Pancreatic cancer recurrence - can we do better?

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Learning objectives

The aim of this poster is to give an overview in the diagnosis of pancreatic cancer recurrence by means of imaging techniques and to review the typical and less common presentation or pancreatic cancer relapse.

Background

Pancreatic cancer is one of the most common deadly cancers and represents the fourth leading cause of cancer-related death in Europe and the United States. Worldwide, its incidence ranges from 1 to 10 cases per 100,000 people, and it is higher among men in developed countries. [1,2]

The majority of pancreatic tumors (95%) are exocrine carcinomas, most of them being adenocarcinomas (85%), localized in the head of the pancreas (60-70%). [2]

Surgical intervention is the only potentially curative treatment for pancreatic cancer, but because of its late presentation, only 15 to 20 % of the patients are candidates for pancreatectomy. Unfortunately, up to 70% of the resected tumors present microscopically positive margins (R1 resection), and the overall 5-year survival rate is lower than 5%. [3]

When complete resection (R0) is achieved survival increases to 15-27% at 5 years (25-30% in node negative vs. 10% in node positive disease). [4] However, pancreatic cancer is very aggressive and most of the patients who had undergone tumor resection will have recurrence of cancer within the first two years after resection [5].

Detection of recurrence will allow patient eligibility for investigational studies and new treatment options that are being studied in order to improve the aforementioned poor outcomes of pancreatic cancer. Thus, properly assessing radiological patterns of recurrence in the surveillance of pancreatic cancer represents a current challenge that needs to be addressed.

The following section will summarize the most representative radiological features of pancreatic cancer recurrence.
Findings and procedure details

Computed tomography (CT) is the imaging technique of choice to identify the disease and plan a therapeutical approach on pancreatic cancer. It is also used to identify surgical complications and detect tumor reappearance. [6]

Before evaluating the most common patterns of recurrence, we need to understand which patients are candidates for surgery, and the typical aspect of normal CT after resection. Differential diagnosis between normal findings, complications and recurrence are difficult to establish and will be further described. Sometimes other imaging techniques can be performed to assess the proper diagnosis. But quite often only follow-up might help in establishing whether changes are benign or malignant.

STAGING

An accurate radiological examination of pancreatic tumors is paramount to select candidates for surgical resection and optimal patient management. [4,7]. Moreover, an appropriate tumor staging allows more effective treatments.

Depending on the stage of the tumor at the time of diagnosis, pancreatic cancer can be categorized into three different types[8):

- Localized (8-15%)
- Locally advanced (30-40%)
- Advanced with distant/metastatic disease (>50%)

As previously mentioned, an accurate staging is crucial in regards to resectability (changing criteria over time). Thus, pancreatic cancer might be preferably classified as [5]:

- Non metastatic

  - Resectable Fig. 1 on page 11
  - Borderline resectable (or potential candidates for downstaging) Fig. 2 on page 12
  - Locally advanced/unresectable

- Metastatic Fig. 3 on page 13
\begin{itemize}
\item Unresectable
\end{itemize}

\textbf{NORMAL CT FINDINGS AFTER SURGERY}

The following normal findings can be observed [6,9,10]:

- **Anatomical changes**
  - Anastomoses
  - Surgical material (clips, pancreatic stent)

- **Acute inflammatory changes**
  - Fluid, edema, fat stranding
  - Reactive lymph nodes. In the surgical bed and mesentery.

- **Pseudomass/mass-like focal lesion**
  - Unopacified bowel loop. Differential diagnose with abscesses vs. recurrence
  - Induration surrounding vessels (Superior mesenteric vein and artery -SMV, SMA)

- **Duct dilatation**

\textbf{Anatomical changes}

\textit{Anastomoses}

Knowledge of the type of surgery and the site of anastomoses is important for radiologic understanding of imaging studies.

Surgical procedures can be classified according to the tumor localization as follows:

- **Tumors in the head**:
  - pancreateoduodenectomy
    - classic Whipple or cephalic pancreateoduodenectomy
    - pylorus-preserving Fig. 4 on page 14
• subtotal stomach-preserving (pancreatogastric anastomosis) Fig. 5 on page 14

- Tumors in the body or the tail:
  • distal pancreatectomy Fig. 6 on page 14
  • with or without spleen preservation

It should be mentioned that central pancreatectomy is rarely used, and total pancreatectomy is to be avoided at diagnosis, but is sometimes used for local recurrent disease.

**Surgical material**

Location of surgical material can help understand the type of surgical procedure, but can interfere interpretation due to beam hardening. Fig. 7 on page 15

Pancreatic stent may be used for draining the pancreaticojejunostomy to avoid obstructive problems when there is no significant dilatation of the main pancreatic duct. Fig. 8 on page 16

**Acute inflammatory changes**

Non-malignant changes in the CT analysis associated to normal inflammatory processes are frequent and should not be confused with tumor recurrence or abnormal inflammation. Most of these changes are typically resolved by 3 to 6 months after resection (stability or regression). Fig. 9 on page 16

**Mass-like focal lesion**

Unopacified bowel loops can be mistaken as a focal lesion. Fig. 10 on page 17

Induration surrounding vessels. With time (>3-6 months after resection) fat stranding that decreases or persists unchanged is interpreted as scar or fibrosis.

**Duct dilatation**
Edema can cause mild dilatation of the common bile duct in the early postoperative period. Fig. 11 on page 18

COMPLICATIONS

The majority of complications are typically evaluated in the early CT after pancreatectomy.

Typically:

- Collections. They often occur within the first two weeks and resolve by four-six weeks. Usually localized in the surgical bed, and around the anastomosis. Fig. 12 on page 19

- Abscesses. Secondary to pancreatic fistula, infection of collection or anastomotic leakage. These collections are most frequently treated by percutaneous drainage. Fig. 13 on page 20

Note that the term collection can be used for both collection and abscess.

Others types of complications are fistula, haemorrhage, haemathoma Fig. 14 on page 20, pancreatitis, vein thrombosis, anastomotic leakage, hepatic infarction, delayed gastric emptying, among others.

Some complications can appear or persist as delayed complications:

- Anastomotic stricture is the most common delayed complication
- Recurrence.

RECURRENCE

Recurrence is generally not an early complication Fig. 15 on page 21. It is detected within the first two years after resection, but median time of diagnosis is at 20 months. [12]
Subtle abnormalities in early CT scans are difficult to interpret and difficult to distinguish from inflammatory changes (e.g. stranding) Fig. 16 on page 21. Thus, follow-up CTs are needed to evaluate progressive changes in a possible early relapse.

Different common patterns of recurrence can be described:

- Local recurrence (approx. 30%) around the remnant pancreas
- Distant or metastatic (40%)
- Both local and metastatic simultaneously (approx. 30%)

**Local recurrence**

Local recurrence is localized in the retroperitoneum around the mesenteric vessels (celiac axis and superior mesenteric artery), in the:

- remnant pancreas
- soft tissue Fig. 17 on page 22
  - tumor bed
  - epatic hilium
- regional nodes Fig. 18 on page 23

Presented as:

- Infiltrating mass
- Soft tissue attenuation
- Perineural invasion
- Encasement of the vessels

**Metastatic recurrence**

The most typical pattern of recurrence is metastasis, either alone or a combination of both local and distant relapse Fig. 19 on page 24. This is partly due to presumed micrometastases, not detected at diagnosis, that evolve.
Different patterns detected:

- Liver metastasis
- Peritoneal metastasis Fig. 20 on page 25
- Others:
  - node metastasis, e.g. para-aortic lymph node metastasis
  - extraabdominal: lung among others Fig. 21 on page 26

**CT CHANGES AFTER CHEMOTHERAPY AND RADIOTHERAPY**

After surgery alone, rates of pancreatic cancer relapse are high for both systemic (>80 %) and local (> 20 %) recurrence. In an effort to improve both survival and healing rates, additional treatment, such as chemotherapy and/or radiation therapy (CRT), should be offered.

Locally advanced pancreatic cancer patients can be downstaged in 30% of the cases and receive following R0 resection, and consequently improve survival. Fig. 22 on page 27. Regardless of the extent of decrease in tumor size or the degree of residual vascular involvement, partial regression of tumor-vessel contact indicates suitability for surgical exploration. [13]

CT postprocessing images is a very useful tool for vascular contact evaluation.

Following neoadjuvant CRT, the aforementioned contact may be replaced by:

- Perivascular haziness or
- Fat stranding

These changes may respond to post-treatment fibrosis, tissue replacement or viable tumor (residual or recurrent), and thereby making the assessment of tumor resectability a challenging task. [5]

Other changes are:
- Necrotic, fibrous or inflammatory changes.

- Steatosis. Mostly in the left hepatic lobe.

Response of CRT can be evaluated with PET-CT Studies.

**OTHER IMAGING STUDIES**

Apart from CT, the following imaging studies can be performed to detect recurrence.

**Magnetic Resonance Imaging**

- Similar sensitivity and specificity in pancreatic cancer diagnosis than CT (no conclusive data in pancreatic cancer recurrence are found in the literature, but similar numbers could be expected)

- Problem solving (isoattenuating lesions, indeterminate liver lesions, fibrosis, use in allergic-to-contrast patients) Fig. 23 on page 27

- Not as readily available as CT (elevated cost)

**Ultrasound (US) imaging**

- Low complication rates

- Small or isoattenuating tumors in CT can be detected in US

- Ultrasound guided fine needle aspiration is highly sensitive for recurrence detection

**Positron emission tomography - Computed tomography (PET/CT)**

Contrast enhanced PET -CT can be used for:

- *Early detection* (since metabolic changes might occur prior to morphologic ones)
• minimum 6 weeks after procedure: Inflammatory changes like surgery, radiotherapy or stent placement might also cause fluodeoxyglucose (FDG) uptake.
• 3 months after surgical intervention

Note: some studies indicate that a significant FDG uptake before treatment is related to early recurrences and could be associated with tumor aggressiveness. Early follow up studies with PET-CT would be particularly indicated for these patients. [6]

- Confirmation of suspected recurrence
  • Distinguishing fibrosis vs. recurrence. Sometimes if FDG uptake is discrete, PET-CT does not permit diagnose, and further follow-up is needed. Fig. 24 on page 28

TREATMENT AND FUTURE PERSPECTIVES:

As discussed in this poster, pancreatic cancer has a poor prognosis and there is no consensus on the adequate follow-up schedule after surgery, or whether periodical follow-up after resection is needed. [12].

Moreover, it remains controversial whether diagnosis and treatment of recurrence will improve survival. Some studies reveal that asymptomatic recurrence or repeated pancreatectomy are associated with improved survival rates. [5,13].

We believe that patients’ prognosis is expected to increase in the following years, due to the development of new forms of treatment.

Some available used treatments are outlined below:

- Repeat pancreatectomy
  Could be beneficial on the prognosis of pancreatic cancer in patients that show isolated local recurrence in the remnant pancreas after initial pancreatectomy. [5]

  Fig. 25 on page 29

Local tumor and local recurrence have a better prognosis than advanced disease, and repeating pancreatectomy might increase survival in these cases (7 to 25months if R0 achieved).
- **Adjuvance**

Will be performed after surgery.

- **Focal ablation** Fig. 26 on page 29

Some therapies used for locally advanced/unresectable disease can be used for recurrence treatment

Thermal ablation (percutaneous or intrasurgical) is a feasible alternative, and may increase survival. [14]

- **New therapeutic strategies**, such as minimimally invasive surgical techniques, focused radiotherapy and several *different clinical studies* may play an important role in the near future.

**Images for this section:**
**Fig. 1:** Multidetector CT image of a 79 year-old patient with unspecific jaundice and 5kg of weight loss shows an almost isodense mass of 12mm in the head of the pancreas (orange arrow). Distended gallbladder and discrete Wirsung dilatation is identified. Discrete mesenteric fat stranding around the pancreas is observed, corresponding to mesenteric paniculitis. Neither vascular invasion nor distant metastasis are observed indicating potencially resectable tumor. Note: This patient presented pancreas divisum as anatomic variant.

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Fig. 2: CT scan shows borderline-resectable pancreatic cancer. A pancreatic mass in the head of the pancreas with surrounding fat stranding and vascular involvement is observed (orange rectangle).

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**Fig. 3:** Different patterns of pancreatic metastatic disease. A. Multiple hypodense liver metastases can be observed. B. Pancreatic mass in the head of the pancreas, with dilated pancreatic duct and atrophy of the rest of pancreatic body. Infracentimetric implants in the liver capsule can also be observed (white arrows).

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![Fig. 3](image1)

**Fig. 4:** Pylorus-preserving cephalic pancreatoduodenectomy. A. At diagnosis, a 12mm focal mass is identified in the head of the pancreas (same patient as in fig 1). B. CT scan 18 months after pylorus-preserving cephalic pancreatoduodenectomy. Surgical material (green arrowhead) and discrete pancreatic duct dilatation (white arrow) are observed.

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![Fig. 4](image2)

**Fig. 5:** A series of 3 CT scans of a 70-year-old woman that underwent a cephalic pancreatoduodenectomy with gastropancreatic anastomoses. A. Biliary duct dilatation is showed. B. Peripancreatic fat stranding indicating pancreatitis secondary to pancreatic head obstruction. C. Post procedure pancreatic anastomoses is shown.

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![Fig. 5](image3)
Fig. 6: Distal pancreatectomy.

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**Fig. 7**: Anastomoses and clips.

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**Fig. 8**: A pancreatic duct stent (yellow arrows) is depicted inside the main pancreatic duct.

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Fig. 9: Normal postoperative findings after a cephalic duodenopancreatectomy procedure performed for a pancreatic head adenocarcinoma. A. Axial multidetector CT image days after surgery shows appreciable edema at the pancreaticojejunostomy loop. B. CT image obtained one month later still shows some edema. Other inflammatory changes such as fat stranding are also observed.

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Fig. 10: Axial multidetector CT image 15 months after resection shows a mesenteric node recurrence (red arrow). Unopacified bowel loops (yellow arrows) can also be mistaken for recurrence in this section.

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**Fig. 11:** Multidetector CT image shows mild dilatation of the main pancreatic duct (white arrow), a normal postsurgical finding.

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**Fig. 12:** A. Multidetector CT images shows a postoperative homogeneous collection in a patient who underwent distal pancreatectomy. B. Endoscopic drainage was performed (drainage catheter is observed.)
**Fig. 13:** Three different CT scans show a postoperative abscess (yellow stars) with partial response to broad spectrum antibiotherapy in a patient that underwent distal pancreatectomy. A. Retrogastric collection showing air bubbles in its interior is observed. B. At percutaneous drainage purulent material was removed. C. Residual collection 6 days after previous CT scan.

**Fig. 14:** Early complications after Whipple procedure. CT image shows an hyperdense lesion that correspond to a mesenteric haematoma (orange arrow) and a homogeneous collection in the surgical bed (yellow star).
Fig. 15: Contrast-enhanced multidetector CT of an 81-year-old woman with jaundice and 7 kg of weight loss. A. CT image at diagnosis shows a potentially resectable mass in the head of the pancreas. B. After surgery a pancreatic adenocarcinoma was diagnosed. C. Inflammatory changes are observed 1 month after surgical procedure. D. 9-month follow-up CT show fat stranding around the surgical bed. E. 15-month follow-up CT shows local recurrence (red arrow).
Fig. 16: Inflammatory changes vs. Recurrence? (same patient as fig. 12). Contrast-enhanced CT image show the following changes: A. Early postoperative complication. B. Small soft tissue focal lesion is observed in the surgical bed (white arrow), less than 1 month after surgery. C. Progressive changes in the 6-month follow-up CT suggest local recurrence (white arrow).

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Fig. 17: Early relapse is sometimes difficult to distinguish from fibrosis. A. Soft tissue band is detected around the mesenteric artery (white arrows) in the 6-month follow up CT. B. Changes that decrease in the 12-month follow-up CT indicate fibrosis. A fat necrotic area is observed (yellow arrow) after distal pancreatectomy.

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Fig. 18: Mesenteric node recurrence (same patient as in fig 15) A. Follow up 9 months after resection. B. Axial multidetector CT image 15 months after resection shows a mesenteric node recurrence (red arrow). Unopacified bowel loops (yellow arrows) can also be mistaken for recurrence in this section.

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Fig. 19: Simultaneous local and metastatic recurrence of pancreatic cancer. A. Pancreatic mass. B. Liver metastases. C. Partial response after chemotherapy. D. Tumor recurrence.

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Fig. 20: Peritoneal metastases. Discrete amount of perihepatic fluid (arrows) and peritoneal lesions are observed and are suggestive of peritoneal carcinomatoses.

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Fig. 21: Extraabdominal metastasis (same patient as in fig 12 and 17). A. Local recurrence (white arrow). B. 9-Month follow-up CT shows a 4mm solid pulmonary node (yellow arrow) that was not present in the previous control.

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Fig. 22: Locally advanced pancreatic cancer in a 55-year-old patient that underwent neoadjuvant CRT and surgery. A. Multidetector CT at diagnosis shows a neoplastic pancreatic lesion with superior mesenteric vein infiltration (borderline resectable). B. Metallic main biliary duct stent is observed. C. After 45Gy radiotherapy the tumor is smaller in size (discrete) and vascular contact is reduced. Plastic stent inside metallic biliary duct stent was placed due to obstruction. D. Perivascular fibrosis after surgery (18 months after diagnosis). E. Atrophy of the remnant pancreas. F. Soft tissue enlargement next to the mesenteric vein. PET-CT shows significant FDG-uptake. G. Perivascular soft tissue progression indicates local recurrence (4 years after first diagnosis; 2 years and 8 months after surgical resection).

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Fig. 23: A 68 year-old-woman with pancreatic adenocarcinoma underwent duodeno-duodepancreatectomy 4 years before. A. CT scan without contrast in this allergic patient shows a retroperitoneal mass (arrow). B. MR imaging in LAVA Multiphase T1 weighted sequence shows encasement of the mesenteric vessels, suggesting recurrence (arrow). C. Pancreatic recurrence is also suspected in the single shot fast spin echo (SSFSE) T2-weighted sequence.

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Fig. 24: Fibrosis vs. Recurrence (Same patient in fig 16) A. 6-month follow-up: Perivascular fibrosis? B. 12-month follow-up. Stability or decrease of fibrosis. C. 15-month follow up shows stability, indicating fibrosis. D. A PET-CT, was performed at 12 month follow-up, in order to detect an early recurrence. Unfortunately, it shows a discrete FDG caption, being unspecific for cancer.
Fig. 25: A. A patient with pancreatic cancer. B Partial pancreatectomy, with splenectomy and left nephrectomy is performed C. 3-month follow-up study shows inflammatory changes. D. A year later total pancreatectomy is performed after local recurrence is diagnosed. E. 6 month follow up after re-pancreatectomy. F. Changes after adjuvant therapy (radiotherapy).

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Fig. 26: Can we treat metastatic disease? A. Percutaneous focal ablation of a liver metastasis. B. CT control 3 months after ablation shows an hypodense lesion without focal enhancement, indicating adequate postablative changes (no relapse is observed).

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Conclusion

CT changes after pancreatic cancer treatment (surgery, chemotherapy and radiotherapy) are difficult to understand and present a challenge in current radiology.

Before analyzing radiological patterns of recurrence, the typical aspects of normal CT after resection need to be understood. Differential diagnosis between normal findings, complications and recurrence are difficult to establish and need to be carefully studied.

In this regard, CT is the gold standard for identifying normal appearance of the surgical bed and complications after surgery. CT plays also an important role in pancreatic cancer recurrence diagnosis. Nonetheless, sometimes other imaging techniques may be used to assess a proper interpretation.

New therapies are being developed in order to more effectively treat pancreatic cancer and its recurrence, thus it is expected that patient survival will increase in the future. The success of these treatments relies on an accurate radiological interpretation. Therefore radiologists should become familiar with surgical procedures to correctly interpret postoperative changes. In this regard, follow-up after resection might help to establish whether changes are benign or malignant.

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