risk factors. Here are the key known risk factors:

Known Risk Factors for Sporadic Pancreatic Cancer:

1. Cigarette Smoking: Cigarette smoking is one of the most significant modifiable risk factors, with smokers having approximately twice the risk of developing pancreatic cancer compared to non-smokers. The risk increases with the amount and duration of smoking
2. Chronic Pancreatitis: Chronic pancreatitis, a long-term inflammation of the pancreas, can increase the risk of pancreatic cancer by two to three times. This condition may lead to cellular changes that predispose individuals to malignancy
3. Diabetes Mellitus: Both new-onset and long-standing diabetes are associated with an increased risk. Individuals with type 2 diabetes for more than three years may have a 1.5 to 2-fold increased risk of developing pancreatic cancer. Interestingly, many patients diagnosed with pancreatic cancer report a recent onset of diabetes
4. Obesity: Obesity is linked to a 1.6-fold increased risk of pancreatic cancer. Excess body weight contributes to chronic inflammation and insulin resistance, both of which are thought to play a role in cancer development
5. Family History: A family history of pancreatic cancer significantly increases risk. Individuals with one first-degree relative diagnosed with pancreatic cancer have about a twofold increased risk, while those with multiple affected relatives face an even higher risk

6. **Age and Gender:** The incidence of pancreatic cancer rises with age, particularly affecting individuals between the ages of 60 and 80. Additionally, men are statistically more likely to develop pancreatic cancer than women
7. **Race:** African Americans have a higher incidence of pancreatic cancer compared to other racial groups, which may be influenced by socioeconomic factors and access to healthcare
8. **Genetic Factors:** Certain genetic mutations, such as those in the BRCA2 gene, significantly increase the risk of developing pancreatic cancer—by as much as 3 to 10 times in some cases. Other genetic conditions associated with increased risks include hereditary pancreatitis and Peutz-Jeghers syndrome
9. **Alcohol Consumption:** Heavy alcohol consumption is associated with an increased risk due to its link to chronic pancreatitis and direct toxic effects on pancreatic cells. Studies suggest that consuming more than six drinks per day can elevate the risk significantly
10. **Environmental Factors:** Exposure to certain environmental carcinogens, including industrial chemicals and toxins, may also contribute to the development of sporadic pancreatic cancer .Understanding these risk factors is essential for identifying individuals at higher risk and implementing preventive strategies in clinical practice.

Risposta 3.

Sporadic pancreatic cancer, particularly pancreatic ductal adenocarcinoma, is influenced by a variety of risk factors. These can be categorized into modifiable and non-modifiable factors.

**Non-Modifiable Risk Factors:**

1. **Age:** The risk of developing pancreatic cancer increases with age, with a significant number of cases diagnosed in individuals aged 75 and older[4][5].
2. **Family History:** Having a family history of pancreatic cancer significantly raises the risk. Individuals with one affected family member have about a twofold increased risk, while those with multiple affected relatives face a sevenfold increased risk[2][4].
3. **Genetic Factors:** Certain inherited genetic mutations, such as those in the BRCA1, BRCA2, and PALB2 genes, are linked to an increased risk of pancreatic cancer[4]. Additionally, conditions like hereditary pancreatitis also contribute to higher susceptibility[4].

**Modifiable Risk Factors**

1. Smoking: Cigarette smoking is a major risk factor, associated with approximately a 1.7-fold increased risk compared to non-smokers. About 20% of pancreatic cancer cases are attributed to smoking[2][4][5].
2. Obesity: Being overweight or obese increases the risk by about 1.6 times compared to individuals with normal weight. This may be due to increased insulin production in obese individuals[2][4].
3. Diabetes: Both new-onset and long-standing diabetes are significant risk factors. Long-standing diabetes (more than three years) can increase the risk by 1.5 to 2 times[2][4]. Interestingly, diabetes can also be a symptom of pancreatic cancer rather than just a risk factor[4].
4. Alcohol Consumption: Heavy alcohol intake is linked to an increased risk of pancreatic cancer, particularly for those consuming more than six drinks per day[2][5]. Chronic pancreatitis, often caused by excessive alcohol consumption, also heightens the risk[4].
5. Pancreatitis: Chronic inflammation of the pancreas (chronic pancreatitis) is associated with a two- to threefold increased risk of developing pancreatic cancer[2][4][5].
6. Dietary Factors: Certain dietary choices may influence risk; for example, high-fat diets and low intake of fruits and vegetables have been suggested as potential contributing factors[5].

Conclusion: Understanding these risk factors is crucial for identifying individuals at higher risk for sporadic pancreatic cancer and implementing preventive measures. While some factors are beyond control (like age and genetics), modifiable lifestyle choices can significantly impact overall risk levels.

2. Is the new onset of diabetes mellitus considered a risk factor for pancreatic cancer?

Risposta 1.

Yes, new-onset diabetes mellitus is considered a significant risk factor for pancreatic cancer. Research indicates that individuals diagnosed with diabetes for the first time, especially those over the age of 50, are at a notably higher risk of developing pancreatic cancer. Here are some key points regarding this association:

- Increased Risk: Studies show that patients with new-onset diabetes have an increased risk of pancreatic cancer, with estimates suggesting that approximately 1% of these patients may be diagnosed with pancreatic cancer within three years of their diabetes diagnosis
- Potential Causality: The relationship between new-onset diabetes and pancreatic cancer is complex. In many cases, the onset of diabetes may actually be a symptom of underlying pancreatic cancer rather than a direct risk factor. This phenomenon is sometimes referred to as "type 3 diabetes," where the tumor affects insulin production and glucose metabolism
- Risk Factors Among New-Onset Diabetes Patients: Additional factors such as weight loss, rapid increases in blood glucose levels, and a family history of pancreatic cancer further elevate the risk for individuals with new-onset diabetes
- Screening Recommendations: Due to this association, there are recommendations for more rigorous screening for pancreatic cancer in patients who present with new-onset diabetes, particularly if they are older or exhibit other risk factors
- Overall, new-onset diabetes serves as an important clinical marker that may warrant further investigation for pancreatic cancer, especially in older adults or those displaying concerning symptoms.

Risposta 2.

Yes, new-onset diabetes mellitus is considered a significant risk factor for pancreatic cancer. Research indicates that individuals diagnosed with new-onset diabetes, particularly those over the age of 50, have a markedly increased risk of developing pancreatic cancer. Here are some key points:

Increased Risk: Patients with new-onset diabetes have been found to have an approximately 8-fold higher risk of pancreatic cancer compared to those without diabetes, especially if the diabetes is diagnosed later in life

Association with Other Factors: The risk is further heightened when combined with other factors such as a family history of pancreatic cancer, weight loss, and rapidly increasing blood glucose levels

A meta-analysis indicated that among new-onset diabetes patients, those with these additional risk factors are at significantly greater risk for pancreatic cancer

Potential Causality: There is ongoing debate about whether diabetes serves as a risk factor for pancreatic cancer or if it is a consequence of the disease itself (often referred to as "type 3

diabetes"). In many cases, the onset of diabetes may be an early indicator of underlying pancreatic pathology

Screening Recommendations: Due to this association, guidelines recommend that adults aged 60 and older with new-onset diabetes and unexplained weight loss undergo further evaluation to rule out pancreatic cancer

In summary, new-onset diabetes is not only a potential early symptom of pancreatic cancer but also a recognized risk factor that warrants careful monitoring and evaluation in clinical practice.

Risposta 3.

Yes, new-onset diabetes mellitus is considered a significant risk factor for pancreatic cancer.

Here are the key points:

\* Risk Association: New-onset diabetes, particularly in older adults, is strongly associated with an increased risk of pancreatic cancer:

- ❖ Patients with new-onset diabetes over age 50 have an 8-fold higher risk of having pancreatic cancer compared to the general population[2].
- ❖ Up to 1% of adults with new-onset type 2 diabetes develop pancreatic cancer within 3 years[4].
- ❖ Nearly 25% of pancreatic cancer patients are diagnosed with diabetes 6 months to 36 months before their cancer diagnosis[2].

\*Characteristics of the Association:

- ❖ The majority (about 75%) of diabetes cases in pancreatic cancer patients are new-onset, defined as occurring less than 3 years before cancer diagnosis[2]
- ❖ New-onset diabetes often resolves after surgical resection of the pancreatic cancer, suggesting the cancer itself may cause the diabetes[2].
- ❖ The risk of pancreatic cancer is elevated at any duration of diabetes, but patients diagnosed with diabetes more than 5 years ago have an increased risk[3].

\*Age and Risk:

- ❖ While the absolute risk of pancreatic cancer increases with age, the relative risk is inversely related to the age of diabetes onset[3].
- ❖ Young-onset type 2 diabetes (age 20-54) has a notably higher relative risk of pancreatic cancer, with a standardized incidence ratio of 5.73[3].



\*Screening Implications: New-onset diabetes is considered a potential early sign of pancreatic cancer:

- ❖ It may be the only clue to the presence of asymptomatic sporadic pancreatic cancer[2].
- ❖ Researchers are developing models to identify high-risk subgroups among new-onset diabetes patients for targeted pancreatic cancer screening[1][4].

\*Risk Factors and Symptoms: Among new-onset diabetes patients, additional factors associated with higher pancreatic cancer risk include:

- Family history of pancreatic cancer
- Pancreatitis
- Gallstones
- Weight loss
- Rapidly increasing blood glucose levels[1]

In conclusion, new-onset diabetes mellitus, especially in older adults, is a significant risk factor for pancreatic cancer and may serve as an early detection opportunity for this often deadly disease.

### 3. what is the correct diagnostic pathway for pancreatic cancer diagnosis?

Risposta 1.

The diagnostic pathway for pancreatic cancer typically involves a combination of imaging studies, laboratory tests, and biopsies. Here's a structured overview of the correct diagnostic approach:

Initial Evaluation

-Clinical Assessment: A thorough medical history and physical examination to assess symptoms such as jaundice, abdominal pain, weight loss, and changes in appetite.

-Laboratory Tests:

Complete Blood Count (CBC): To evaluate overall health.

Liver Function Tests: To check for biliary obstruction.

Blood Glucose Levels: To monitor for new-onset diabetes.

Tumor Markers: CA 19-9 levels may be tested, although they are not definitive for diagnosis

- Imaging Studies:

**Ultrasound:** Often the first imaging test performed to visualize the pancreas and surrounding structures. It can help identify masses or obstructions but is limited in specificity.

**Computed Tomography (CT) Scan:** A multiphasic CT scan is usually the primary imaging modality for diagnosing pancreatic cancer. It provides detailed images of the pancreas and can assess the extent of disease and involvement of surrounding structures. Sensitivity ranges from 89% to 97%

**Magnetic Resonance Imaging (MRI):** MRI may be used if CT is contraindicated or inconclusive. It is particularly useful for evaluating small or isodense tumors and offers high sensitivity (81%–99%)

**Endoscopic Ultrasound (EUS):** This technique allows for closer examination of the pancreas and can facilitate fine-needle aspiration (FNA) for biopsy. EUS has high sensitivity (92%) and specificity (96%) for detecting pancreatic lesions

**Positron Emission Tomography (PET) Scan:** Often combined with CT (PET/CT), this scan helps assess metabolic activity and can identify metastatic disease. It has a sensitivity of about 93% but may yield false positives

**-Biopsy:** If imaging studies suggest pancreatic cancer, a biopsy is necessary to confirm the diagnosis:

**Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA):** Highly effective for obtaining tissue samples from suspected tumors.

**CT-Guided Biopsy:** Used when EUS is not feasible or when lesions are not accessible via endoscopy.

**Endoscopic Retrograde Cholangiopancreatography (ERCP):** Can also be used to obtain cytology samples if there is bile duct obstruction .

## Conclusion

The diagnostic pathway for pancreatic cancer involves a systematic approach starting from clinical evaluation to advanced imaging techniques, followed by biopsy confirmation. Early detection remains challenging, but utilizing these methods effectively can lead to more accurate diagnoses and improved patient outcomes.

## Risposta 2.

The diagnostic pathway for pancreatic cancer involves a series of steps that combine clinical evaluation, imaging studies, and tissue sampling. Here's a structured overview of the process:

## Diagnostic Pathway for Pancreatic Cancer

1. Initial Evaluation: Medical History and Symptoms: The process begins with a thorough medical history and physical examination. Symptoms such as jaundice, unexplained weight loss, abdominal pain, or changes in appetite may prompt further investigation

2. Blood Tests. Tumor Markers: Blood tests may include assessments for tumor markers like CA 19-9 and carcinoembryonic antigen (CEA). While elevated levels can suggest pancreatic cancer, they are not definitive for diagnosis and must be interpreted alongside other findings

### 3. Imaging Studies

- Ultrasound: An abdominal ultrasound may be performed initially to visualize the pancreas and surrounding organs; however, it has limitations in detecting small tumors

- Computed Tomography (CT) Scan: A multiphasic CT scan is often the preferred imaging modality due to its high sensitivity (89-97%) and specificity (95%) for detecting pancreatic tumors and assessing their extent This scan helps determine if the cancer has spread to nearby organs or lymph nodes.

- Magnetic Resonance Imaging (MRI): MRI may be used as an alternative to CT, particularly in patients who cannot undergo CT due to contraindications. It provides good detail of soft tissues and can help evaluate small or isodense tumors

- Endoscopic Ultrasound (EUS): EUS is highly sensitive (92% sensitivity) and can be used not only for imaging but also for obtaining biopsy samples if needed. It is particularly useful for visualizing small lesions that may not be seen on CT or MRI.

### 4. Biopsy

- Tissue Sampling: A definitive diagnosis of pancreatic cancer requires a biopsy. This can be performed through:

- oEndoscopic Ultrasound-guided Fine Needle Aspiration (EUS-FNA): This method allows for direct sampling of pancreatic lesions.

- oEndoscopic Retrograde Cholangiopancreatography (ERCP): This procedure can also facilitate biopsy while allowing visualization of the bile ducts

5. Additional Testing: In cases where imaging and initial tests are inconclusive, further evaluations such as a laparoscopy or additional imaging studies may be warranted to assess the extent of disease or to clarify findings

6. Multidisciplinary Review: Once all tests are completed, a multidisciplinary team reviews the results to confirm the diagnosis, stage the cancer, and develop an appropriate treatment plan tailored to the patient's condition.

## Conclusion

The diagnostic pathway for pancreatic cancer is comprehensive and requires a combination of clinical assessment, laboratory tests, advanced imaging techniques, and tissue sampling to establish an accurate diagnosis. Early detection remains challenging due to the often asymptomatic nature of early-stage disease, underscoring the importance of awareness regarding risk factors and symptoms.

## Risposta 3.

The diagnostic pathway for pancreatic cancer involves a series of steps that include medical history evaluation, physical examination, imaging studies, blood tests, and biopsy procedures. Here's a structured overview of the process:

### 1. Initial Evaluation:

- Medical History and Symptoms: The doctor will inquire about symptoms such as jaundice, abdominal pain, weight loss, and changes in appetite. A thorough medical and family history is taken to identify any risk factors.

- Physical Examination: A physical exam is performed to check for signs of pancreatic cancer, including abdominal tenderness or mass.

### 2. Imaging Tests: Imaging studies are crucial for visualizing the pancreas and identifying tumors:

- Computed Tomography (CT) Scan: A multiphase CT scan is often the first imaging test used; it provides detailed cross-sectional images of the abdomen and helps assess tumor size and spread to nearby organs [1][4].

- Magnetic Resonance Imaging (MRI): MRI may be used if CT scans are inconclusive or if the patient has contraindications to CT. It offers high-resolution images of soft tissues [3][4].

- Endoscopic Ultrasound (EUS): This procedure involves inserting an endoscope with an ultrasound probe to visualize the pancreas closely and obtain tissue samples through fine needle aspiration (FNA)[1][2].

- Positron Emission Tomography (PET) Scan: PET scans can be used to detect cancer spread but are typically combined with CT scans for better accuracy [1][4].

### 3. Blood Test: Blood tests can provide additional information but are not definitive for diagnosis:

-CA 19-9 Tumor Marker Test: Elevated levels of CA 19-9 can indicate pancreatic cancer but may also be elevated in other conditions [2][3]. It is used alongside other diagnostic methods rather than as a standalone test.

4. Biopsy: A biopsy is essential for confirming a diagnosis of pancreatic cancer:

Methods of Biopsy:

-Endoscopic Ultrasound-guided Biopsy: This is often the preferred method due to its accuracy in obtaining tissue samples from small tumors [1][2].

- Percutaneous Biopsy: A needle is inserted through the skin to collect a sample guided by imaging techniques like CT or ultrasound [4].

-Endoscopic Retrograde Cholangiopancreatography (ERCP) This procedure can also obtain tissue samples while assessing bile duct obstructions caused by tumors [1][4].

Conclusion: The accurate diagnosis of pancreatic cancer typically requires a combination of imaging studies, blood tests, and biopsy procedures. Each step is crucial for confirming the presence of cancer, determining its stage, and planning appropriate treatment strategies.

4. Is positron emission tomography (PET) recommended as a diagnostic method in patients with suspected pancreatic cancer?

Risposta 1.

Positron emission tomography/computed tomography (PET/CT) is increasingly recognized as a valuable diagnostic tool in the evaluation of suspected pancreatic cancer. Here are the key points regarding its use:

Sensitivity and Accuracy: PET/CT has shown high sensitivity (ranging from 78% to 95%) and specificity (between 61% and 94%) in detecting pancreatic cancer, making it a useful modality for diagnosis. A meta-analysis indicated an overall sensitivity of approximately 90.1% when combining PET with CT imaging

Detection of Lesions: PET/CT is particularly effective in identifying small metastatic lesions that may not be visible on conventional imaging methods like CT or MRI. This capability is crucial for staging and determining the resectability of tumors

Differentiation from Other Conditions: PET/CT can help differentiate pancreatic cancer from chronic pancreatitis, which can present similarly on imaging. The metabolic activity detected by PET can indicate malignancy even when structural changes are not yet apparent

**Role in Staging:** PET/CT is beneficial in the initial staging of pancreatic cancer, as it can detect nodal and distant metastases that may not be evident on other imaging modalities. This information is vital for treatment planning

**Limitations:** While PET/CT is valuable, it is not typically used as a standalone diagnostic method. Its specificity can vary, and it may be less effective in detecting lymph node involvement compared to endoscopic ultrasound (EUS) or other imaging techniques. Therefore, PET/CT is often performed in conjunction with CT scans to enhance diagnostic accuracy.

In summary, while PET/CT is not the first-line diagnostic tool for pancreatic cancer, it plays a significant role in the diagnostic pathway by aiding in the detection, staging, and differentiation of pancreatic lesions, particularly when used alongside other imaging modalities.

Risposta 2.

Positron emission tomography (PET), particularly when combined with computed tomography (CT) to form PET/CT, is increasingly recognized for its role in the diagnosis and management of pancreatic cancer. Here are the key points regarding its use:

**Diagnostic Utility of PET/CT in Pancreatic Cancer**

**Sensitivity and Specificity:** PET/CT has demonstrated high sensitivity (approximately 90%) and specificity (ranging from 70% to 100%) in detecting pancreatic cancer. This makes it a valuable tool for identifying both primary tumors and metastases, particularly in cases where conventional imaging may be less effective

**Detection of Metastases:** One of the strengths of PET/CT is its ability to detect small metastases that may not be visible on standard CT or MRI scans. This capability is crucial for accurate staging and determining resectability

**Differentiation from Other Conditions:** PET/CT can help differentiate pancreatic cancer from other conditions, such as chronic pancreatitis, by highlighting areas of hypermetabolism associated with malignant lesions

**Role in Staging and Treatment Planning:** PET/CT is particularly useful in the initial staging of pancreatic adenocarcinoma, helping to assess the extent of disease spread and informing surgical planning

It can identify lymph node involvement and distant metastases, which are critical for treatment decisions.

**Limitations:** While PET/CT is beneficial, it has limitations, particularly in detecting lymph node metastases compared to other imaging modalities like endoscopic ultrasound (EUS). Therefore, it is often used in conjunction with other diagnostic methods rather than as a standalone test

**Monitoring Treatment Response:** Beyond diagnosis, PET/CT can also be employed to monitor treatment response and detect recurrence after therapy, making it a versatile tool in the management of pancreatic cancer

### Conclusion

While PET/CT is not universally recommended as the first-line diagnostic method for pancreatic cancer due to its limitations in certain scenarios, it plays a significant role in the overall diagnostic pathway. Its combination of metabolic and anatomical information enhances the accuracy of diagnosis and staging, thereby aiding clinical decision-making for patients with suspected pancreatic cancer.

### Risposta 3.

Positron emission tomography (PET), particularly when combined with computed tomography (CT), is increasingly recognized as a valuable diagnostic tool for pancreatic cancer. However, its role is nuanced and depends on specific clinical contexts.

#### Key Points on PET/CT in Diagnosing Pancreatic Cancer:

1. **Sensitivity and Specificity:** PET/CT has shown high sensitivity in detecting pancreatic tumors, with reported sensitivity ranging from 78% to 95% and specificity from 50% to 87% when used alone. When combined with CT, the sensitivity can improve to between 85% and 97% [2][5].
2. **Utility in Staging:** PET/CT is particularly useful for staging pancreatic cancer, as it can detect small metastases and lymph node involvement that might not be visible on conventional imaging like CT alone. This capability aids in determining the resectability of tumors [1][3].
3. **Differentiation from Other Conditions:** PET/CT can help differentiate pancreatic cancer from chronic pancreatitis, which is crucial for avoiding unnecessary surgeries [3][4].
4. **Guiding Biopsies:** The metabolic information from PET can guide biopsies to target the most hypermetabolic areas of a tumor, potentially increasing the diagnostic yield, especially in heterogeneous tumors [1].

5. Limitations: Despite its advantages, PET/CT has limitations in detecting lymph node metastases compared to other imaging modalities. It is generally not used as a standalone diagnostic tool but rather in conjunction with other imaging techniques [2][4].

Conclusion: While PET/CT is recommended as part of the diagnostic pathway for suspected pancreatic cancer, especially for staging and guiding treatment decisions, it is typically used alongside other imaging modalities like CT and endoscopic ultrasound. Its role is particularly beneficial in complex cases where conventional imaging may be insufficient.

5. When is the surgical approach indicated as first-line therapy for pancreatic cancer?

Risposta 1.

Surgical intervention is indicated as the first-line therapy for pancreatic cancer under specific conditions. Here are the key criteria for surgical candidacy:

Indications for Surgical Approach

**Resectable Tumors:** Surgery is primarily indicated for patients with resectable pancreatic tumors, meaning the cancer has not spread beyond the pancreas and can be completely removed. This typically includes tumors that are confined to the pancreas without vascular invasion or distant metastasis.

**Stage of Cancer:** The tumor stage plays a crucial role. Surgical options are most effective in early-stage pancreatic cancer (Stage I and some Stage II) where the tumor is localized and has not invaded major blood vessels or lymph nodes.

**Patient's Overall Health:** Candidates for surgery must have a good performance status, often assessed using the Eastern Cooperative Oncology Group (ECOG) scale, where a score of 0 or 1 indicates that the patient is capable of carrying out daily activities with minimal assistance.

**Absence of Metastatic Disease:**

Patients should be free from distant metastases. If cancer has spread to other organs (Stage IV), surgical options are generally not recommended as first-line therapy.

**Evaluation by a Multidisciplinary Team:** A thorough evaluation by a multidisciplinary team, including surgeons, medical oncologists, and radiologists, is essential to determine the best course of action and to confirm that surgery is appropriate.



**Surgical Procedures:** The most common surgical procedure for resectable pancreatic cancer is the Whipple procedure (pancreaticoduodenectomy), which involves removing the head of the pancreas along with parts of the small intestine, bile duct, gallbladder, and surrounding lymph nodes. For tumors located in the tail of the pancreas, a distal pancreatectomy may be performed.

## Conclusion

In summary, surgical intervention is indicated as first-line therapy for pancreatic cancer when tumors are resectable, localized, and when patients are in good health with no evidence of metastatic disease. Early detection and appropriate patient selection are critical to improving outcomes in pancreatic cancer treatment.

## Risposta 2.

Surgical intervention is indicated as the first-line therapy for pancreatic cancer primarily under specific conditions. Here's a detailed overview of when surgery is appropriate:

### Indications for Surgical Approach in Pancreatic Cancer

1. **Resectable Disease:** The tumor is classified as resectable when it has not invaded major blood vessels or metastasized to distant organs. This typically includes tumors confined to the pancreas or those that may involve nearby lymph nodes but do not compromise the vascular structures.

**Surgical Procedures:** Common surgical options include:

- o **Whipple Procedure (Pancreaticoduodenectomy):** This is the most common surgery for tumors located in the head of the pancreas.
- o **Distal Pancreatectomy:** This involves removing the tail and body of the pancreas, often indicated for tumors located in those areas.
- o **Total Pancreatectomy:** In cases where the tumor involves all parts of the pancreas, this procedure may be necessary.

2. **Early-Stage Diagnosis: Stage I and II:** Patients diagnosed with Stage I (localized) or Stage II (locally advanced but resectable) pancreatic cancer are often candidates for surgical resection, especially if they have a good performance status and no significant comorbidities.

3. **Multidisciplinary Assessment:** A thorough evaluation by a multidisciplinary team, including surgical oncologists, medical oncologists, and radiologists, is essential. Imaging

studies (such as CT or MRI) are performed to assess the extent of disease and determine resectability.

4. Preoperative Considerations: Neoadjuvant Therapy: In some cases, neoadjuvant chemotherapy (such as FOLFIRINOX or gemcitabine plus nab-paclitaxel) may be administered before surgery to shrink the tumor and improve surgical outcomes. This approach is particularly relevant for borderline resectable tumors.

5. Postoperative Follow-Up: After surgical resection, patients typically undergo adjuvant chemotherapy to reduce the risk of recurrence. Guidelines recommend this approach based on evidence showing improved survival rates.

### Conclusion

Surgery is indicated as a first-line therapy for pancreatic cancer when the disease is deemed resectable, typically at early stages (I and II), and after a comprehensive evaluation by a multidisciplinary team. The goal is to achieve complete tumor removal, which is currently the only potential cure for pancreatic cancer.

### Risposta 3.

Surgical intervention is indicated as the first-line therapy for pancreatic cancer primarily when the tumor is deemed resectable. Here are the key criteria and considerations for surgical eligibility:

#### Indications for Surgical Approach:

##### 1. Resectability Criteria:

- The tumor must not have spread beyond the pancreas (no distant metastases).
- There should be no significant invasion of major blood vessels (such as the celiac, hepatic, or superior mesenteric arteries) or adjacent organs.
- The primary tumor should be free from involvement with the hepatic portal and superior mesenteric veins, allowing for potential complete surgical resection.

##### 2. Types of Surgical Procedures:

- Whipple Procedure (Pancreaticoduodenectomy): Commonly performed for tumors located in the head of the pancreas.
- Distal Pancreatectomy: Used for tumors in the body or tail of the pancreas.
- Total Pancreatectomy: Considered in cases of multifocal disease.

##### 3. Staging and Assessment:

- Preoperative imaging (CT or MRI) is essential to assess tumor characteristics and determine resectability.

- In some cases, staging laparoscopy may be performed to evaluate the extent of disease and confirm surgical candidacy.

#### 4. Exclusion Criteria:

- Distant metastases or extensive local invasion (e.g., into major blood vessels) are contraindications for curative surgery.

- Regional lymph node involvement does not automatically exclude patients from surgical options, provided other criteria are met.

#### 5. Multimodal Treatment Considerations:

- Surgery is often part of a multimodal approach that may include chemotherapy and radiation therapy, especially in borderline resectable cases.

- The timing and sequence of these treatments can influence overall outcomes and survival rates.

#### 6. Patient Health Status:

- The patient's overall health and ability to tolerate surgery are critical factors in determining eligibility for surgical intervention.

Conclusion: Surgery offers the only potential cure for pancreatic cancer when tumors are resectable. It is essential to conduct thorough preoperative evaluations to ensure that patients meet the criteria for surgery, maximizing their chances for successful outcomes.

#### 6. Is prophylactic extended lymph node and nerve plexus dissection recommended in patients with resectable pancreatic cancer undergoing surgery?

Risposta 1.

Prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer is a topic of ongoing research and debate. Here are the key findings regarding its recommendation:

##### Current Recommendations and Evidence

Selective Extended Dissection (SED): Recent studies suggest that selective extended dissection (SED), which focuses on dissecting specific nerve plexuses potentially invaded by

the tumor, may improve disease-free survival in patients with extrapancreatic perineural invasion (EPNI) compared to standard dissection. This approach has shown promising results in terms of reducing regional recurrence and improving outcomes for specific patient subsets

**Extended Lymphadenectomy:** The evidence regarding extended lymphadenectomy (ELA) remains mixed. Some studies, particularly from Japan, initially indicated potential survival benefits associated with ELA compared to standard lymphadenectomy. However, subsequent randomized trials in Europe and the United States have not confirmed these survival benefits, suggesting that extended lymphadenectomy does not significantly impact overall survival when compared to standard procedures

**Morbidity and Complications:** Extended procedures may lead to increased surgical time and blood loss without a clear benefit in terms of negative resection margins or overall survival. The consensus suggests that while extended dissection might provide additional staging information, it does not universally confer a therapeutic advantage.

**Guidelines and Consensus Statements:** The International Study Group of Pancreatic Surgery (ISGPS) has emphasized the importance of complete resectability and appropriate lymph node evaluation but has not definitively endorsed routine prophylactic extended dissection for all patients due to the lack of conclusive evidence supporting improved outcomes

## Conclusion

In summary, while selective extended dissection may be beneficial for certain patients with identified perineural invasion, routine prophylactic extended lymph node and nerve plexus dissection is not universally recommended as a first-line approach in all patients undergoing surgery for resectable pancreatic cancer. Decisions regarding surgical techniques should be individualized based on patient characteristics, tumor biology, and clinical judgment, ideally within the context of a multidisciplinary team.

## Risposta 2.

Prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer is a topic of ongoing debate. Here are the key points based on the current literature:

**Selective Extended Dissection (SED):** Recent studies suggest that Selective Extended Dissection (SED), which targets specific nerve plexuses potentially invaded by the tumor, may improve disease-free survival for patients with extrapancreatic perineural invasion

(EPNI) compared to standard dissection. This approach focuses on dissecting areas where metastasis is more likely, particularly in cases of EPNI, showing a significant survival benefit

**Extended Lymphadenectomy:** The concept of extended lymphadenectomy—removing additional lymph nodes beyond the standard protocol—has been explored. Initial reports indicated potential benefits in survival rates; however, subsequent randomized trials have not consistently confirmed these findings. For example, studies from Europe and the U.S. found no significant survival advantage from extended lymphadenectomy compared to standard lymphadenectomy

**Current Recommendations:** The consensus among experts is that while extended lymphadenectomy may provide better staging information and possibly improve outcomes in select cases, it does not universally confer a survival benefit for all patients with resectable pancreatic cancer. Extended dissection may be more beneficial for those with specific risk factors, such as EPNI

**Risks and Complications:** Extended surgical procedures often come with increased operative time and potential complications without guaranteed improvement in survival outcomes.

Therefore, careful patient selection is crucial

## Conclusion

Prophylactic extended lymph node and nerve plexus dissection may be indicated in certain high-risk patients, particularly those with evidence of nerve invasion. However, routine use of extensive dissection for all patients with resectable pancreatic cancer is not currently recommended due to mixed evidence regarding its impact on survival and increased risk of complications. A multidisciplinary approach is essential to tailor surgical strategies based on individual patient characteristics and tumor biology.

## Risposta 3.

Prophylactic extended lymph node and nerve plexus dissection in patients with resectable pancreatic cancer is a topic of ongoing debate, with current evidence suggesting that it is not routinely recommended as a standard practice. Here are the key points regarding this surgical approach. **Current Evidence and Recommendations:**

1. **Lack of Survival Benefit:** Multiple studies have indicated that extended lymphadenectomy does not significantly improve overall survival compared to standard lymphadenectomy. For instance, randomized controlled trials have shown little to no

difference in survival rates between patients undergoing standard versus extended lymph node resection [1][2].

2. Increased Morbidity: Extended procedures may lead to longer operating times and increased blood loss, raising the risk of postoperative complications without a corresponding survival advantage [2][4].

3. Pathological Considerations: While some proponents argue that extended dissection might improve staging and potentially remove more malignant tissue, the actual clinical benefit remains unclear. Studies suggest that only a small fraction of patients may derive a survival benefit from such extensive procedures [1][2].

4. Guidelines and Consensus: Guidelines from surgical oncology societies generally do not endorse routine extended lymphadenectomies for all patients with resectable pancreatic cancer. Instead, they recommend careful selection based on individual patient factors, tumor characteristics, and existing evidence [5].

5. Focus on Complete Resection: The primary goal in surgical management remains achieving complete resection (R0 resection) of the tumor. The emphasis is on ensuring negative margins rather than extending lymph node dissection indiscriminately [4][5].

Conclusion: In summary, prophylactic extended lymph node and nerve plexus dissection is not routinely recommended for patients with resectable pancreatic cancer due to the lack of demonstrated survival benefits and potential for increased morbidity. Surgical strategies should focus on complete tumor resection while considering individual patient circumstances and existing evidence-based guidelines.

## 7. What is the definition of borderline resectable pancreatic cancer?

Risposta 1.

Borderline resectable pancreatic cancer (BR-PDAC) is defined as a subset of pancreatic ductal adenocarcinoma that presents characteristics placing it between resectable and unresectable stages. Here are the key elements of this definition:

Definition of Borderline Resectable Pancreatic Cancer

**Anatomical Features:** BR-PDAC is characterized by tumors that exhibit certain anatomical relationships with surrounding vascular structures, indicating a high risk of incomplete resection (R1) if surgery is attempted without prior treatment. This includes:

- Involvement of the superior mesenteric artery or celiac trunk by less than 180 degrees.
- Non-reconstructable occlusion of the portal vein or superior mesenteric vein, but with potential for vascular reconstruction.
- Tumors that may be technically resectable but are at significant risk for margin-positive resection due to their proximity to major blood vessels.

**Biological Behavior:** BR-PDAC typically exhibits more aggressive biological behavior compared to fully resectable tumors, leading to a higher likelihood of early recurrence post-surgery.

**Clinical Considerations:** Patients with BR-PDAC are often recommended to undergo neoadjuvant therapy (such as chemotherapy or chemoradiation) before considering surgical resection. This approach aims to downstage the tumor, potentially improving the chances of achieving a complete surgical resection (R0).

**Consensus Definitions:** Various international guidelines and consensus statements have been established to standardize the definition and management of borderline resectable pancreatic cancer, acknowledging its unique challenges in treatment planning.

In summary, borderline resectable pancreatic cancer refers to tumors that are anatomically challenging due to their relationship with critical vascular structures and are associated with a higher risk of incomplete surgical margins, necessitating careful evaluation and often a neoadjuvant treatment approach before any surgical intervention.

Risposta 2.

Borderline resectable pancreatic cancer (BR-PDAC) refers to a specific category of pancreatic ductal adenocarcinoma that presents challenges in surgical resection due to its anatomical and biological characteristics. Here's a detailed definition based on current understanding:

#### Definition of Borderline Resectable Pancreatic Cancer

**Intermediate Stage:** BR-PDAC is characterized as an intermediate stage between resectable and locally advanced pancreatic cancer. It includes tumors that are technically resectable but have features that increase the risk of incomplete resection (R1) or early recurrence after surgery

Anatomical Features: The tumors classified as borderline resectable typically exhibit:

- o Limited involvement of major blood vessels, such as the superior mesenteric artery or celiac trunk, but not to the extent that they are considered unresectable.
- o Potential invasion of surrounding structures that raises concerns about achieving clear surgical margins

Biological Behavior: These tumors often demonstrate aggressive biological behavior, which necessitates careful consideration for treatment strategies. Neoadjuvant therapy

(chemotherapy and/or radiation prior to surgery) is frequently recommended to shrink the tumor and improve the chances of achieving a complete resection

Consensus Definitions: Various guidelines, including those from the International Study Group of Pancreatic Surgery (ISGPS), have attempted to standardize the definition of borderline resectability. For example, criteria may include:

- o Evidence of vascular involvement that is not extensive enough to classify the tumor as unresectable.
- o Elevated tumor markers (e.g., CA 19-9) or lymph node involvement that does not preclude surgical options

Management Approach: The management of BR-PDAC often involves an initial neoadjuvant treatment approach to optimize surgical outcomes, followed by reassessment through imaging studies before proceeding with surgery

## Conclusion

Borderline resectable pancreatic cancer represents a critical category where surgical intervention may still be possible but carries significant risks. The definition encompasses both anatomical and biological considerations, emphasizing the need for a tailored approach involving multidisciplinary evaluation and potential neoadjuvant therapy to enhance surgical success rates.

## Risposta 3.

Borderline resectable pancreatic cancer (BR-PDAC) refers to a specific category of pancreatic ductal adenocarcinoma that exhibits characteristics placing it between resectable and locally advanced tumors. Here's a concise definition based on current literature:

Definition of Borderline Resectable Pancreatic Cancer



1. Anatomical Considerations: BR-PDAC is characterized by limited involvement of adjacent vascular structures, such as the superior mesenteric vein (SMV) or portal vein, where the tumor may cause distortion or encasement but does not completely invade these vessels.

Specifically, it may involve:

- Contact with the SMV or portal vein without complete occlusion.
- Limited abutment of major arteries (e.g., less than 180 degrees of the circumference of the vessel) allowing for potential safe resection and reconstruction.

2. Biological Factors: The tumor may exhibit aggressive biological behavior, indicated by elevated levels of tumor markers (e.g., CA 19-9) or clinical suspicion of subclinical metastatic disease that cannot be definitively proven.

3. Conditional Factors: Patient-related factors such as poor performance status or significant comorbidities can also categorize a tumor as borderline resectable, affecting surgical candidacy.

Clinical Implications:

- Neoadjuvant Therapy: Due to the high risk of incomplete resection (R1 margins) and early recurrence, patients with BR-PDAC are often considered for neoadjuvant therapy before surgical intervention to improve the chances of achieving a negative margin (R0 resection).
- Management Challenges: The definition of BR-PDAC can vary among institutions, leading to inconsistencies in treatment approaches and outcomes. This highlights the need for standardized criteria to guide clinical management effectively.

In summary, borderline resectable pancreatic cancer is defined by anatomical, biological, and conditional factors that complicate surgical resection but still allow for potential curative intervention with appropriate preoperative management.

8. Is combined arterial resection recommended in patients with BR pancreatic cancer?

Risposta 1.

Combined arterial resection (AR) in patients with borderline resectable pancreatic cancer (BR-PDAC) is increasingly considered in clinical practice, particularly following neoadjuvant therapy (NAT). Here are the key points regarding its recommendation:

Indications for Combined Arterial Resection

**Potential for R0 Resection:** Combined AR may enhance the likelihood of achieving an R0 resection (complete removal of the tumor with negative margins) in patients with BR-PDAC, especially when there is limited contact with major arteries such as the celiac trunk or superior mesenteric artery (SMA)

**Survival Outcomes:** Studies indicate that pancreatectomy with major arterial resection after NAT can prolong survival rates for patients with BR-PDAC. This approach allows for radical excision of tumors that might otherwise be deemed unresectable due to vascular involvement

**Complication Rates:** While combined AR is associated with a higher incidence of postoperative complications, the mortality rate remains low (around 2%). The pooled morbidity rate can reach up to 60%, indicating a significant risk that must be considered when planning surgery

**Neoadjuvant Therapy:** NAT is often employed before considering combined AR to downstage the tumor and improve surgical outcomes. This treatment strategy has shown to increase the rates of R0 resections and overall survival

**Current Guidelines and Practices:** Although there is no universal consensus on routine combined AR for all BR-PDAC patients, it is increasingly accepted in specialized centers where multidisciplinary teams evaluate individual cases. The decision often hinges on the extent of arterial involvement and the patient's overall health status

## Conclusion

In summary, combined arterial resection is recommended for select patients with borderline resectable pancreatic cancer, particularly when it follows neoadjuvant therapy and aims to achieve R0 resection. While it carries a risk of complications, the potential for improved survival outcomes supports its consideration in appropriate clinical contexts. Further prospective studies are needed to refine patient selection criteria and optimize surgical techniques.

## Risposta 2.

Combined arterial resection is increasingly being considered in patients with borderline resectable pancreatic cancer (BR-PDAC), particularly after neoadjuvant therapy. Here are the key points regarding its recommendation:

1. **Indications for Combined Arterial Resection:** **Definition of BR-PDAC:** Patients with BR-PDAC typically have tumors that exhibit limited involvement of major blood vessels, such as

the celiac trunk or superior mesenteric artery, but still present a challenge for complete surgical resection.

**Neoadjuvant Therapy (NAT):** Neoadjuvant therapy is often employed to shrink the tumor and improve surgical outcomes. Studies suggest that following NAT, patients may achieve higher rates of R0 resection (complete removal with no cancer cells at the margins) even when arterial involvement is present.

**2. Potential Benefits: Improved Survival Rates:** Evidence indicates that pancreatectomy with major arterial resection following NAT can enhance survival rates for patients with BR-PDAC. Achieving an R0 resection is crucial for long-term survival.

**High R0 Resection Rates:** Combined arterial resection has been associated with increased R0 rates, which are vital for improving prognosis.

**3. Risks and Considerations: Postoperative Complications:** While combined arterial resection can improve outcomes, it also carries a significant risk of postoperative complications. The pooled morbidity rate in studies has reached around 60%, although mortality rates remain low (approximately 2%).

**Individualized Approach:** The decision to perform combined arterial resection should be individualized based on the patient's overall health, tumor characteristics, and response to neoadjuvant therapy.

**4. Current Recommendations:** While there is a growing body of evidence supporting combined arterial resection in selected patients with BR-PDAC, further prospective studies are needed to validate its effectiveness and safety comprehensively. Current guidelines suggest that such procedures should be performed at high-volume centers by experienced surgical teams to minimize risks and optimize outcomes.

## Conclusion

Combined arterial resection may be recommended for patients with borderline resectable pancreatic cancer who have undergone neoadjuvant therapy, as it can potentially lead to improved survival outcomes through enhanced R0 resection rates. However, careful consideration of the associated risks and individual patient factors is essential in making surgical decisions.

Risposta 3.

Combined arterial resection in patients with borderline resectable pancreatic cancer (BR-PDAC) is increasingly considered in clinical practice, particularly following neoadjuvant therapy (NAT). Here are the key points regarding this approach:

#### Recommendations for Combined Arterial Resection

1. **Indications:** Combined arterial resection is indicated for BR-PDAC when the tumor involves major arteries, such as the superior mesenteric artery (SMA) or common hepatic artery (CHA), but does not show complete invasion, allowing for potential resection and reconstruction.
2. **Neoadjuvant Therapy:** The use of NAT prior to surgery has been shown to improve outcomes. Studies indicate that patients who undergo NAT followed by pancreatectomy with arterial resection have higher rates of R0 resection, which is critical for long-term survival. This approach helps downstage the tumor and reduce the risk of early recurrence post-surgery [1][3].
3. **Survival Outcomes:** Evidence suggests that major arterial resection combined with pancreatectomy can enhance survival rates in patients with BR-PDAC. Although this procedure carries a risk of increased postoperative complications, the potential for achieving R0 status may outweigh these risks [1][3].
4. **Complications and Mortality:** While the pooled morbidity rate for combined arterial resections can be high (around 60%), mortality rates remain relatively low (approximately 2%). This indicates that while complications are common, they are manageable, and the procedure can be performed safely in selected patients [1].
5. **Current Guidelines:** Current clinical guidelines do not universally recommend routine combined arterial resections due to variability in patient selection and outcomes. However, they suggest that such procedures should be considered in well-selected patients who have undergone effective neoadjuvant therapy and have a reasonable performance status [3][4].

**Conclusion:** Combined arterial resection in patients with borderline resectable pancreatic cancer is recommended in specific cases, particularly after neoadjuvant therapy, as it may improve surgical outcomes and survival rates. The decision should be individualized based on tumor characteristics, vascular involvement, and overall patient health. Further prospective studies are needed to solidify these recommendations and optimize patient selection criteria.

9. What is the first-line treatment recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

For patients with locally advanced, unresectable pancreatic cancer, the first-line treatment typically involves chemotherapy. Here are the main options currently recommended:

#### First-Line Treatment Options

- 1.FOLFIRINOX: This regimen combines 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin. It is considered a standard first-line treatment for patients with good performance status (ECOG 0-1) and has shown improved overall survival compared to gemcitabine alone.
- 2.Gemcitabine plus Nab-Paclitaxel: This combination therapy involves gemcitabine and albumin-bound paclitaxel (nab-paclitaxel). It is another recommended first-line treatment option, particularly for patients who may not tolerate FOLFIRINOX due to its toxicity profile.
- 3.Modified FOLFIRINOX: A less intensive version of the standard FOLFIRINOX regimen, modified FOLFIRINOX can be used for patients with borderline performance status or those who may experience significant side effects from the full regimen. It has demonstrated comparable efficacy with potentially fewer adverse events.
4. Chemotherapy Alone or Combined with Radiation: In some cases, especially in clinical trials, chemotherapy may be combined with radiation therapy to improve local control and potentially extend survival, although the benefits of this approach can vary.

#### Recent Developments

The European Medicines Agency (EMA) recently approved a new combination regimen known as NALIRIFOX, which includes liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin as a first-line treatment for metastatic pancreatic cancer. While this specific approval is for metastatic cases, it reflects ongoing advancements in treatment strategies for advanced pancreatic cancer.

#### Conclusion

In summary, the first-line treatment for locally advanced, unresectable pancreatic cancer primarily consists of chemotherapy regimens like FOLFIRINOX or gemcitabine plus nab-paclitaxel. The choice between these options depends on the patient's overall health,

performance status, and potential side effects. Ongoing clinical trials continue to explore additional combinations and treatment strategies to improve outcomes for these patients.

Risposta 2.

For patients with locally advanced, unresectable pancreatic cancer, the recommended first-line treatment is typically chemotherapy. The two primary regimens that are widely endorsed include:

1. FOLFIRINOX: This regimen consists of a combination of oxaliplatin, irinotecan, fluorouracil, and leucovorin. It is generally preferred for patients who have a good performance status and can tolerate the associated side effects. FOLFIRINOX has been shown to improve overall survival compared to gemcitabine alone and is considered a standard treatment for advanced pancreatic cancer in fit patients
2. Gemcitabine plus Nab-Paclitaxel (GEM+NPTX): This combination therapy involves gemcitabine and nanoparticle albumin-bound paclitaxel. It is often used for patients who may not be suitable for FOLFIRINOX due to comorbidities or poor performance status. This regimen has also demonstrated improved outcomes over gemcitabine monotherapy

Additional Considerations

- Neoadjuvant Therapy: In some cases, neoadjuvant chemotherapy may be considered to shrink the tumor before any potential surgical intervention, although this is more common in borderline resectable cases.
- Clinical Trials: Participation in clinical trials may also be an option for patients, as ongoing research continues to explore new treatment combinations and approaches.

In summary, the first-line treatment for locally advanced, unresectable pancreatic cancer primarily involves chemotherapy regimens such as FOLFIRINOX or gemcitabine plus nab-paclitaxel, tailored to the patient's overall health and performance status.

Risposta 3.

The first-line treatment recommended for patients with locally advanced, unresectable pancreatic cancer (LAPC) typically involves systemic chemotherapy, with two main regimens being widely used:

Recommended First-Line Treatments

1. FOLFIRINOX: This regimen consists of a combination of leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin. It has demonstrated improved overall survival compared to gemcitabine alone and is often considered for patients with good performance status due to its efficacy, although it can have significant toxicity.

2. Gemcitabine plus Nab-Paclitaxel (GnP): This combination therapy includes gemcitabine and nab-paclitaxel. It has shown favorable results in terms of tumor shrinkage and overall survival, making it a strong option for first-line treatment in LAPC. Studies indicate that this regimen can also enable conversion to surgical resection in some patients.

#### Additional Considerations:

- Neoadjuvant Therapy: Neoadjuvant approaches, where chemotherapy is administered before any potential surgical intervention, are increasingly recommended to downstage the tumor and improve resectability. This strategy can help in managing micrometastatic disease early on.

- Chemoradiotherapy: While not universally adopted as the first-line treatment, chemoradiotherapy may be considered in some cases, particularly when there is a goal of local control alongside systemic treatment.

Conclusion: For locally advanced, unresectable pancreatic cancer, FOLFIRINOX and gemcitabine plus nab-paclitaxel are the primary first-line treatment options. The choice between these regimens depends on the patient's overall health, performance status, and the specific clinical scenario. The integration of neoadjuvant therapy is also becoming a standard consideration to enhance treatment outcomes.

10. What is the chemoradiotherapy regimen recommended for patients with locally advanced, unresectable pancreatic cancer?

Risposta 1.

For patients with locally advanced, unresectable pancreatic cancer, chemoradiotherapy (CRT) is a recommended treatment approach. Here's an overview of the typical regimens and considerations:

#### Recommended Chemoradiotherapy Regimens

1. Concurrent Chemoradiotherapy:

5-Fluorouracil (5-FU): Often used as a radiosensitizer in combination with radiation therapy.

The total radiation dose typically ranges from 50.4 to 60 Gy, delivered in daily fractions.

Gemcitabine: This can also be used concurrently with radiation. A notable regimen includes gemcitabine at 600 mg/m<sup>2</sup> weekly for six weeks during radiation, followed by maintenance gemcitabine.

## 2. Induction Chemotherapy Followed by Consolidation Chemoradiotherapy:

Patients may first receive induction chemotherapy (e.g., FOLFIRINOX or gemcitabine plus nab-paclitaxel) to control systemic disease before transitioning to CRT. This approach aims to improve local control and select candidates for potential surgery later.

After induction chemotherapy, consolidation CRT may involve a regimen of radiation (50-60 Gy) combined with 5-FU or gemcitabine.

## 3. Recent Trials and Findings:

Studies have shown mixed results regarding the overall survival benefits of CRT compared to chemotherapy alone. Some trials indicate that CRT can lead to improved progression-free survival and local control but do not consistently demonstrate a significant increase in overall survival. For example, a trial by the Eastern Cooperative Oncology Group (E4201) reported that chemoradiation was associated with slightly improved survival compared to chemotherapy alone (11 months vs. 9.2 months).

Considerations: The choice of regimen often depends on patient-specific factors such as performance status, tumor characteristics, and response to initial chemotherapy. While CRT can improve local control and potentially prolong survival, the benefits must be weighed against the risk of increased toxicity and complications. Ongoing research continues to explore the optimal sequencing and combination of therapies for maximizing patient outcomes in locally advanced pancreatic cancer.

In summary, chemoradiotherapy is a key component of treatment for locally advanced, unresectable pancreatic cancer, with various regimens available depending on individual patient circumstances and treatment goals.

## Risposta 2.

For patients with locally advanced, unresectable pancreatic cancer, the recommended chemoradiotherapy regimen typically involves a combination of chemotherapy followed by radiation therapy. Here are the key components based on current practices:

### Recommended Chemoradiotherapy Regimen



### 1. Induction Chemotherapy:

**FOLFIRINOX:** This regimen consists of oxaliplatin, irinotecan, leucovorin, and fluorouracil. It is often used as the first-line treatment for patients who are fit enough to tolerate it.

o **Gemcitabine plus Nab-Paclitaxel:** An alternative regimen that combines gemcitabine with nab-paclitaxel is also commonly utilized.

### 2. Consolidative Chemoradiotherapy (CRT):

After completing induction chemotherapy, patients may receive chemoradiotherapy to enhance local control. This typically involves:

**Radiation Therapy:** A total dose of 50.4 to 60 Gy delivered in daily fractions (often 1.8 to 2 Gy per fraction) over several weeks.

**Concurrent Chemotherapy:** Commonly, 5-fluorouracil (5-FU) or gemcitabine is used during radiation therapy to sensitize the tumor to radiation.

**3. Clinical Evidence:** Studies have shown that this approach can improve overall survival compared to chemotherapy alone, although results can vary. For instance, one trial indicated a median overall survival improvement from 9.2 months with chemotherapy alone to 11 months with chemoradiotherapy.

**4. Patient Selection and Monitoring:** Patient selection is crucial, and ongoing assessment through imaging and clinical evaluations is necessary to determine response and adjust treatment plans accordingly.

### Conclusion

The standard chemoradiotherapy regimen for locally advanced, unresectable pancreatic cancer typically involves initial induction chemotherapy (FOLFIRINOX or gemcitabine plus nab-paclitaxel) followed by consolidative chemoradiotherapy with radiation doses of 50-60 Gy and concurrent chemotherapy. This approach aims to improve survival outcomes while managing disease progression effectively.

### Risposta 3.

For patients with locally advanced, unresectable pancreatic cancer (LAPC), chemoradiotherapy (CRT) is often recommended as part of the treatment regimen. The following outlines the typical CRT approaches based on recent findings:

**Recommended Chemoradiotherapy Regimens:**

1. **Concurrent Chemoradiotherapy:**

- 5-Fluorouracil (5-FU): A common approach involves using 5-FU in conjunction with radiation therapy. For example, a regimen may deliver radiation at a total dose of **\*\*50.4 Gy in 28 fractions\*\*** while administering continuous infusion of 5-FU (600 mg/m<sup>2</sup> weekly) during radiation treatment.

- Gemcitabine: Another effective regimen combines radiation with gemcitabine. In a notable study, patients received gemcitabine (600 mg/m<sup>2</sup> weekly for 6 weeks) alongside radiation, followed by additional cycles of gemcitabine.

## 2. Radiation Therapy Dosage:

- The radiation doses typically range from 40 to 60 Gy, delivered in standard fractionation (1.8 to 2.0 Gy per fraction). This is aimed at maximizing local control while minimizing toxicity.

## 3. Efficacy and Survival Outcomes:

- Studies have shown that chemoradiotherapy can improve median overall survival in LAPC patients compared to chemotherapy alone, with some trials indicating survival benefits ranging from 10 to 12 months in those receiving CRT versus chemotherapy alone.

## 4. Palliative Benefits:

- Beyond survival, CRT has been associated with improved pain control and management of obstructive symptoms, enhancing the quality of life for patients with LAPC.

**Conclusion:** In summary, chemoradiotherapy, particularly using regimens that include 5-FU or gemcitabine alongside radiation, is recommended for patients with locally advanced, unresectable pancreatic cancer. This approach aims to improve overall survival and provide symptomatic relief, making it a critical component of the treatment strategy for this challenging disease.

11. What is the first-line chemotherapy recommended for pancreatic cancer patients with distant metastases?

Risposta 1.

The first-line chemotherapy recommended for patients with metastatic pancreatic cancer includes the following regimens:

### Recommended First-Line Chemotherapy Regimens

1. **FOLFIRINOX:** This regimen combines 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin. It is particularly effective for patients with good performance status (ECOG 0-1) and has shown improved overall survival compared to other regimens.

2. Gemcitabine plus Nab-Paclitaxel (GEM+NPTX): This combination of gemcitabine and albumin-bound paclitaxel (nab-paclitaxel) is also a standard first-line treatment. It has demonstrated significant survival benefits and is widely used in clinical practice.

3. Modified FOLFIRINOX: A less intensive version of the standard FOLFIRINOX regimen, modified FOLFIRINOX has shown comparable efficacy with potentially fewer side effects, making it suitable for patients who may not tolerate the full regimen.

4. NALIRIFOX: Recently approved by the European Medicines Agency (EMA), this regimen combines liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin as a first-line treatment option for metastatic pancreatic cancer. This approval marks a significant advancement in treatment options available for patients with this condition.

#### Summary of Efficacy

- Clinical studies have consistently shown that both FOLFIRINOX and GEM+NPTX are associated with better outcomes in terms of overall survival compared to older regimens like gemcitabine alone. The recent systematic review highlighted that FOLFIRINOX had the largest area under the curve for survival, followed by GEM+NPTX, indicating their effectiveness as first-line therapies for metastatic pancreatic cancer.

In conclusion, the first-line chemotherapy regimens for metastatic pancreatic cancer include FOLFIRINOX, gemcitabine plus nab-paclitaxel, and the newly approved NALIRIFOX, with treatment choice tailored based on patient performance status and tolerance to therapy.

#### Risposta 2.

The first-line chemotherapy recommended for patients with distant metastatic pancreatic cancer is typically gemcitabine-based therapy or FOLFIRINOX. Here are the details regarding these regimens:

##### 1. Gemcitabine-Based Therapy

- Gemcitabine Alone: Historically, gemcitabine has been a standard treatment for metastatic pancreatic cancer. It is often used as a single agent for patients who may not tolerate more aggressive regimens.

- Gemcitabine plus Nab-Paclitaxel: This combination has become a preferred first-line treatment option. Studies have shown that this regimen improves overall survival compared to gemcitabine alone, making it a common choice for patients with good performance status.

##### 2. FOLFIRINOX

- This regimen includes a combination of oxaliplatin, irinotecan, leucovorin, and fluorouracil. FOLFIRINOX is recommended for patients who are fit enough to tolerate its side effects, as it has demonstrated superior efficacy in terms of overall survival compared to gemcitabine alone in clinical trials.

### 3. Clinical Considerations

- The choice between these regimens depends on the patient's overall health, performance status, and ability to tolerate potential side effects. FOLFIRINOX may be more effective but also comes with increased toxicity.

- Ongoing clinical trials continue to explore new combinations and targeted therapies that may further improve outcomes for patients with metastatic pancreatic cancer.

In summary, the first-line chemotherapy for patients with distant metastatic pancreatic cancer generally involves either gemcitabine-based therapy (preferably combined with nab-paclitaxel) or FOLFIRINOX, tailored to the individual patient's condition and tolerance

Risposta 3.

The first-line chemotherapy recommended for patients with distant metastatic pancreatic cancer is typically one of the following regimens:

#### 1. FOLFIRINOX:

- This regimen consists of leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin. It has shown superior efficacy in terms of overall survival compared to other treatments and is particularly suitable for patients with good performance status. Studies indicate that FOLFIRINOX can significantly improve median overall survival [1][3].

#### 2. Gemcitabine plus Nab-Paclitaxel (GnP):

- This combination includes \*\*gemcitabine and albumin-bound paclitaxel\*\*. It has also demonstrated improved outcomes in terms of overall survival and progression-free survival compared to gemcitabine alone. The combination is often preferred for patients who may not tolerate the more intensive FOLFIRINOX regimen due to its side effects [1][5].

Summary of Efficacy: Both regimens have been validated through clinical trials, with FOLFIRINOX generally providing better survival outcomes but with higher toxicity.

Gemcitabine plus nab-paclitaxel serves as a valuable alternative, especially for patients with more significant comorbidities or poorer performance status.

In conclusion, the choice between FOLFIRINOX and gemcitabine plus nab-paclitaxel depends on the patient's overall health, tolerance for chemotherapy, and specific clinical circumstances.

12. Is surgical resection recommended for pancreatic cancer patients with postoperative metastases/recurrences?

Risposta 1.

Surgical resection for pancreatic cancer patients with postoperative metastases or recurrences is a complex decision that depends on several factors, including the location and extent of the recurrence, the patient's overall health, and the time elapsed since the initial surgery. Here are the key considerations regarding surgical resection in this context:

Surgical Resection for Postoperative Recurrences

1. Isolated Local Recurrence: Surgical resection may be considered for patients with isolated local recurrence of pancreatic cancer, particularly if there is no evidence of distant metastases. Studies indicate that repeat surgical resection can offer a significant survival benefit for selected patients with isolated local recurrence. The median overall survival after re-resection can reach up to 28 months in favorable cases, with low procedure-related morbidity (6% to 33%) and mortality rates (approximately 1.1%)

2. Factors Influencing Resection Feasibility: Key prognostic factors that influence the decision to proceed with surgical resection include:

Time to Recurrence: A longer interval from the initial surgery to recurrence (ideally more than 10 months) is associated with better outcomes.

Patient Age: Younger patients (<65 years) tend to have better survival rates post-resection.

Preoperative Chemotherapy: Patients who receive chemotherapy before re-resection may have improved outcomes

3. Distant Metastases: If the recurrence involves distant metastases (e.g., liver, lung), surgical resection is generally not recommended as a curative approach. In such cases, palliative care or systemic therapies are preferred.

4. Multidisciplinary Approach: Decisions regarding surgical intervention should involve a multidisciplinary team, including surgical oncologists, medical oncologists, and radiologists. This ensures a comprehensive evaluation of the patient's condition and available treatment options.

5. Clinical Trials and Emerging Strategies: Ongoing clinical trials are exploring various strategies for managing recurrent pancreatic cancer, including novel therapies and combinations that may improve outcomes for patients who are not candidates for surgery.

## Conclusion

In summary, surgical resection may be recommended for selected patients with isolated local recurrences of pancreatic cancer after initial surgery, particularly when certain favorable conditions are met. However, in cases of distant metastases or extensive local disease, other treatment modalities such as chemotherapy or palliative care are typically pursued. Each case should be evaluated individually to determine the best course of action based on clinical circumstances and patient preferences.

## Risposta 2.

Surgical resection for pancreatic cancer patients with postoperative metastases or recurrences is generally not recommended as a standard approach. Here are the key points based on current guidelines and literature:

### 1. Limited Role of Surgery

- **Postoperative Recurrence:** After surgical resection, many patients experience local or distant recurrence. The prognosis for those with metastatic disease is typically poor, and surgery is not usually indicated for patients with distant metastases.
- **Local Recurrence:** In cases of isolated local recurrence (without distant spread), repeat surgical resection may be considered. Studies indicate that repeat surgery can be safe and may offer a survival benefit, with reported median overall survival times around 28.7 months for patients undergoing repeat resection for local recurrence

**Surgical Guidelines: Current Recommendations:** Guidelines from various organizations suggest that surgery should not be performed on patients with synchronous distant metastases due to the extremely poor prognosis associated with such cases. Instead, systemic therapies are preferred.

**Selection Criteria:** For patients with isolated local recurrence, careful patient selection is essential. Factors such as overall health, tumor biology, and previous treatment responses play a significant role in determining candidacy for repeat surgical intervention.

3. **Alternative Treatments: Chemotherapy and Palliative Care:** For patients with metastatic disease post-resection, systemic chemotherapy is the primary treatment modality. Palliative care options may also be explored to manage symptoms and improve quality of life.

## Conclusion

In summary, while repeat surgical resection may be an option for select patients with isolated local recurrence after initial surgery, it is generally not recommended for those with postoperative metastases. The focus in such cases shifts to systemic therapy and supportive care to manage the disease effectively.

## Risposta 3.

Surgical resection for pancreatic cancer patients with postoperative metastases or recurrences is a complex and evolving area of treatment. Here are the key insights based on the search results:

1. **Local Recurrence:** Surgical resection may be indicated for patients with isolated local recurrence after initial resection. Evidence suggests that reoperation can lead to improved median overall survival (OS). For instance, in a study of 57 patients with local recurrence, those who underwent surgical resection had a median OS of 16.4 months, compared to 9.4 months for those who did not undergo surgery[1].
2. **Distant Metastases:** For patients with distant metastases, surgical intervention is generally not recommended as standard practice due to the palliative nature of the disease. However, recent studies indicate that selected patients with stable disease following neoadjuvant chemotherapy may benefit from surgical resection of both the primary tumor and metastases, particularly in cases involving limited metastases such as pulmonary lesions[1][3].
3. **Emerging Evidence:** There is growing evidence supporting the idea that surgical resection can be beneficial even in cases of postoperative recurrence, challenging previous assumptions that such interventions are futile. Some reports indicate long-term survival benefits for patients undergoing repeat pancreatectomy for local recurrences or metastasectomy for isolated metastatic disease[1][5].
4. **Considerations for Surgery:** The decision to proceed with surgical resection in the context of recurrence should be individualized based on factors such as the extent of disease, patient performance status, and response to prior treatments. Multidisciplinary evaluation is crucial to determine the appropriateness of surgery.

**Conclusion:** Surgical resection may be recommended for select patients with isolated local recurrence after initial surgery, showing potential for improved survival outcomes. In contrast, distant metastases typically preclude surgical intervention unless specific conditions

are met, such as stability after neoadjuvant therapy. The evolving landscape of treatment emphasizes the need for personalized approaches in managing postoperative recurrences in pancreatic cancer patients.

13. Which of the two types of stents—plastic stents or metallic stents—are recommended in resectable or borderline resectable pancreatic cancer patients with obstructive jaundice?

Risposta 1.

In patients with resectable or borderline resectable pancreatic cancer who present with obstructive jaundice, the choice between plastic stents (PS) and metallic stents (MS) for preoperative biliary drainage (PBD) is an important consideration. Here's a summary of the findings regarding stent selection:

#### Stent Comparison

1. **Metallic Stents (MS): Advantages:** Metallic stents are generally preferred for patients with unresectable pancreatic cancer due to their longer patency and lower rates of reintervention compared to plastic stents. They are associated with fewer complications related to biliary obstruction, making them a suitable option in cases where long-term drainage is necessary. **Efficacy in Neoadjuvant Therapy:** Studies suggest that MS may be beneficial for patients undergoing neoadjuvant therapy (NAT) before surgical resection, as they can reduce the need for additional interventions and maintain effective biliary drainage during treatment.

2. **Plastic Stents (PS): Advantages:** Plastic stents are often used due to their lower initial cost and ease of placement. However, they have a shorter duration of patency and may require more frequent replacements. **Limitations:** In the context of obstructive jaundice, PS may lead to more complications and require more endoscopic interventions compared to MS.

#### Recommendations

- **Current Consensus:** While both types of stents can be used, metallic stents are increasingly recommended for patients with obstructive jaundice undergoing neoadjuvant therapy for resectable or borderline resectable pancreatic cancer. This recommendation is based on their superior performance in terms of patency and reduced need for reintervention, which is critical during the treatment process.

- **Clinical Context:** The decision should consider individual patient factors, including the expected duration of biliary obstruction, overall health status, and potential complications associated with each stent type.



In conclusion, metallic stents are generally favored over plastic stents for preoperative biliary drainage in patients with resectable or borderline resectable pancreatic cancer experiencing obstructive jaundice, particularly when undergoing neoadjuvant therapy

Risposta 2.

For patients with resectable or borderline resectable pancreatic cancer who present with obstructive jaundice, the choice between plastic stents (PS) and metallic stents (MS) for preoperative biliary drainage (PBD) has been a topic of investigation. Here are the key findings regarding the use of these stents:

#### Recommendations for Stent Type

1. Metallic Stents (MS): Advantages: Metallic stents are generally preferred for patients with obstructive jaundice due to their longer patency period and lower rates of reintervention compared to plastic stents. They are particularly advantageous in cases where prolonged biliary drainage is required, such as when neoadjuvant therapy (NAT) is planned before surgery.

Clinical Evidence: Studies have shown that MS can reduce complications such as cholangitis and recurrent biliary obstruction (RBO), making them a suitable choice for patients undergoing NAT followed by surgical resection.

2. Plastic Stents (PS): Usage: While plastic stents are still used, they typically have a shorter duration of patency and may necessitate more frequent replacements. They might be considered in specific situations or for patients who cannot tolerate metallic stents.

Limitations: The increased need for reintervention and potential complications make PS less favorable compared to MS for patients requiring long-term drainage.

#### Conclusion

In summary, metallic stents are generally recommended over plastic stents for preoperative biliary drainage in patients with resectable or borderline resectable pancreatic cancer experiencing obstructive jaundice. Their advantages in terms of longer patency and reduced complication rates make them the preferred choice, especially when neoadjuvant therapy is involved.

Risposta 3.

In patients with resectable or borderline resectable pancreatic cancer experiencing obstructive jaundice, self-expanding metal stents (SEMS) are generally recommended over plastic stents for preoperative biliary drainage (PBD). Here are the key points supporting this recommendation:

#### Advantages of Metal Stents

1. **Longer Patency:** Metal stents have a longer duration of efficacy compared to plastic stents, which translates to fewer instances of stent occlusion and the need for reintervention. This is particularly important in patients undergoing neoadjuvant therapy (NAT), as maintaining biliary drainage is critical during treatment.
2. **Lower Reintervention Rates:** Studies indicate that patients with metal stents experience lower rates of reintervention for stent-related complications compared to those with plastic stents. This can enhance patient comfort and reduce the overall burden of treatment.
3. **Fewer Complications:** While both types of stents have associated risks, metal stents tend to have fewer complications related to biliary drainage than plastic stents, making them a safer option in many cases.
4. **Clinical Evidence:** A systematic review and meta-analysis have shown that SEMS are associated with lower rates of reintervention, delayed neoadjuvant therapy, and complications like cholangitis when compared to plastic stents in the context of PBD for operable pancreatic cancer.

**Conclusion:** For patients with resectable or borderline resectable pancreatic cancer who require biliary drainage due to obstructive jaundice, self-expanding metal stents are recommended due to their superior patency, lower complication rates, and reduced need for further interventions. This approach is particularly beneficial in the setting of neoadjuvant therapy, where maintaining effective biliary drainage is crucial for patient management.

14. Is anticoagulant therapy for preventing venous thromboembolism recommended in patients with unresectable pancreatic cancer undergoing chemotherapy?

Risposta 1.

Anticoagulant therapy for preventing venous thromboembolism (VTE) in patients with unresectable pancreatic cancer undergoing chemotherapy is recommended under specific conditions. Here are the key points regarding this recommendation:

## Recommendations for Anticoagulant Therapy

1. **High-Risk Patients:** Patients with cancer, including those with unresectable pancreatic cancer, are at an increased risk of VTE. The Khorana score is often used to assess this risk, where a score of 2 or higher indicates a high risk for VTE. In such cases, thromboprophylaxis is recommended.
2. **Types of Anticoagulants:** **Low-Molecular-Weight Heparin (LMWH):** LMWH is commonly recommended for high-risk patients undergoing chemotherapy due to its efficacy in reducing the incidence of symptomatic VTE. **Direct Oral Anticoagulants (DOACs):** Recent studies have shown that DOACs like apixaban and rivaroxaban can also be effective in preventing VTE in high-risk cancer patients. These agents are particularly useful for outpatient settings and have demonstrated a significant reduction in VTE rates compared to placebo.
3. **Clinical Guidelines:** The American Society of Hematology (ASH) guidelines suggest that high-risk ambulatory patients receiving systemic therapy should be offered thromboprophylaxis with LMWH or DOACs, provided there are no contraindications such as significant bleeding risk or drug interactions.
4. **Balancing Risks and Benefits:** While anticoagulant therapy can significantly reduce the risk of VTE, it is essential to consider the potential risks of bleeding. The decision to initiate prophylaxis should involve discussions with the patient regarding the relative benefits and harms, as well as individual risk factors.
5. **Duration of Therapy:** The duration of anticoagulant therapy may vary based on individual patient circumstances and ongoing assessment of VTE risk throughout the course of chemotherapy.

## Conclusion

In summary, anticoagulant therapy is recommended for patients with unresectable pancreatic cancer who are at high risk for venous thromboembolism, particularly those undergoing chemotherapy. Both LMWH and DOACs are viable options for thromboprophylaxis, with the choice depending on individual patient factors and clinical judgment.

## Risposta 2.

Anticoagulant therapy for preventing venous thromboembolism (VTE) in patients with unresectable pancreatic cancer undergoing chemotherapy is increasingly recognized as beneficial, although guidelines remain somewhat ambiguous. Here are the key points based on the current literature:

1. Hypercoagulable State: Patients with pancreatic cancer often experience a hypercoagulable state, which significantly increases the risk of VTE, occurring in approximately 20% of these patients. This condition can lead to serious complications and increased morbidity and mortality.

2. Anticoagulant Therapy Benefits: Long-Term Systemic Anticoagulation: Evidence suggests that long-term systemic anticoagulation may improve clinical outcomes for pancreatic cancer patients by reducing the risk of thromboembolic events and potentially enhancing survival rates. Studies indicate that patients receiving anticoagulants had lower risks of sepsis, shock, acute kidney injury, and in-hospital mortality compared to those who did not receive anticoagulation

Trousseau's Syndrome: In cases like Trousseau's syndrome, where patients develop VTE due to malignancy, anticoagulant therapy has been shown to be effective even in the context of chemotherapy and surgical interventions

3. Current Recommendations: While there is a growing body of evidence supporting the use of anticoagulants in this patient population, clinical guidelines do not universally recommend routine anticoagulant therapy for all outpatients with pancreatic cancer. Instead, it is often suggested that anticoagulation should be considered for hospitalized patients or those at high risk for VTE. The decision to initiate anticoagulation should be individualized based on patient-specific factors, including performance status, existing comorbidities, and the overall treatment plan.

Conclusion: Anticoagulant therapy is recommended for preventing VTE in patients with unresectable pancreatic cancer undergoing chemotherapy, particularly for those at higher risk or with existing thromboembolic complications. However, clinical judgment is essential in determining the necessity and duration of such therapy based on individual patient circumstances.

Risposta 3.

Anticoagulant therapy for preventing venous thromboembolism (VTE) in patients with unresectable pancreatic cancer undergoing chemotherapy is a complex decision. Here are the key considerations based on the search results:

Recommendations and Considerations

1. High Risk of VTE: Patients with pancreatic cancer, particularly those undergoing chemotherapy, are at a significantly increased risk of developing VTE, with reported rates between 10% and 25%. This risk can be exacerbated by factors such as tumor burden, immobilization, and the effects of chemotherapy itself [4]
2. Thromboprophylaxis Benefits: While therapeutic anticoagulation is beneficial for patients who develop VTE, the effectiveness of prophylactic anticoagulation in improving overall outcomes remains unclear. Studies indicate that thromboprophylaxis can reduce the incidence of VTE to about 5%–10%, but there is no strong evidence that it improves survival rates [4].
3. Risk-Benefit Analysis: The decision to initiate anticoagulant therapy should involve a careful risk-benefit analysis. Patients with pancreatic cancer often have underlying gastrointestinal dysfunction, which increases the risk of bleeding associated with anticoagulants. Therefore, clinicians must consider individual patient factors, including their overall health status and specific risk factors for both VTE and bleeding [4]
4. Guidelines and Recommendations: There is currently no consensus on uniform recommendations for thromboprophylaxis in this patient population. Some guidelines suggest considering prophylactic anticoagulation for high-risk patients, particularly those undergoing intensive chemotherapy or those with additional risk factors for thrombosis [4][5].
5. Clinical Judgment: The initiation of anticoagulant therapy should be individualized based on clinical judgment, taking into account the patient's risk profile for VTE and bleeding complications. Continuous monitoring and reassessment during treatment are crucial to adapt the approach as needed.

Conclusion: While anticoagulant therapy may be considered in patients with unresectable pancreatic cancer undergoing chemotherapy to prevent VTE, its use should be tailored to the individual patient's risk factors and overall clinical scenario. The lack of clear evidence supporting improved survival outcomes necessitates a careful evaluation of risks versus benefits in each case.