Exocrine Pancreatic Tumors

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41.1 Definition and Classification [1]

- **Malignant tumors.**
  Origin:
  - Ductal cells.
    Ductal adenocarcinoma—75–90%.
    Giant-cell carcinoma—5%.
    Cystadenocarcinoma—rare.
    Mucinous carcinoma—rare.
    Small-cell carcinoma—rare.
    Anaplastic carcinoma—rare.
  - Acinar cells:
    Acinar cell carcinoma.
    Acinar cell cystadenocarcinoma.

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  - Conjunctive tissue.
    Sarcoma—rare.
    Lymphoma—rare.
  - Pancreatic metastasis (more frequently from breast carcinoma, lung carcinoma, melanoma, or non-Hodgkin lymphoma).
- **Tumors with malignant potential.**
  - Solid pseudopapillary tumors.
  - Intraductal papillary mucinous neoplasia (IPMN).
- **Benign tumors.**
  - Serous cystadenoma.
  - Mucinous cystadenoma.
  - Solid serous adenoma.
  - Lymphoepithelial cyst.
  - Hamartoma.

41.2 Pancreatic Ductal Adenocarcinoma

41.2.1 Epidemiology [2]

- Aggressive, 5-year survival rate < 10%,
- Rare before the age of 45, incidence rises sharply thereafter,
- Men > women,
- Risk factors [2, 3]:
  - Cigarette smoking,
  - Obesity,
  - Diabetes mellitus, metabolic syndrome,
  - Family history (>2 first-degree relatives),
  - Familial pancreatitis (PRSS1),
  - Peutz–Jeghers syndrome (STK11).
  - familial atypical multiple mole melanoma syndrome FAMMM (P16),
  - Lynch syndrome (MLH1, MSH2, MSH6, or PMS2).
  - Ataxia-telangiectasia (ATM),
  - Hereditary ovarian and breast cancer (BRCA1, BRCA2),
  - PALB2, CHECK2 mutations.

41.2.2 Pathogenesis [4]

– Precursor lesions: pancreatic intraepithelial neoplasia (PanIN).
  PanIN-1: flat/papillary without atypia.
  PanIN-2: papillary with atypia.
  PanIN-3: severe architectural and cytonuclear abnormalities, but invasion through the basement membrane is absent.
– The most frequent genetic abnormalities in invasive pancreatic adenocarcinoma:
  Mutational activation of Kras oncogene,
  Inactivation of tumor suppressor genes: CDKN2A/p16, TP53 si SMAD4.

41.2.3 Diagnostic [4, 5]

- Clinical signs.
  – Asthenia.
  – Weight loss.
  – Abdominal/epigastric/back pain.
  – Nausea, vomiting.
  – Steatorrhea.
- Physical exam.
  – Hepatomegaly or epigastric mass.
  – Jaundice,
  – Courvoisier's sign (nontender but palpable distended gallbladder at the right costal margin).
  – Cachexia.
  – Ascites.
- Laboratory tests:
  – Increased total and conjugated (direct) bilirubin, alkaline phosphatase (AP), GGT (obstructive jaundice—pancreatic head tumors),
  – CA 19–9 usually elevated.
  – Mild normochromic anemia, thrombocytosis,
  – Increased liver enzymes and AP (liver metastasis).

- Imaging tests:
  - Transabdominal ultrasound: indicates presence and level of obstruction, rarely the tumor (lesions smaller than 3 cm are usually missed).
  - CT with pancreatic protocol: preferred imaging tool for staging and resectability status [3].
  - MRCP: provides supplementary information; noninvasive method for imaging the biliary tree and pancreatic duct [3].
  - PET-CT: in high-risk patients to detect metastasis.

41.2.4 Role of Endoscopy

- EUS significantly improved PDAC diagnosis, especially for small-size tumors [3, 6–8].
  - Identifies dilated biliary ducts (Fig. 41.1) and the level of obstruction (Fig. 41.2).
  - Allows for the characterization of pancreatic lesions (using EUS-elastography and contrast-enhanced EUS) (Fig. 41.2).
  - EUS can be used for staging as it allows for the identification of liver metastasis (Fig. 41.3).
- EUS-FNA/FNB is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and lower risk of peritoneal seeding (Fig. 41.4) [3, 6].

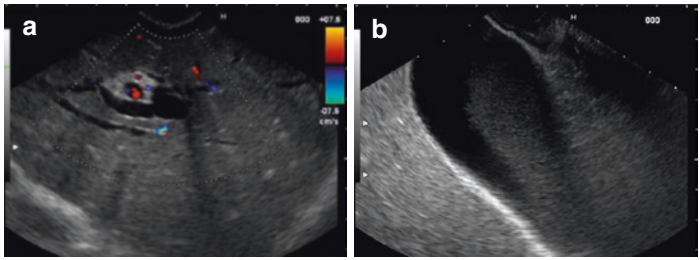

Fig. 41.1 EUS showing dilated intrahepatic biliary ducts in the left liver lobe (**a**) and a distended gallbladder with sludge (**b**) in a patient with pancreatic ductal adenocarcinoma

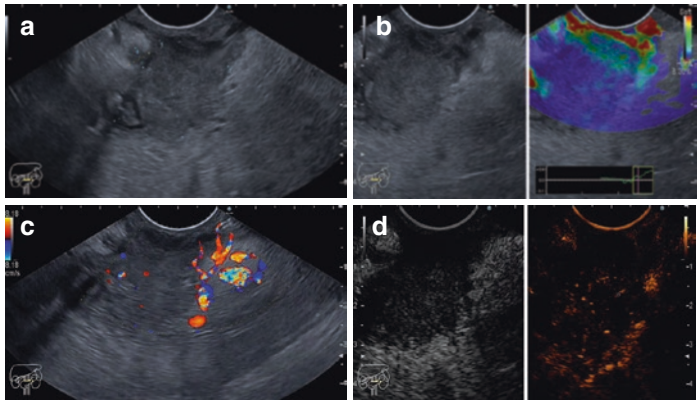

Fig. 41.2 EUS showing a hypoechogenic, irregular pancreatic tumor (**a**) with a "hard" appearance on EUS-elastography (**b**) with a poor Doppler signal and collateral circulation (**c**), hypoenhanced in the arterial and venous phase on contrast-enhanced EUS (**d**)

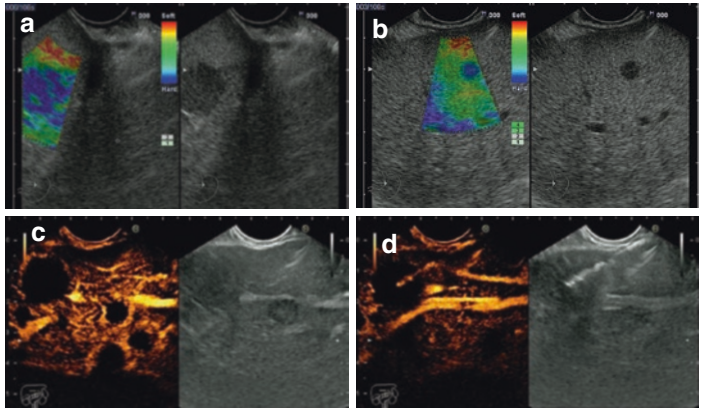

Fig. 41.3 EUS elastography showing liver metastasis (lesions with "hard" appearance on elastography) in left liver lobe in patient with pancreatic ductal adenocarcinoma (**a**, **b**); contrast-enhanced EUS showing liver metastasis with hypoenhancement in the arterial phase (**c**) and allows for guidance of EUS-FNA (**d**)

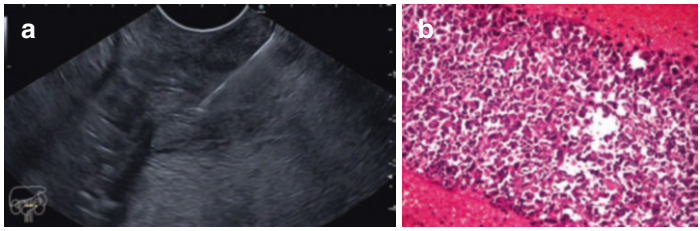

Fig. 41.4 EUS-guided fine-needle biopsy of a pancreatic tumor (**a**) with a histopathology examination showing pancreatic ductal adenocarcinoma (**b**)

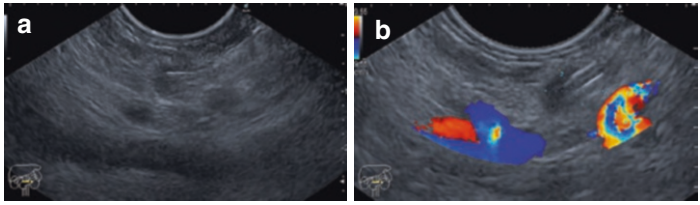

Fig. 41.5 EUS-guided fiducial marker placement (**b**) inside a pancreatic tumor (**a**) for guidance of radiotherapy

- EUS-FNA can be used for interventional procedures such as celiac plexus neurolysis, fiducial markers placement for guidance of radiotherapy (Fig. 41.5), or biliary drainage with metallic stents [9].
- A pathologic diagnosis is not required for resectable tumors before surgery [3].
- ERCP is used for confirmation of diagnosis (by brush cytology/direct biopsies) and for drainage with plastic stents or SEMS.

41.2.5 Staging [3]

2.5.1 TNM Staging

- **Tumor (T).**
  - TX—Primary tumor cannot be assessed.
  - T0—No evidence of primary tumor.

  - Tis—Carcinoma in situ.
  - T1—Tumor limited to the pancreas, 2 cm or smaller in greatest dimension.
  - T2—Tumor limited to the pancreas, larger than 2 cm in greatest dimension.
  - T3—Tumor extension beyond the pancreas (duodenum, bile duct, portal or superior mesenteric vein) but not involving the celiac axis or superior mesenteric artery.
  - T4—Tumor involves the celiac axis or superior mesenteric arteries.
- **Regional lymph nodes (N).**
  - NX—Regional lymph nodes cannot be assessed.
  - N0—No regional lymph node metastasis.
  - N1—Regional lymph node metastasis.
- **Distant metastasis (M).**
  - MX—Distant metastasis cannot be assessed.
  - M0—No distant metastasis.
  - M1—Distant metastasis.

41.2.6 Criteria Defining Resectability Status at Diagnosis [3]

1. **Resectable.**
   (a) No arterial tumor contact with celiac axis (CA), superior mesenteric artery (SMA), common hepatic artery (CHA).
   (b) No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤ 180 vein contact.
2. **Borderline resectable.**
   (a) Tumor contact with CHA without extension with CA allowing for safe and complete resection and reconstruction.
   (b) Tumor contact with the CA or SMA ≤ 180°.
   (c) Tumor contact with the SMV or PV > 180°, allowing for safe and complete resection and reconstruction (Fig. 41.6).

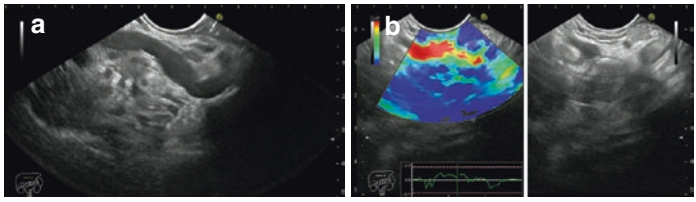

Fig. 41.6 EUS showing a ductal pancreatic adenocarcinoma with 180° tumor contact with SMV (**a**) with a hard appearance of the tumor on EUS elastography (**b**)

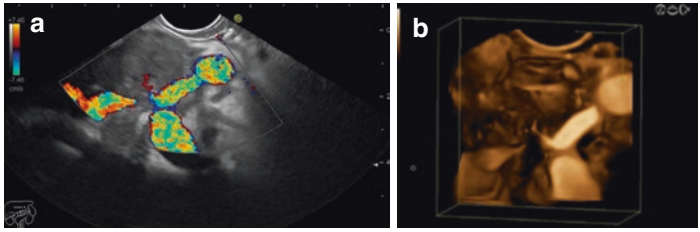

Fig. 41.7 Contrast-enhanced EUS showing a pancreatic ductal adenocarcinoma with circumferential invasion of the celiac axis and the hepatic artery visible on Doppler (**a**), with 3D reconstruction in harmonic mood with low mechanical index (**b**)

3. **Locally advanced, unresectable.**
   (a) Tumor contact with CA or SMA > 180° (Fig. 41.7).
   (b) Unreconstructible SMV/PV due to tumor involvement or occlusion.

41.2.7 Treatment [3, 10, 11]

- **Resectable disease (<20%).**
- Complete resection with negative margins (R0) is the only curative treatment.
- Surgical procedures:
  Pancreatoduodenectomy Whipple (or modified Whipple with pylorus preservation)—for tumors of the pancreatic head and uncinate.

Distal pancreatectomy with en-bloc splenectomy—for tumors of the pancreatic body and tail.

- Adjuvant therapy: mFOLFIRINOX* (fit patients, good performance status, and no important comorbidities); capecitabine + gemcitabine; fluorouracil/folinic acid.
- **Borderline disease.**
- Neoadjuvant chemotherapy (FOLFIRINOX or gemcitabine), followed by chemoradiation (with capecitabine).
- **Locally advanced disease.**
- Obstructive jaundice: stent placement (ERCP) or bypass surgical interventions (cholecystic-jejunostomy/choledochal-jejunostomy).
- Palliative chemotherapy: gemcitabine, 6 months.
- Chemoradiation improves local control.
- **Metastatic/recurrent disease.**
  - **First line.**

    FOLFIRINOX (European standard)/gemcitabine + nab-paclitaxel (American standard)—for patients with performance status 0–1.

    Gemcitabine monotherapy—for patients with performance status 2.

    BRCA1/BRCA 2 mutations: maintenance therapy with Olaparib after minimum 16 weeks of platinum-based chemotherapy.
- **Second line.**

  Performance status 0–1: fluoropyrimidine in combination with oxaliplatin, irinotecan, or nanoliposomal irinotecan (after gemcitabine +/− nab-paclitaxel in first line); gemcitabine +/− nab-paclitaxel (after FOLFIRINOX in first line).

  Performance status 2: monotherapy with a fluoropyrimidine (after gemcitabine in first line) or gemcitabine (after FOLFIRINOX in first line).

**FOLFIRINOX:5-fluorouracil + folinic acid + irinotecan + oxaliplatin.*

41.3 Pancreatic Cystic Neoplasms

41.3.1 Classification [1, 12]

- Benign.
  - Serous cystadenoma,
  - Lymphangioma/hemangioma/teratoma.
- Premalignant/malignant.
  - Mucinous cystadenoma,
  - Intraductal papillary mucinous neoplasms (**IPMN**),
  - Mucinous cystadenocarcinoma,
  - Cystic neuroendocrine tumors.

41.3.2 Epidemiology [12]

- Detected in approximately 10–15% of general population,
  - Without history of pancreatitis,
  - Discovered incidentally on IRM/CT scans.
- Represent 1–2% of malignant pancreatic tumors,
  - Better prognosis than pancreatic ductal adenocarcinoma.

41.3.3 Serous Cystadenoma [13]

- Almost always benign and occur more commonly in women,
- Classified into serous microcystic adenomas and serous macrocystic adenomas,
- Unifocal, round, well-demarcated, and often honeycombed,
- Contain serous fluid that is mucin-free,
- Characteristic aspect on EUS as described in Fig. 41.8.

41.3.4 Mucinous Cystadenoma [12]

- Premalignant lesions.
  - Frequent in women, incidentally discovered, commonly located in the pancreatic head/body.

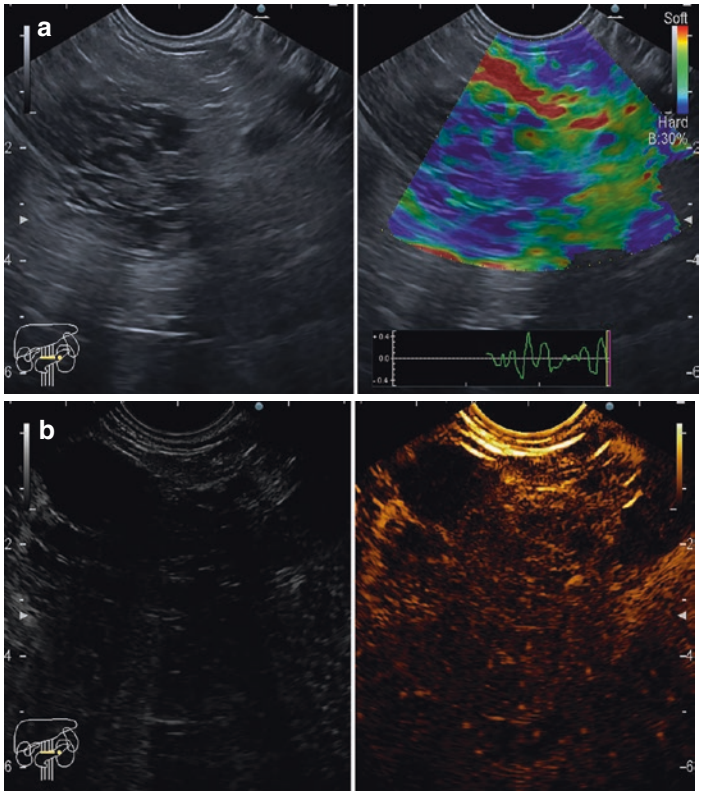

Fig. 41.8 Serous microcystic adenoma with pseudo- "hard" appearance on EUS elastography due to artifacts induced by microcysts and blood vessels located on the septations (a), with hypoenhanced septations on contrast-enhanced EUS (b)

  - Survival >60% for resected mucinous cystadenoma.
  - Survival <5% pentru resected mucinous cystadenocarcinoma.
- EUS aspect in described in Fig. 41.9.
  - EUS-FNA with fluid aspiration (amylase, CEA, CA 19–9) + cytological examination.
  - Risk factors for malignancy.
    Mural nodules and thick wall.
    Size >3 cm.

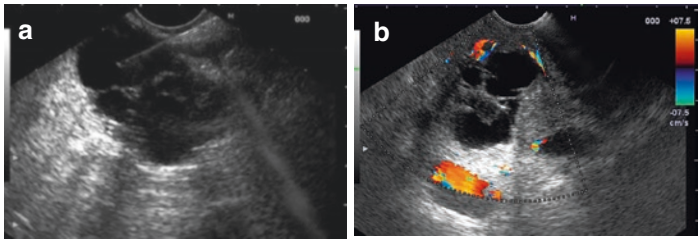

Fig. 41.9 Mucinous macrocystic adenoma with thick wall (**a**) and mural nodules (**b**) that requires EUS-FNA for diagnosis confirmation

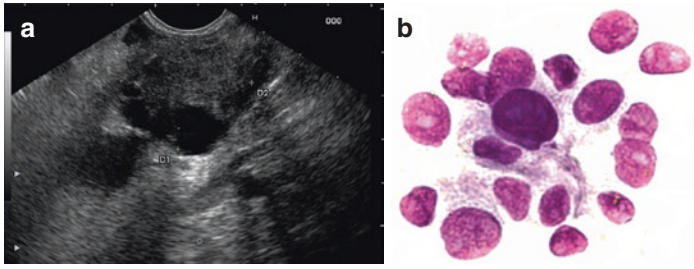

Fig. 41.10 Mucinous cystadenocarcinoma with hypoechogenic solid component (**a**), with EUS-FNA and cytological examination showing hyperchromatic nuclei, with decreased nuclei-cytoplasm ratio (**b**)

41.3.5 Mucinous Cystadenocarcinoma [12]

- Arises from mucinous cystadenoma.
- Characteristic EUS aspect as described in Fig. 41.10.
  - Irregular cystic lesions with solid areas and thick wall.
  - requires aspiration of the cystic lesions and EUS-FNA from the solid component.

41.3.6 Intraductal Papillary Mucinous Neoplasms (IPMN) [12]

- Premalignant lesions,

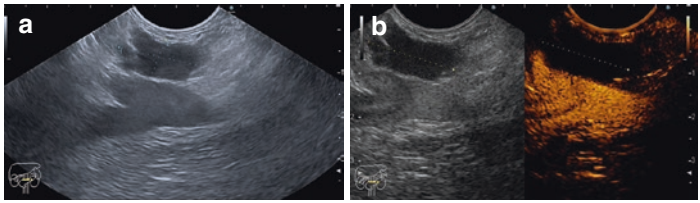

Fig. 41.11 Side branch IPMN located in the pancreatic isthmus, closed to the spleno-mesenteric confluent (**a**) without enhancement in the arterial and venous phase on contrast-enhanced EUS (**b**)

- EUS/EUS-FNA superior to CT and IRM.
  - Allows for the detection of mural nodules and differential diagnosis with mucus plugs using contrast enhanced EUS,
  - Identifies the communication with the pancreatic duct,
  - EUS-FNA enables the aspiration of the cystic fluid (positive "string sign").
  - Depicts concomitant pancreatitis changes.
- Types of IPMN:
  - Branch duct (Fig. 41.11), incidentally discovered, incidence increases with age,
  - Main duct, frequently located in the pancreatic head, symptomatic (weight loss, abdominal pain, jaundice).

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