Review article

The role of endoscopic ultrasound in diagnosing pancreatic neuroendocrine tumours

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ABSTRACT

Pancreatic tumour imaging poses one of the greatest challenges in gastroenteropancreatic tumour diagnostics. Though much less common than adenocarcinomas, tumours deriving from pancreatic islets are the second most common group of pancreatic tumours. The manifestations and growth rate of neuroendocrine tumours (NETs) differ from adenocarcinomas; thus, these tumour types require different diagnostic and therapeutic approaches. With its high sensitivity and specificity, endoscopic ultrasound (EUS) seems to be indispensable in pancreatic NET diagnostics. A negative EUS practically excludes the presence of a pancreatic tumour, while in definitive tumour cases, EUS is helpful in tumour staging, and in determining its precise anatomical location. One especially important benefit of EUS is the option of performing a biopsy for subsequent cytological and histopathological examinations. The use of contrast and additional computerized image analysis increases the diagnostic accuracy of EUS. This article presents current views on the use of EUS in pancreatic tumour diagnostics, with a particular emphasis on diagnosing NETs.

Key words: pancreatic neuroendocrine tumour, endoscopic ultrasound, ultrasonography

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INTRODUCTION

Pancreatic cancer is the most common and most dangerous gastrointestinal tumours. In Poland, its incidence has nearly doubled over the past 30 years. Experts from United European Gastroenterology (UEG) have confirmed that pancreatic cancer incidence has been on the rise in a number of European Union countries. It is estimated that in 2025 the number of deaths caused by pancreatic cancer will amount to 111.5 thousand in Europe, which is a 50% increase as compared with the year 2010. Pancreatic cancer will then become the third most common cause of death due to malignancy in Europe, following lung and colorectal cancers [1].

PANCREATIC ADENOCARCINOMA

Standardized incidence ratios for pancreatic cancer in the Polish population are virtually tantamount to the mortality ratios in that case, amounting to 6.2 and 4.2/100 000/year for male and female patients, respectively [2]. Malignant pancreatic tumours include adenocarcinomas, neuroendocrine tumours, solid pseudopapillary tumours, stromal tumours, lymphomas and metastatic lesions. Amongst the above mentioned tumours, adenocarcinoma is the one with the poorest prognosis, with mean survival after the diagnosis of advanced or metastatic cancer totalling less than 6 months. 5-year survival is reached by just under 5% of patients [3]. Adenocarcinoma is also the most frequent primary malignant tumour of the exocrine pancreas, constituting around 90–95% of all cases. It is mostly located within the pancreatic head (60%), and less frequently its body (15%) or tail (5%) [4, 5]. Ca. 20% of the cases involve metastatic lesions. Tumour resection is the only chance of a cure, but fewer than 30% of the diagnosed cases may be qualified for surgical management due to the early spread of disease via the lymphatic system or bloodstream. The 5-year survival rate of post-resection patients has increased slightly over the recent years, still not exceeding 10–20%, though, with median survival amounting to 18–20 months [4, 6]. One cause behind the high mortality is late tumour detection, mostly caused by the fact that pancreatic adenocarcinoma often grows for a long time with no clinical symptoms. Emergence of clinical symptoms (as a result of local disease advancement or metastases) significantly reduces the patient's chances of curative treatment. Thus, early diagnosis of pancreatic cancer appears to be a crucial factor that improves patient prognosis [7].

PANCREATIC NEUROENDOCRINE TUMOURS

The second most common group of pancreatic neoplasms are islet cells tumours. They are much less common, though, accounting for only 1–5% of pancreatic cancers, with their incidence estimated as ca. 1 case per 100 thousand persons per year [8–11].

They are usually diagnosed in the patient's fourth and fifth decade of life, and are slightly more common in women than in men. They may further be divided into functioning (70% of all cases) and non-functioning, hereditary and sporadic, malignant and benign ones [8–10].

Malignant tumours are often hormonally non-functioning, which makes it all more difficult to diagnose and delays diagnosis, as their development is not accompanied by any specific syndrome of endocrine symptoms. On the other hand, functioning tumours are usually detected as small lesions, accompanied by clinical symptoms (e.g. Cushing's syndrome or Schwartz–Bartter syndrome) that enable an earlier initiation of the diagnostic process. Non-functioning tumours are larger at the time of diagnosis, and their clinical symptoms are associated with the tumour mass effect and the presence of metastases. The presence of liver metastases may trigger the symptoms associated with the carcinoid syndrome, when serotonin and its metabolites enter the general circulation. Insulinoma constitutes ca. 50% of pancreatic neuroendocrine tumours, with as many as 90% of the cases being histologically benign ones, and with hypoglycaemia being the prevailing clinical symptom [8–11]. Gastrinoma is also a relatively common pancreatic NET that leads to recurrent peptic ulcers associated with increased secretion of hydrochloric acid, caused by hypergastrinemia.

Compared to adenocarcinomas, pancreatic NETs involve different symptoms, and a different growth rate, thus requiring a different diagnostic and therapeutic approach. Accurate localization diagnostics and possibility of harvesting material for histopathology assessment are of particular significance from the point of view of patient prognosis (fig. 1).

ENDOSCOPIC ULTRASOUND IN THE DIAGNOSIS OF PANCREATIC TUMOURS

Focal pancreatic lesions constitute an important diagnostic problem. Solid tumours require special attention. Detection of a solid pancreatic lesion results in a number of diagnostic problems, starting from its localization through the assessment of the stage of disease and determination of an effective treatment method. It appears that there is no ideal diagnostic method that would meet all the requirements pertaining to the assessment of malignancy and operability of solid pancreatic tumours. Usually, such lesions are detected incidentally, under abdominal ultrasound, and later verified with the use of computer tomography (CT),

FIGURE 1.
EUS image of a pancreatic head NET.

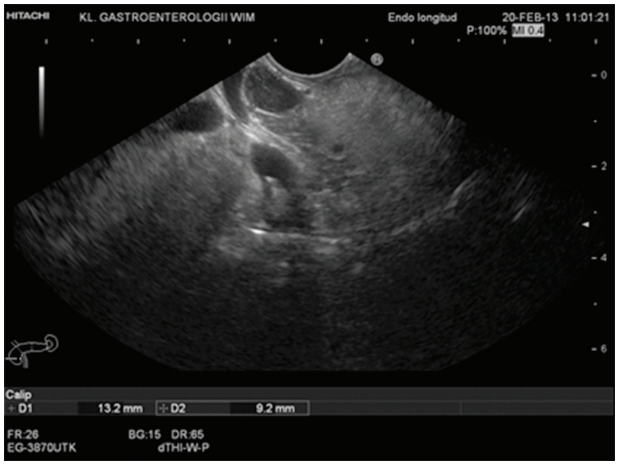
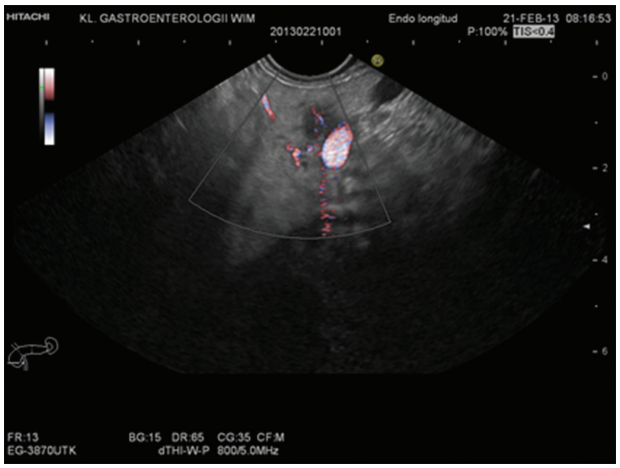


FIGURE 2.
Vasculature assessment of a pancreatic head NET.



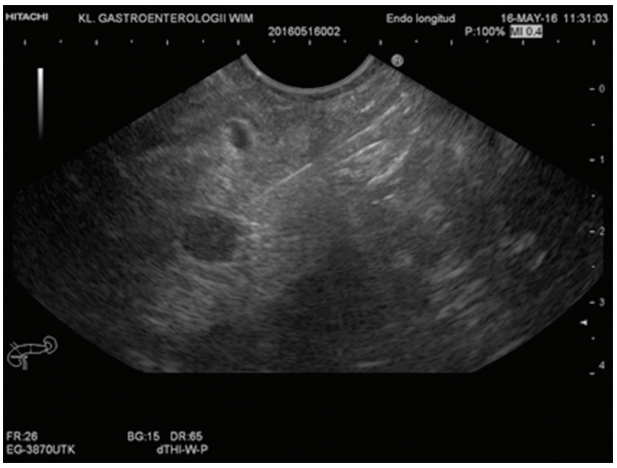
magnetic resonance (MR) or endoscopic ultrasound (EUS) [5], currently believed to be the best method with regard to solid pancreatic lesions.

Endoscopic ultrasound was first performed in a human patient in 1982 at the Mayo Clinic (Rochester, USA). A prototype instrument was used at the time, consisting of an endoscope, and an ultrasound probe placed on its stiff tip [12]. Miniaturization of the equipment as well as the advances in ultrasound and endoscopic techniques enabled a broad spectrum of application of the 2 methods in clinical practice. The ultrasound examination complements endoscopic assessment, making it possible to evaluate the deeper structures. It is due to a good tissue and spatial resolution, and from a significant reduction in the distance between the ultrasonic probe and the organ under examination. An important limitation of EUS, though, is the restricted field of vision. Hence, the method is mostly applied in the diagnosis of small tumours (that diameter is smaller than 2 cm), located in an area that is accessible to ultrasound evaluation [13–16] (fig. 2).

ENDOSCOPIC ULTRASOUND IN THE DIAGNOSIS OF PANCREATIC NETS

Neuroendocrine tumours may be revealed on EUS in different forms, including solid lesions, uniformly or non-uniformly (as a result of necrosis) hypoechogenic. Sometimes they take the form of encapsulated cystic lesions (ca. 10–20% of the cases), and much more rarely, they are manifested as normo- and hyperechogenic nodules [9, 10]. In Doppler ultrasound, an enhanced flow within the tumour is usually revealed, which is associated with a rich vasculature (fig. 3).

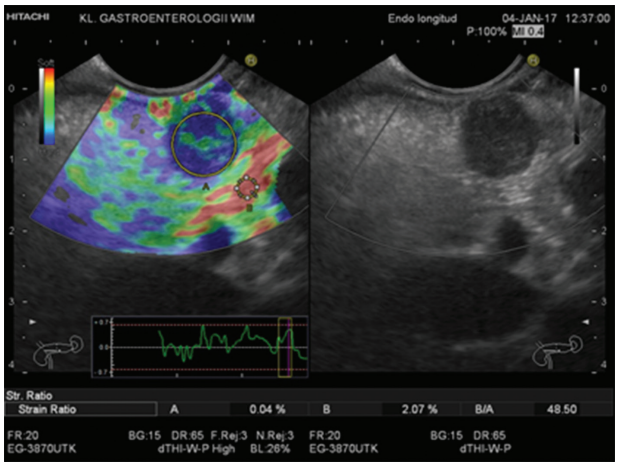
FIGURE 3.
EUS-guided biopsy of a pancreatic head NET.



What is important in the diagnosis of pancreatic NETs is a much higher resolution of the method as compared with the classical ultrasound assessment, and the possibility of acquiring images from the immediate vicinity of the pancreas, with no limitations related to the presence of intestinal gas. EUS is the most sensitive of the currently available imaging methods applied in the diagnostics of pancreatic focal lesions, as it is capable of detecting lesions as small as 1–2 mm in diameter. Sensitivity of the test for tumours located within the head and tail of the pancreas is 90–100%, whereas for those with peripheral location it is 75–80% [17–20]. In the case in small insulinomas, EUS sensitivity reaches 94–100% [17–20], while in gastrinomas the diagnostic sensitivity of the test is nearly 100%. On the other hand, the sensitivity drops in multifocal lesions and those located outside of the pancreas. Therefore, we might conclude that a negative EUS result virtually excludes the presence of a pancreatic tumour [9, 10].

An important advantage of the method is the possibility to perform biopsy, for further histopathological and cytological examination, which confirms the nature of the lesions (fig. 4). It is of particular significance for the diagnosis of neuroendocrine tumours, their appropriate classification and further management.

FIGURE 4.
Elastography assessment of a pancreatic body NET.



Additionally, it is believed that EUS-guided biopsy is associated with a lower risk of tumour cell dissemination as compared with percutaneous biopsy [16, 17]. Moreover, EUS examination is an ever more frequently applied diagnostic technique due to the fact that it proves very useful, when staging the neoplastic process. Lymph node assessment is of key significance in this respect, enabling the evaluation of the "N" category in TNM classification of pancreatic cancers. EUS is also helpful in the assessment of lesion advancement, and accurate determination of anatomic relationship, which in turn facilitates decisions concerning surgical treatment of NETs. Placement of the ultrasonic probe in the vicinity of the lesion makes it possible to assess the location of the tumour with respect to the biliary tract and main vascular trunks, and to reveal potential infiltration of the blood vessels [21, 22]. When performed as part of preoperative diagnostics, EUS also enables injection of a special ink into the tumour, facilitating its localization during the surgery [22, 23]. Accurate localization of the lesion ensures appropriate resection margin, and spares as much of the healthy pancreatic tissue as possible [24]. The above listed facts render EUS the most sensitive diagnostic method that is recommended in pancreatic NET patients, as early detection of pancreatic lesions enable radical treatment of the disease [9, 10].

EUS DEVELOPMENT PROSPECTS

Endoscopic ultrasound is a continuously developing method, both in terms of its diagnostic and therapeutic applications. The elastography technique enables real time assessment of tissue rigidity, and the test result is displayed in the form of a colour image, i.e. elastogram. The examination is based on the premise that neoplastic tissues differ from healthy tissues in terms of their rigidity/elasticity [25] (fig. 4). Giovannini et al. presented results of combined EUS and elastography as helpful in the differentiation between focal neoplastic and inflammatory lesions within the pancreas, together with the associated enlarged lymph nodes [26]. Hocke et al. demonstrated that the use of contrast EUS is superior to conventional EUS in the differentiation of pancreatic cancer from chronic pancreatitis [27]. Saftoiu et al. evaluated pancreatic EUS elastography tests in 68 patients who were then followed up for 6 months. 32 of them were diagnosed with pancreatic cancer, 11 were diagnosed with chronic pancreatitis, neuroendocrine tumours were revealed in 2 patients, and in the remaining 22 patients pancreas was healthy. The study made use of calculation techniques aimed at objectivizing the assessment of tissue rigidity. Digital elastograms were analysed on completion of the endoscopic examination with the help of specially designed computer software. Throughout the follow-up period, the sensitivity of the method was estimated as 91.4%, and its specificity as 88.9%, which testifies to a high diagnostic accuracy of the test [28].

SUMMARY

Endoscopic ultrasound is a highly sensitive and specific method in the imaging diagnostics of focal pancreatic lesions, including neuroendocrine tumours. Thanks to the possibility of acquiring images from the immediate vicinity of the pancreas, EUS is capable of detecting lesions as small as 1–2 mm in diameter. An additional advantage of the method is the possibility of performing biopsy, for further histopathological and cytological examination, which confirms the nature of the lesions, before planned surgical management. Therefore, alongside scintigraphy and hormonal assessment, endosonography is an essential diagnostic method in those rare digestive tract neoplasms.

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