Computer tomography in pre-oprative staging of pancreatic cancer
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Chapter 7

Staging of pancreatic cancer, current opinions on new diagnostic modalities

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Introduction

The prognosis of pancreatic cancer has remained poor over the decades. The five years survival rate is less than 10 %, although higher survival rates have been found in selected groups of patients, that had undergone a radical resection of the tumor\(^1\)\(^2\). Peri-operative mortality and morbidity have declined from more than 10% to less than 5% in specialised centres. In approximately 20% of the patients with a pancreatic carcinoma a surgical exploration is performed, but a resection of the tumor is possible in only half of the explored patients. In the majority of patients the tumor is already irresectable at the time of the diagnosis. On the other hand, surgical exploration may be under-utilised as many patients regarded as having stage I disease do not receive a surgical exploration\(^2\).

Early detection of tumor and improved pre-operative selection of patients may benefit the results of surgery. Diagnostic imaging techniques, such as Doppler ultrasonography (US), endoscopic and laparoscopic US, multidetector CT, and MRI have developed rapidly. In this paper their relative value and role in a (cost-) effective diagnostic strategy are discussed.

Demography, etiology and risk factors.

The incidence of pancreatic carcinoma is about 8-10 per 100,000 persons per year and is relatively increasing. In Western countries pancreatic carcinoma is responsible for 5% of all cancer related deaths, preceded by lung cancer, colorectal cancer and breast cancer. Pancreatic carcinoma affects approximately 29,000 patients each year in the United States. The related direct costs (mostly hospital based) are estimated to be nearly 900 million dollars per year. In the Netherlands the incidence of pancreatic cancer is 2% of all new cancers, approximately 1500 cases per year. Due to the high mortality from pancreatic cancer, the number of annual deaths due to pancreatic cancer is approximately equal to the incidence\(^3\).

There is a predominance of pancreatic cancer in men over women of 1.5 to one\(^4\).

Established environmental risk factors are a previous history of pancreatitis (hereditary and alcoholic), diabetes mellitus, cholelithiasis, and exposure to tobacco and salted foods. Fresh fruits and vegetables are thought to lower the risk for pancreatic cancer\(^5\)\(^7\). The mortality of pancreatic carcinoma seems to be increased by smoking of cigarettes. Other factors associated with increased mortality are a family history of pancreatic cancer, black race, and an increased body mass index\(^7\).

Most pancreatic tumors (85%) are invasive ductal adenocarcinoma arising from the exocrine pancreatic ducts. Approximately 75% of ductal adenocarcinoma are located
in the pancreatic head, 15% in the pancreatic body and 10% in the pancreatic tail. Other epithelial malignant tumors are serous and mucinous cystadenocarcinomas, and these mainly arise in the body and tail of the pancreas. Intraductally located pancreatic neoplasms consist of papillary adenomas and adenocarcinomas (mucinous ductectatic tumors). Tumors originating from the endocrine part of the pancreas such as apudoma, insulinoma, vipoma, gastrinoma, and glucagenoma contribute to less than 2% of pancreatic neoplasms.

Clinical presentation
Pancreatic cancer usually produces symptoms, when the disease is already in an advanced stage. The most important symptoms are weight loss and jaundice. Invasion of the celiac plexus causes severe pain radiating to the back. A painless and palpable gallbladder (Courvoisier’s sign) has been called pathognomonic for peri-ampullary tumors. A recent onset of diabetes mellitus may be the first symptom and is highly specific for pancreatic cancer.

A study in 1020 patients with suspected pancreatic disease showed that clinical examination and simple laboratory findings can discriminate between the patients with pancreatic cancer and those without. A high risk of having cancer was found for patients with recent onset diabetes (with a likelihood ratio of 8), a distended gallbladder (LR 3.7), or weight loss (LR 2.4).

Molecular aspects
The molecular profile of pancreatic cancer has been studied extensively. Overexpression of important oncogenes such as K-ras and bcl-2 have been described, as well as deletions or mutations of tumor suppression genes, such as p53, DPC4, p16, CDKN2, and the Rb gene.

Nearly all pancreas cancers show one alteration or a combination of oncogenic mutations and inactivations of tumor suppressor genes in hyperplastic and dysplastic ductal lesions, that are assumed to be non-malignant precursors lesions of pancreatic carcinoma, mutations of K-ras and p16 have also been described.

In bilio-pancreatic secretions of patients with pancreatic carcinoma, and in samples such as duodenal aspirates, stool or blood, identical K-ras mutations and 18q deletions have been detected. These findings raise the possibility to screen clinical samples for molecular markers in order to detect pancreatic cancer or even premalignant lesions (in patients of well defined populations at risk). Well known serum markers for gastrointestinal malignancies as CEA, CA 19-9, CA 50 and CA 242 are elevated in pancreatic
cancer as well. They show a high sensitivity for detection of tumor, but in symptomatic patients the sensitivity and accuracy of markers are lower than of CT. Serum markers are frequently used for monitoring disease activity in patients who receive non-surgical treatment and it has been shown that these markers have prognostic value for survival \(^{15,20}\).

In pancreatic cancer a variety of growth factors as well as growth factor receptors are expressed at increased levels eg: fibroblast growth factors, nerve growth factors, platelet-derived growth factors, insulin-like growth factors, and their respective ligands. All these factors contribute to the malignant phenotype of pancreatic cancer and eventually influence the prognosis. For example, presence of the EGF-receptor (epidermal growth factor) has been shown concomitantly with its ligands EGF and TGF-alpha (transforming growth factor). This was shown to be associated with enhanced tumor aggressiveness and lower survival rates after tumors had been resected \(^{21,22}\).

Furthermore sex hormones, such as estrogens, progesterone and androgens, seem to play a role in pancreatic cancer \(^{23}\). Estrogen receptors and androgen receptors have been found in ductal pancreatic cancer. In experimental pancreatic cancer an influence of estrogens on tumor growth has been shown. Some clinical studies suggest that Tamoxifen has an inhibitory effect on tumor growth in pancreatic cancer \(^{24,25,27}\).

### Imaging and staging

Diagnostic imaging is aimed at the detection of tumor and at establishing the resectability of a tumor. The TNM-classification is used for staging and has prognostic value for survival \(^{28}\). Usually, the diagnostic work-up includes ultrasonography, ERCP and multidetector helical CT.

Ten to twenty percent of patients with a pancreatic carcinoma have a tumor, that can be treated by an intentionally curative resection.

Tumors generally regarded as resectable are those staged as T1 or T2 tumors, with infiltration limited to the bile ducts or to the duodenum. In some institutions tumors staged as T3, with invasion of major veins, are also treated with venous resection.

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Ultrasonography

Ultrasonography (US) is an operator dependent modality of which the yield is partly dependent on to the specific experience of the performing radiologist. Most pancreatic carcinomas present as a mass that is hypo-echoic compared to normal pancreatic parenchyma. Indirect signs of a tumor are dilatation of the common bile duct and of the pancreatic duct. A diameter of the pancreatic duct of > 2.5 mm in the head and of > 2 mm in the tail is regarded as abnormal. The sensitivity of US for detection of a lesion in the pancreatic head is 72 - 98% \(^{29,30}\). Due to overlying bowel gas, visualisation of the pancreatic body and tail by sonography may be difficult. However, if the pancreas is seen well, the sensitivity for a carcinoma is up to 95% \(^{31}\). In a large prospective study (in 919 patients) the sensitivity of US for pancreatic cancer was 90%, with a specificity of 98.9 % (770/779) \(^{32}\). In a smaller series the sensitivity of US for detection of peri-ampullary tumors was 88% (78/488). The sensitivity of helical CT in the same series was 94% \(^{33}\).

Differentiating a pancreatic carcinoma from a focal pancreatitis, lymphoma or a metastasis is difficult by US imaging. US guided needle biopsy is a safe procedure with few major complications reported (0.18%). Needle tract seeding is a rare complication of abdominal biopsies, but seeding of a pancreatic carcinoma has been reported relatively frequently \(^{34-36}\). The use of endosonographic guided biopsy, performed transduodenally, might reduce the risk of tract seeding, as the tract of the needle would be resected together with the tumor.

A major problem of biopsies is the yield of false negative results due to sampling errors. Even at endosonographic guided biopsy, performed in the presence of a cytologist, the number of false negative biopsies is reported to be up to 7% \(^{37,41}\). In our institution a biopsy of a pancreatic mass suspected to be malignant is not performed if the mass is potentially resectable. However, a biopsy may be useful, if there is suspicion of a metastatic lesion to the pancreas, as results of this biopsy may alter the therapeutic strategy. Also a biopsy may be useful to confirm the presence of a malignancy in patients who have an unresectable tumor.

For staging bilio-pancreatic malignancies, US visualization is adequate in more than 90% of cases \(^{42}\). Porto-venous invasion is the most important determinator that precludes a resection. An abnormal pulsed Doppler signal obtained from the portal venous system is due to vascular narrowing and indicates vascular involvement. The finding of a normal pulsed Doppler signal however, does not exclude vascular involvement by tumor.

An additional sonographic sign for vascular invasion is loss of the echogenic interface
between tumor and vessel. This sign had a positive predictive value for invasion of 77% (10/13) in a study of 48 patients, although the sensitivity of this sign was low (50%). Color doppler US is also helpful for evaluation of vessels, compared to greyscale US alone. Involvement of the porto-mesenteric veins was detected by color doppler US in 79% (26/33) of patients, that had surgically confirmed vascular invasion by a pancreatic tumor. Demonstration by US of tumor involvement of > 50 % of the vessel circumference had a predictive value for surgical irresectability of 90% (26/29). Another study showed that a resection was technically possible in only 13% of patients with these findings on US examination, and in no patient with this finding resection margins could be obtained that were free of tumor. Arterial invasion can equally well be demonstrated with color doppler US.

In enlarged lymph nodes the US finding of a hyper-echoic centre is indicative for benign disease (reactive lymph nodes). The size of a lymph node is a poor discriminator between a benign or a malignant node. In nodes that are enlarged (smallest node diameter of > 1 cm), or nodes, that have a long axis to short axis ratio of < 2, needle biopsy is therefore mandatory, in order to confirm the presence of a metastasis. The sensitivity of US for detection of liver metastases is lower than the sensitivity of CT. Liver metastases and peritoneal metastases are often small in pancreatic carcinoma and may only be detectable during laparoscopy and/or laparoscopic sonography (LUS). In approximately 14 % of patients, examined with LUS after a negative abdominal US examination, metastases were detected by LUS.

Further improvement of pancreatic sonography is expected of tissue harmonic imaging. By this technique echo's of high frequency (harmonics) are sampled, which reduces the amount of sonographic image artefacts. Also this technique enables contrast enhanced imaging by administration of sonographic contrast media intravenously.

**ERCP**

ERCP (Endoscopic Retrograde Cholangio Pancreaticography) will be performed in almost all patients with obstructive jaundice. It allows differentiation between an obstruction caused by biliary stone disease and a biliary stenosis caused by a tumor. A “double duct-sign” (= simultaneous stenosis of both the hepatobiliary duct and the pancreatic duct) is indicative for a pancreatic head carcinoma. Occasionally, a focal pancreatitis can lead to a single or double duct obstruction. In larger retrospective studies the sensitivity of ERCP to detect a pancreatic carcinoma was 80-90% 51,52, which is slightly higher than the sensitivity of CT or US. However, the sensitivity of combined
CT and US was found to be equal to the sensitivity of ERCP. In a recent prospective study, the sensitivity of ERCP for diagnosing pancreatic cancer was 70%, with a specificity of 94%, comparable to the results of MRCP. Other imaging modalities may therefore replace diagnostic ERCP.

The most important aspect of ERCP is the ability to accomplish biliary drainage by placing an endoprosthesis into the bile ducts. Stent placement may diminish complaints related to the obstruction temporarily, during pre-operative work-up, or more permanently, as a palliative treatment for irresectable tumors. Palliation by an endoprosthesis is preferable to a surgical palliation (bilio-digestive anastomosis) because of the lower mortality, morbidity and associated costs. Sphincterotomy, needed prior to endoscopic stent placement, does have a mortality of approximately 0.2%. Another disadvantage of endoprosthesis placement is that the procedure may give rise to cholangitis or to focal pancreatitis, due to the intraductal cannulation, sphincterotomy and contrast injection. This focal pancreatitis may interfere with CT interpretation, and make statements on dimensions and vascular involvement of the tumor more difficult. Also the stent itself may cause image artefacts on CT scans.

The use of pre-operative drainage, in patients with potentially resectable pancreatic cancer, has been questioned. While most studies show no beneficial effects of pre-operative drainage on surgical morbidity or mortality, others have found an association with post-operative infection and mortality. Self-expandable metallic stents should not be used for preoperative drainage as these are difficult to remove during surgery.

PTCD

If endoscopic drainage by ERCP is not possible, PTCD (Percutaneous Transhepatic Cholangiography with Drainage) may be an alternative procedure. Via a transhepatic route a bile duct is punctured, using US guidance, and a catheter is introduced over a guidewire. Using fluoroscopy a stenosis of the biliary duct can be visualized. A biliary drainage catheter can be left proximal to a stenosis, to drain externally, or the stenosis may be passed with a catheter to obtain internal drainage. Risks of the procedure are haemorrhage, and leakage of bile into the abdominal cavity. The risk of cholangitis after PTCD seems to be lower than after an endoscopic drainage procedure. Diagnostic PTC is no longer performed for pancreatic cancer.
CT

Until recently, dual phase helical CT (performed during arterial and porto-venous phase) with 3 mm slice thickness has been regarded as the state of the art technique for staging. Arterial phase scanning, with a delay of 20 sec after iv contrast injection, is now only performed if endocrine tumors are suspected, as these may show early contrast enhancement. Most tumors are equally well detected during the so-called pancreatic parenchymal phase at 40 s delay. During this phase both the peri-pancreatic arteries and the veins are well enhanced, while the tumor is shown as a hypodense lesion compared to normal pancreas.

With this CT technique the detection rate of pancreatic cancer is 92-97%. For detection of small peri-ampullary tumors EUS and MRI are regarded as superior to CT.

For local tumor staging, the determination of venous invasion is the most important aspect. Arterial encasement is rarely present without concomitant presence of venous invasion. Criteria that are considered to be conclusive for invasion are narrowing, occlusion, complete encirclement of the vessel by tumor, and irregularity of the vessel wall. If encirclement of a vein is > 180 degrees, the changes for surgical irresectability of the tumor are high (83-95%). However, this finding may also rarely be caused by a pancreatitis.

If a tumor shows contact with the porto-mesenteric veins, the tumor may show a convex border towards the vessel or this border may be concave. In 15 tumors that showed concavity towards a vessel, only one (7%) was found to be resectable without having to perform a resection of the vein (actually in this series 6 patients underwent a venous resection). In another series 15% (2/15) of tumors that showed concavity were found to be curatively resectable (having tumor negative resection margins at pathology).

A teardrop shape of mesenteric vein on CT has been described as an additional sign of vascular invasion. In 8 of 32 patients, who underwent surgical exploration and who had been regarded by CT as having tumors without venous invasion, presence of the teardrop sign was noted. Venous invasion was surgically confirmed in seven of these patients.

The sensitivity of CT for hepatic metastases varies from 73 to 79%. However, the actual number of missed metastases in surgical candidates is relatively low (7-12% of patients). In patients in whom CT shows a tumor to be completely separated from the veins or to have less than 90 degrees of circumferential contact with the vein, laparoscopy to detect metastases is no longer advocated, as the resectability rate of
these tumors is over 95% \(^\text{84}\). If a pancreatic tumor appears to be unresectable at CT, and this cannot be confirmed in a less invasive way, laparoscopy may be useful as it may help to prevent a surgical exploration \(^\text{85}\).

**MRCP**

Magnetic resonance cholangio-pancreatography (MRCP) is used for non-invasive imaging of the biliary and pancreatic ducts. By using heavily T2-weighted sequences and fat suppression, only static fluids like bile are imaged, while background signal of tissue and fat is suppressed. Thick-slab MRCP renders ERCP-like images in a short acquisition time. Another, more time consuming, technique is multislice MRCP. This technique produces multiple thin-slices (source-images), from which ERCP-like images can be rendered using a MIP projection (maximum intensity projection). Although ERCP-like images are appealing and easy to view, it should be noted that bile duct stones may only be detectable on source-images, and that they may be missed if only ERCP-like projections and thick slabs MRCP’s are used \(^\text{86-90}\).

ERCP and MRCP are regarded as being equivalent for the diagnosis of extrahepatic bile duct abnormalities \(^\text{86,87,91}\). Imaging the pancreatic duct with MRCP is more difficult because of its smaller size. Approximately 80% of normal pancreatic ducts are visible on MRCP. The development of ultrafast MR techniques may improve pancreatic duct imaging. Also, the intravenous administration of secretin may facilitate pancreatic duct imaging with MR by stimulating the pancreatic secretion. Besides giving functional information, the use of secretin may also reduce the number of false positive findings of ductal stenosis \(^\text{86,90,92,95}\).

Interpreting MRCP findings is similar to ERCP interpretation. A double duct obstruction is highly suggestive of a pancreatic head malignancy. Irregular dilatation of side branches of the pancreatic duct suggests a chronic pancreatitis. In a prospective study the sensitivity and the specificity to detect a pancreatic carcinoma were equivalent for MRCP (84% and 97%, respectively) and ERCP (70% and 94%, respectively) \(^\text{53}\). Some advantages of ERCP over MRCP are the better spatial resolution of ERCP and the possibility to inspect the papilla of Vater. In this area MRCP may demonstrate obstruction, but establishing the cause of the obstruction may be very difficult. Also, at ERCP contrast injection into the ducts can unequivocally proof leakage from the duct or establish fistulous communications with the duct. In favour of MRCP is the capability to image ducts that are proximal to a complete obstruction. Both techniques are not sufficient to exclude a pancreatic cancer or for staging a pancreatic cancer.
MRI

Contrast enhanced Magnetic Resonance Imaging (MRI) is used for detection and staging of pancreatic carcinoma sometimes after MRCP, and sometimes combined with MR angiography (one-stop-shop). MRI for staging was found to be equivalent to CT in most series. Pancreatic carcinomas usually show a low signal intensity on T1- and T2-weighted images, compared to normal pancreatic tissue, and have little or no contrast enhancement. Endocrine tumors may show an intermediate or high signal on T2-weighted images and may show early enhancement after intravenous contrast administration with gadolinium (Gd). MR sequences are developing rapidly. Detection of endocrine tumors and pancreatic tumors was found to be equivalent in recent series that compared dual phase helical CT and MRI. Because of its high contrast resolution, MRI is probably superior to CT in detection of small tumors. Semelka reported on the use of MR in patients after negative CT findings. MR increased confidence of diagnosis especially in patients in whom CT showed an enlarged pancreatic head.

For staging, some authors found CT to be slightly superior in depiction of vessels and peri-pancreatic infiltration, while other authors slightly favoured the use of MRI. In a recent study, that used a 3D multiphase gradient recalled echo (GRE) sequence, the sensitivity of MR angiography for vascular invasion was 85% with a predictive value of 83%, which is comparable to CT. This GRE MRI technique allows rapid acquisition of multiple series of thin slices through the pancreas, during breath hold of the patient. Analogous to multiphase CT scanning, these series allow evaluation of arteries and veins, as well as the pancreatic tumor. Another MRI technique is 3D phase contrast MR angiography, which only allows evaluation of the vessels. Phase contrast MRA should therefore be combined with other MRI sequences. Overall results of phase contrast MRA are comparable with dual phase CT.

Mangafodipir (MnDpDp) is a manganese containing contrast agent for MRI, that selectively accumulates in normal pancreatic tissue. Although the signal-to-noise ratio on MRI improves, and the confidence in diagnosis increases, MRI detection and staging of pancreatic carcinoma were found not to differ significantly from CT. In general, MRI can poorly discriminate between a malignant tumor and an inflammatory mass. The use of MnDpDp with MRI also may show false positive findings of malignancy, due to decrease in uptake of mangafodipir in pancreatitis.
Endosonography

Endosonography (EUS) is a combination of endoscopy and US. Close proximity to the tumor can be achieved by endoscopy and this allows the use of high frequency sonographic transducers (7.5-12 MHz). These transducers have a limited depth of view, but show an excellent spatial resolution. Detection of small tumors by EUS is superior to US or to helical CT with 3 mm slice thickness, and sensitivities of EUS were reported between 94-100% \cite{76,96,106}. EUS may therefore be used to confirm presence of a small, potentially resectable, pancreatic mass, especially in the ampullary region. Like other imaging modalities, EUS cannot differentiate between a small carcinoma or an inflammatory mass \cite{107,109}.

Endoluminal ultrasonography has been further developed into intraductal US (IDUS), by using small sonographic catheters that are introduced into the lumen of the pancreatic duct. IDUS is capable of detecting small intraductal pancreatic lesions (solid and cystic), and may suggest malignancy by demonstrating small solid components within intraductal cysts \cite{110,111}.

The role of EUS for staging pancreatic carcinoma is controversial. Some recent reports suggest that T stage accuracy is low (64%), although EUS can demonstrate tumor size well \cite{112,113}. EUS criteria for vascular invasion consist of i) loss of echogenic interface between tumor and vessel and ii) demonstration of tumor mass inside the vessel or iii) complete obstruction or thrombosis of the vessel. With these EUS criteria an accuracy for invasion was reported of 93\% \cite{114}. Few studies on EUS have been performed, that were blinded and prospective. In a blinded retrospective study the sensitivity and specificity of EUS for venous invasion were 43\% and 91\%, respectively. Visualisation of EUS of the SMV was very limited \cite{115}. A comparative and blinded prospective study found EUS for staging comparable to 3mm dual phase helical CT\cite{76}. In a retrospective study CT and EUS were found comparable in staging venous invasion, but CT was superior in staging arterial invasion\cite{106}.

Fine needle puncture under EUS guidance has been used abundantly. Presence of a cytologist during puncture may limit the number of needle passes and increase the yield of “adequate” specimen to 95\% \cite{38}. However, because of the high rate of false-negative biopsies (10-20\%) \cite{37,39,40,116}, a pancreatic biopsy should not be performed pre-operatively in potentially resectable tumors. EUS biopsy is useful for metastases that are suspected and that would preclude a resection, if their presence was confirmed. If surgery is performed for suspected carcinoma without a biopsy being taken, an inflammatory mass will be present in approximately 5\% of the patients \cite{50}. 

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IVUS

In patients with carcinoma of the pancreatic head the portal and the superior mesenteric vein are easily invaded by tumor, making the tumor a locally irresectable T3 tumor, according to the TNM staging. Although in some centres experimental studies are performed with portal resection, the value of this extended resection is still under debate. Intravascular ultrasound catheters with high spatial resolution have previously been used to examine coronary arteries and peripheral vessels, as well as urinary tracts and biliary tracts. Intravascular ultrasound (IVUS) of the portal vein was initially described by Noguchi et al. IVUS, performed during laparotomy, was evaluated in 30 patients with a pancreatico-biliary carcinoma. A branch of the superior mesenteric vein was exposed and cut down to introduce the ultrasound catheter. The sensitivity, specificity and accuracy of IVUS for detection of tumor invasion of the vessel wall were 100%, 93.3%, and 96.7%, respectively. Comparable results were found in other small series.

Because of the disadvantages of a laparoscopic procedure, we evaluated the feasibility of IVUS, performed percutaneously. Percutaneous IVUS, using a transhepatic approach, was performed safely in 20 patients, using a 6 French catheter and local anaesthesia. Percutaneous IVUS had additional value to helical CT for staging, and may be performed pre-operatively if helical CT demonstrates contact between tumor and vessel, without definite invasion. In another small series complications of percutaneous IVUS were found, including one fatal case, and also false-positive findings of tumor invasion occurred that were caused by inflammatory changes. Furthermore, IVUS has limited penetration depth and is not able to demonstrate perivascular structures e.g. lymph node metastases.

Laparoscopy

Laparoscopy (LAP) is accepted as staging method for pancreatic and peri-ampullary tumors. The main additional benefit of laparoscopy is detection of small metastases at the liver surface and on the peritoneum and thus to prevent an unnecessary laparotomy. These metastases can easily be missed with non-invasive imaging techniques and were previously only detected at laparotomy. In early studies laparoscopy, performed after conventional CT, could demonstrate metastases in 40% of patients with pancreatic carcinoma. At present, metastases that are missed by helical CT are found in only 12% of patients with pancreatic carcinoma. Bottger stated that laparoscopy performed after CT and US would detect additional metastases in approximately 7% of patients. Laparoscopic staging can be combined with laparoscopic ultrasound (LUS), which is a sensitive method for detection of intrahepatic metastases. In addition LUS allows...
assessment of vascular invasion by tumor. The relative contribution of LUS compared to LAP is also diminishing. Of 40 patients with pancreatic carcinoma LUS could exclude an additional 7 patients from surgical exploration, after LAP alone had already excluded 14 patients of these 40. In another study, LAP findings were equivocal in 13 of 90 patients with a pancreatic tumor, but LUS could exclude these 13 patients from surgery (14%) LUS had little additional value to LAP in a series of Durup: of 20 patients regarded as resectable after LAP, LUS could exclude only 3 patients from surgical exploration. Pietrabissa found that after dynamic CT, LAP alone could exclude 20% of patients from surgical exploration. Although LUS detected additional liver lesions in 8% of the patients, the majority of those liver lesions were benign. The major advantage of LUS over LAP was establishing vascular invasion, but the predictive value of LUS for invasion of 91% (10/11) was comparable to the predictive value of 100% (8/8) of CT.

LAP and LUS do not seem to have additional value in patients that show no signs of vascular invasion at CT. In a series of 100 patients with peri-ampullary tumors 49 were judged by CT to have no sign of vascular invasion. The resectability rate was over 96% in these patients.

As stated before, laparoscopic staging of patients should no longer be performed for (peri-ampullary) tumors that appear as resectable on CT.

Nuclear scintigraphy

Pancreatic carcinomas, like other malignancies, have an increased biochemical activity and an increased glucose metabolism. This enables the detection of pancreatic carcinomas by using deoxyglucose labeled with 18F (FDG), a positron emitting tracer that accumulates in pancreatic cancer tissue. In the body a positron interacts with a free electron, which produces two photons, radiated in opposite directions. PET scanning (positron emission tomography) can detect both of these simultaneous photons using a gamma camera, which is circumferential around the patient. PET enables imaging in a 3D fashion with high spatial resolution. PET scanners are expensive and few in number. An alternative for PET scanning is FDG-SPECT (single photon emission computed tomography). SPECT only detects one of the paired photons, that are radiating simultaneously, but it is able to produce 3D images, like PET, by rotating a camera around the patient analogous to a CT scanner. Spatial and temporal resolution of SPECT is slightly less than the resolution of PET.

The sensitivity and specificity of FDG PET for detection of a pancreatic carcinoma are
New modalities

reported to be high (over 93%)\(^1\), but in most studies pancreatic lesions had already been detected with other modalities. PET has been used for differentiation of benign and malignant pancreatic masses, with accuracies reported as being 90-92\%\(^2\)-\(^4\). If PET is truly blinded for results of other imaging techniques, the accuracy of PET seems to be lower, approximately 70\%\(^5\).

In chronic and acute pancreatitis FDG uptake is increased, but in most cases this is less than in pancreatic carcinoma. FDG uptake seems to be prolonged in malignant pancreatic lesions compared to uptake in inflammatory masses\(^6\). False negative PET scans for malignancy are rare and may be due to altered glucose metabolism in patients with diabetes\(^7\). Although PET can exclude malignancy more reliable than CT the role of PET in preoperative evaluation of pancreatic masses seems limited.

Potential advantages of PET over CT are the capability to detect lesions distant of the primary tumor, although the number of metastases in reported series is low\(^8\). Also PET is capable to detect recurrent malignant disease in an early stage.

In a series by Romijn it was suggested that survival of patients with malignant tumors, that showed a high uptake of FDG, was lower than for tumors with low uptake of FDG\(^9\). Another potential role of PET may be the monitoring of tumor metabolic activity during non-surgical treatment.

Conclusion

In the past decade many tools have been developed for diagnosing and staging pancreatic cancer. An important goal of diagnostic imaging is a better patient selection for surgical treatment, which may lead to optimal use of surgical resources and perhaps diminish peri-operative morbidity and mortality. The prognosis of pancreatic cancer however is poor, even after a tumor resection.

The use of diagnostic tools should be limited as much as possible.

We feel that in jaundiced patients ultrasonography should be a first screening modality to depict a pancreatic lesion, liver metastases or enlarged lymph nodes. If a pancreatic tumor is demonstrated without liver metastases, Doppler US can confirm vascular involvement.

Contrast enhanced helical CT, with a slice thickness of 3 mm or less, should be the next step to stage pancreatic tumors that seems resectable at US. Preferably CT should be performed prior to biliary drainage or ERCP. Contrast enhanced MRI is regarded as
equivalent to CT and may be used instead of CT. In general, MRI is more expensive and more time consuming than CT.

If no pancreatic mass is demonstrated by US, in a jaundiced patient several alternatives exist. If there is high clinical suspicion for biliary stones, ERCP, with potential stone removal, may be performed. If biliary stones should be excluded, MRCP may be sufficient. If a small peri-ampullary tumor is suspected, EUS or contrast enhanced MRI are the methods of choice. MRCP and ERCP are capable of showing the level of obstruction (double duct lesion), and ERCP allows inspection of the papilla, with potential biopsy or brush of a lesion, but these modalities alone are not sufficient for staging. In daily practice, ERCP is often performed as the first diagnostic modality, probably because biliary drainage is opted for. In fact, drainage after a diagnostic ERCP is mandatory in order to diminish the risk of infection in biliary obstruction. Complications of ERCP may interfere with diagnostic staging, and an acute pancreatitis induced by ERCP may postpone a surgical resection. Whether biliary drainage influences surgical outcome has not been established. Perhaps pre-operative drainage may be avoided if time to surgery can be reduced.

Biopsy should not be performed in pre-operative patients, because of the false negative findings that occur. This policy will also lead to resection of inflammatory pancreatic masses in 5% of patients.

In patients without CT signs of vascular invasion laparoscopy and LUS should not be performed. The role of FDG PET is limited. Perhaps PET may be used to monitor activity of tumor in non-surgical patients or early recurrence of tumor in post-operative patients. IVUS is as yet an experimental tool.

The future role of molecular markers lies further ahead.
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Chapter 7


