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ORIGINAL ARTICLE

Pancreatic cancer—EUS and early diagnosis

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Abstract
Background Over the last decades, the incidence of pancreatic cancer has increased. Prognosis remains poor despite rapid improvements in imaging technologies and therapeutic modalities. Curative treatment is dependant on early diagnosis.
Material and methods One of the most promising techniques for early detection of pancreatic lesions seems to be endoscopic ultrasound (EUS). With or without fine needle aspiration (FNA), it has been described as highly sensitive and accurate in staging. Superior to other imaging modalities in early studies, results in later publications declined.

There are three fundamental different techniques of EUS available at present: radial scanning scopes, linear scanning scopes and radial or linear scanning probes, each with different pros and cons. Indications for EUS are persistent epigastric and/or back pain, acute onset of diabetes in the elderly, unclairified weight loss and suspect results in ultrasonography, especially in individuals over 45 years of age and in high-risk subpopulations.
Results In early studies, EUS was superior or at least equal to other imaging modalities regarding sensitivity, determining tumour size and extent, lymph node involvement and vascular infiltration. With rapid advances in technology, first of all, computed tomography (CT) and magnetic resonance imaging have reached better results. The highest accuracy in assessing extent of primary tumour, locoregional extension, vascular invasion, distant metastasis, tumour TNM stage and tumour resectability seems to have helical CT, whereas EUS has the highest accuracy in assessing tumour size and lymph node involvement. For assessment of tumour resectability, a combination of CT and EUS seems to be the procedure with the highest accuracy.

Some new techniques promise improvement of the diagnostic yield of EUS. In differentiation to focal inflammation, contrast-enhanced EUS has shown to increase sensitivity and specificity for pancreatic cancer. Another major problem is the assessment of vascular invasion. 3D reconstructions additional to conventional EUS seemed to improve the evaluation of vessel–tumour-relationships.

Endoscopic ultrasound is not a foolproof method; there are several reasons for failure, and it shows a high interobserver variety even among experienced endosonographers. Nevertheless, EUS proved to have a high negative predictive value.

Poor overall survival rates and some reports of high survival rates among small resected stage 1 ductal adenocarcinomas suggest a high benefit for screening and early detection of pancreatic neoplasia, and treatment of precursor lesions might prevent their progression to invasive cancer. Because of low incidence and the lack of accurate, inexpensive and non-invasive diagnostic tests for early disease, screening for pancreatic cancer and its precursor lesions in the entire population is not reasonable. But a EUS- and CT-based screening among high-risk individuals discovered pancreatic neoplasms in eight of 78 patients, in contrast to no pancreatic neoplasia among 149 control subjects.
Conclusion Screening for pancreatic cancer and its precursor lesions in the general population is not feasible, but high-risk subpopulations seem to be suitable targets for screening programs. EUS is an essential tool for diagnosis and assessment of extension and resectability of pancreatic tumours.

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Introduction

The incidence of pancreatic cancer has increased continuously over the last decades. Despite rapid improvements in imaging technologies and therapeutic modalities, the prognosis remains poor. The overall 5-year relative survival rate for 1996 to 2002 is estimated to be 5.0% [1]. It seems to be even less, if data is critically reviewed. Carpelan-Holmström et al. collected slides or paraffin blocks from patients recorded as having histologically proven pancreatic ductal adenocarcinoma who survived for at least 5 years after diagnosis. They were re-evaluated in a double-blind fashion by three pathologists with special expertise in pancreatic pathology. In 26 patients recorded as having histologically proven pancreatic ductal adenocarcinoma, re-evaluation of histological specimens confirmed this diagnosis in only ten patients. The adjusted 5-year survival rate for pancreatic ductal adenocarcinoma was 0.2% [2]. At the time of diagnosis, about 20% of patients are meant to be candidates for curative resection, but only 7% of pancreatic cancers are found to be localized to the organ without locoregional spreading or distant metastases (AJCC stage 1) and, therefore, resectable in a curative intention. And even if they are found to be in stage 1, the prognosis remains poor with a 5-year survival rate of 19.6% [1]. These data underline the importance of early diagnosis of pancreatic cancer, but pain, jaundice, weight loss and obstruction usually are late symptoms.

EUS

One of the most promising imaging techniques for early detection of pancreatic cancer is endoscopic ultrasound (EUS). With its high resolution, it is able to detect focal lesions as small as 2–3 mm with the possibility to get tissue samples by fine needle aspiration (FNA) or truecut needle biopsy for histopathological examination. There are three fundamental different techniques of EUS available at present, each with pros and cons: (1) electronic or mechanical radial scanning scopes, in which the electronic scanning scopes seem to produce better B-mode image quality with no apparent difference in maneuverability, endurance and endoscopic images [3], (2) linear scanning scopes, (3) radial or linear scanning probes for use with standard scopes or alone. Frequencies range from 5 to 20 MHz for scopes up to 30 MHz for probes. The accuracy in staging of pancreatic cancer is equivalent for radial and linear scanners [4], in which radial scanners offer a better overview of surrounding structures, whereas linear scanners allow the safe execution of tissue sampling. Indications for EUS, in relation to pancreatic cancer, are listed in Table 1. Endoscopic ultrasound has been described as a highly sensitive method, but results for accuracy, especially in the staging of pancreatic cancer, differ. Initial studies showed excellent accuracy up to 94%, but early euphoria flew away, and results in later publications declined (Table 2 and [5–11]). Accuracy seems to be around 60% to 70%. If tissue diagnosis is necessary before therapy, EUS-guided FNA should be the method of choice. A EUS–FNA is highly sensitive (84%), specific (97%), accurate (84%) and has a high positive predictive value (99%) with rare major complications, but negative predictive value is low with only 64% [12]. If pancreatic cancer is suspected and if EUS–FNA is negative, cancer cannot be excluded, and operation will be the next step despite a positive or negative result in FNA.

Comparing EUS

Early studies showed high sensitivity and accuracy for EUS as mentioned above. Regarding sensitivity, determining tumour size and extent, lymph node involvement and vascular infiltration, EUS was superior or at least equal to other imaging modalities like computed tomography (CT) or magnetic resonance imaging (MRI) in most studies [6, 13]. With rapid advances in technology, first of all, CT and MRI have reached better results. Soriano et al. compared EUS with helical CT, MRI and angiography in a prospective study with histopathological or surgical confirmation of results [11]. When each imaging technique is looked at alone, helical CT reached the highest accuracy in assessing extent of primary tumour, locoregional extension, vascular invasion, distant metastasis, tumour TNM stage and tumour resectability, whereas EUS achieved the highest accuracy in assessing tumour size and lymph node involvement. A major problem in staging pancreatic cancer correctly is the prediction of resectability. The combination of CT and EUS

Table 1 Indications for EUS exam

Persistent epigastric and/or back pain
Acute onset of diabetes in the elderly
Unexplained weight loss
Acute or chronic pancreatitis
Suspect results in other imaging modalities
One of the above, especially in individuals over 45 years of age and in high-risk individuals (e.g. persons with a strong family history of pancreatic cancers, with Peutz-Jeghers syndrome (PJS) or multiple endocrine neoplasia (MEN))

Table 2 Results for accuracy of EUS in literature

	Accuracy (%)
Legmann et al. [6]	93
Akahoshi et al. [7]	94
Cannon et al. [8]	78
Ahmad et al. [9]	69
Meining et al. [10]	72
Soriano et al. [11]	63

proved to be the method with the highest accuracy compared to each single technique to predict tumour resectability. With regard to cost minimization, the combination of CT and EUS seems to increase the price compared with each single method. However, if cost of unnecessary explorative laparotomies was taken into account, the cost minimization analysis favoured a sequential strategy in which EUS was used as a confirmatory technique in those patients in whom helical CT suggested resectability of the tumour (Figs. 1 and 2).

Improving EUS

Differentiation to focal pancreatitis is one of the major problems in diagnosing pancreatic cancer. Contrast-enhanced EUS using perfusion characteristics seems to be to a promising technique to discriminate between focal inflammation and pancreatic carcinoma. Hocke et al. compared conventional endoscopic B-mode to power Doppler ultrasound and contrast-enhanced power mode (SonoVue®). Differentiation between focal pancreatitis and pancreatic cancer is based on perfusion characteristics of microvessels. Eighty-six patients with suspected chronic pancreatitis and pancreatic lesions were examined. The sensitivity and specificity of conventional EUS were 73.2% and 83.3% for pancreatic carcinoma, increasing to 91.1% and 93.3% with contrast-enhanced power mode [14].

Assessment of vascular invasion is another major problem for EUS. Sensitivity and specificity of EUS are 63% and 64% for vascular adherence and 50% and 58% for vascular invasion [15]. In a pilot study of 22 patients, the additional 3D reconstructions appeared to improve the evaluation of vessel–tumour-relationships, but the acquisition system needs to be improved [16].

These promising new techniques to improve EUS may enrich the armamentarium for staging pancreatic cancer correctly, but they need to be evaluated in further studies.

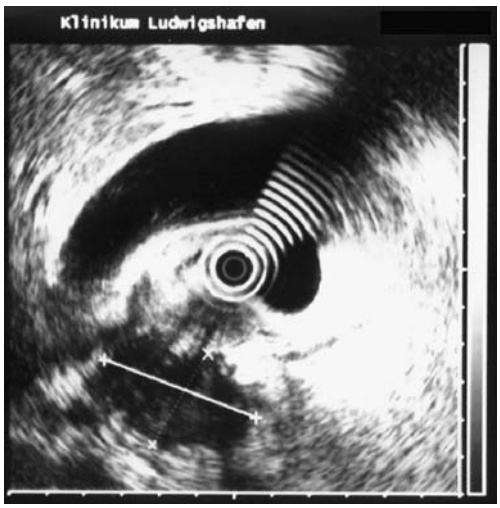

Fig. 1 EUS of an adenocarcinoma in the pancreatic head with a maximum diameter of 4.2 cm

Reasons for failure

Endoscopic ultrasound is not a foolproof method. Even among experienced endosonographers, there is a high interobserver variety [16, 17]. Furthermore, accuracy of EUS seems to be dependant on additional clinical and imaging information [10]. Meining et al. retrospectively analyzed EUS examinations/video tapes of 101 patients with resected tumours of the oesophagus, stomac and pancreas in three different ways: under routine clinical conditions, strictly blinded and in an unblinded fashion with additional information from endoscopic appearance (oesophagus, stomach) or CT (pancreas) [18]. Overall accuracy of T staging for pancreatic cancer was 72.2% and 75.0%, respectively, for routine and unblinded analysis, but only 61.1% for evaluation in strictly blinded fashion. Additional possible associated factors that may increase the likelihood of a false-negative EUS examination are chronic pancreatitis, diffusely infiltrating carcinoma, a prominent ventral/dorsal split and a recent episode of acute pancreatitis [19].

NPV

Like results for accuracy, the results for negative predictive value (NPV) also differ. A normal EUS examination seems to have a high negative predictive value. In two studies with 76 and 135 and a mean follow-up period of 23.9 and 25 months, respectively, none of the patients with clinically indeterminate suspicion of pancreatic cancer and a normal EUS developed pancreatic cancer [20, 21], which means a NPV of 100%. In contrast, Soriano et al. [11] found a NPV for locoregional extension, lymph node involvement and vascular invasion of merely 44%, 65% and 74%, confirmed by intraoperative or histopathological findings.

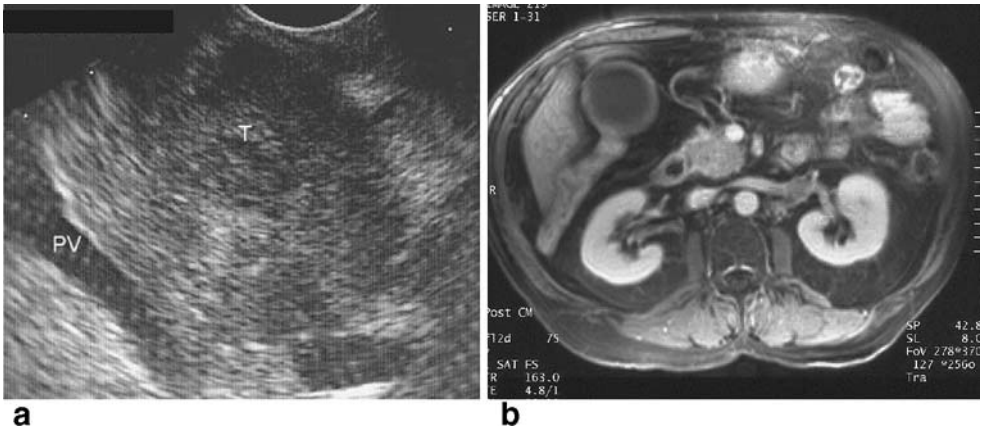

Fig. 2 **a** EUS of a carcinoma in the pancreatic head. **b** Corresponding MRT

Screening for pancreatic cancer

Pancreatic cancer is a disease with a poor overall 5-year survival rate of 5% [1]. There are reports of a 4-year survival rate of 78% in resected stage 1 ductal adenocarcinomas of the pancreas <2 cm in size, in which 42% were not associated with symptoms [22]. These data suggest that screening and early detection of pancreatic neoplasia before occurrence of symptoms might improve the dismal outcome of pancreatic cancer. There are morphologically well-defined non-invasive precursor lesions for invasive pancreatic cancer like pancreatic intraductal neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMNs). Like it is well experienced in other organs, treatment of these precursor lesions might prevent their progression to invasive cancer. Screening for pancreatic cancer and its precursor lesions in the entire population is not reasonable because of the low incidence of pancreatic cancer and the lack of accurate, inexpensive and non-invasive diagnostic tests for early disease. But there are some known high-risk subpopulations like members of families with a strong history of pancreatic cancer or with hereditary pancreatitis and with distinct hereditary cancer syndromes like Peutz-Jeghers syndrome, hereditary breast or ovarian cancer syndrome, familial atypical multiple mole melanoma syndrome and hereditary nonpolyposis colorectal cancer. Canto et al. screened for early pancreatic neoplasia with an EUS-based [23] and a EUS- and CT-based [24] protocol. In the latter protocol, pancreatic abnormalities were compared in high-risk individuals and control subjects. The EUS- and CT-based approach found eight patients among 78 high-risk individuals with pancreatic neoplasms confirmed by surgery or FNA (six patients with eight benign IPMNs, one patient with a IPMN with progression to invasive ductal adenocarcinoma and one patient with PanIN) and no pancreatic neoplasia among 149 control subjects. Abnormalities suggestive of chronic pancreatitis were more common in high-risk individuals.

Conclusions

Over the last decades, the incidence of pancreatic cancer has increased continuously. The prognosis remains poor despite rapid improvements in imaging techniques and therapeutic modalities. Endoscopic ultrasound seemed to be one of the most promising techniques for early diagnosis. With or without FNA, it has a high sensitivity, whereas accuracy in TNM-staging differs. Optimistic results in early studies gave way to a more critical view. Endoscopic ultrasound showed, compared to CT, MRI and angiography, the highest accuracy in assessing tumour size and lymph node involvement, whereas helical CT had the highest accuracy in assessing extent of primary tumour, locoregional extension, vascular invasion, distant metastasis, tumour TNM stage and tumour resectability. The evaluation of tumour resectability should be done by a minimum of two imaging techniques, in which the combination of CT and EUS proved to be the method with highest accuracy at lowest cost. The detection of distant metastases is not possible with EUS. A normal EUS examination seems to exclude a pancreatic tumour with a high probability. Quality of EUS shows a high interobserver variance, accuracy seems to be dependant on further clinical or imaging information. Chronic or recent episode of acute pancreatitis, diffusely infiltrating carcinoma and a prominent ventral/dorsal split are additional reasons for failure. New techniques like contrast-enhanced EUS or additional 3D reconstructions look promising for improving EUS. Screening for pancreatic cancer or its non-invasive precursor lesions in the general population is not feasible because of its low incidence, but high-risk subpopulations like

families with strong history of pancreatic cancer, hereditary cancer syndromes or pancreatitis seem to be suitable targets for screening programs.

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