

Original paper

Usefulness of core biopsy in diagnosis of pancreatic tumours

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Abstract

Purpose: The aim of the study was to analyse the usefulness of core biopsy in the diagnosis of malignant neoplasms of the pancreas – sensitivity and accuracy of diagnosis, safety of the procedure, indication of factors that may increase the risk of complications after biopsy.

Material and methods: A retrospective analysis of data was performed in a group of 100 patients diagnosed with a focal lesion of the pancreas, qualified for a core biopsy.

Results: The results are a sensitivity of 92%, a specificity of 100%, and an accuracy of 93.3%. The incidence of more severe complications according to the Clavien-Dindo classification was 1% (one case in the material studied). The results of the analysis were compared with the results of other authors, showing similar values for the sensitivity and specificity of the method and low rates of serious complications; it also seems that the tissue material obtained by core biopsy has higher diagnostic potential than that obtained by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), currently considered the method of choice. In addition, the costs of transabdominal biopsy and endoscopic biopsy were compared; the lower cost of the former may be an important economic issue when choosing the biopsy method.

Conclusions: The results show core biopsy to be a sensitive, accurate, and safe method for obtaining the tissue necessary to plan treatment in patients with pancreatic cancer.

Key words: pancreatic cancer, core biopsy, complications after biopsy.

Introduction

Early detection of a neoplastic lesion significantly improves the prognosis, enables the implementation of various therapeutic methods, and increases the patient's chances for recovery. Unfortunately, there is a large group of early-stage neoplasms that remain asymptomatic for a long time, in which disturbing symptoms appear when treatment options may be very limited. This group includes one of the most dangerous neoplasms with high mortality and a very low 5-year survival rate: pancreatic cancer.

The incidence of pancreatic cancer has remained high for many years, and it is currently the seventh leading

cause of cancer-related death worldwide. We observe differences in mortality rates, i.e. numbers are lower in less developed countries, probably due to a lack of appropriate diagnosis, treatment, and reliable database.

Development of pancreatic cancer is complex and multifactorial, but dominant causes are cigarette smoking and family history. It is more common in men than in women, and the incidence rate for both sexes increases with age.

Due to the structure of the pancreas, there are 2 types of neoplasms, developing from the exocrine and endocrine parts. The term “pancreatic cancer” refers to malignant epithelial neoplasms originating in the exocrine juice-producing part (almost 95%), while tumours of the endocrine,

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hormone-producing part are referred to as neuroendocrine tumours (NETs, 1-2% of pancreatic tumours) [1]. Approximately 2-5% of malignancies in the pancreas are metastatic, most often from renal cancer (RCC).

The clinical presentation of pancreatic cancer depends on its location, size, and the degree of invasion of adjacent organs. The disease develops asymptotically at an early stage – in more than 20% of cases, at the time of diagnosis, the process infiltrates most of the surrounding organs and structures. Common symptoms are not specific, including abdominal pain, jaundice, and weight loss, and we often observe nausea and vomiting, diarrhoea and/or constipation, fever, anaemia, pancreatitis, diabetes, thrombosis, gallbladder enlargement, ascites, and a palpable tumour in the epigastric region.

A basic point in pancreatic cancer treatment planning is to determine the type and degree of cancer differentiation. This information is obtained from the tissue, so a biopsy is an important element of the diagnostic algorithm. The available methods differ in the type of material (cellular, tissue) and hence in the depth and quality of diagnosis. Therefore, obtaining information on the histological type and degree of tumour differentiation is essential for planning further therapeutic procedures.

The histopathological assessment determines grading (G) – differentiation of tumour cells – from highly differentiated (G1) to poorly differentiated or undifferentiated (G4). In the case of malignancy assessment, the key feature is the value of the Ki67 proliferation index (tested by immunohistochemistry with the MIB1 antibodies) and the number of mitotic figures, determining mitotic activity. These parameters are important especially in case of neuroendocrine neoplasms, where they are the basis for treatment planning [2].

There are several methods of collecting material for histopathological evaluation. Currently the method of choice is endoscopic ultrasound (EUS); due to the anatomical location of the pancreas, imaging through the stomach and duodenum allows optimal images to be obtained even if the lesion is difficult to access, and it is considered the most accurate method of detecting tumours < 3 cm [2]. It is believed that this access pathway is associated with a lower risk of spreading neoplastic cells [3]. There are no typical limitations of ultrasonography, such as the need to penetrate the subcutaneous fat tissue and air artifacts from intestinal loops. Real-time imaging with a high-resolution probe with a choice of position (projection) illustrates changes in the pancreas much more accurately than classic transabdominal ultrasound examination. The usefulness of contrast agent or elastography in transoesophageal ultrasound is currently under investigation, and the results appear to be promising [4]. In the case of this procedure, we can obtain cytologic (endoscopic ultrasound-guided fine needle aspiration – EUS FNA) or tissue (endoscopic ultrasound-guided biopsy – EUS FNB) material depending on the size and nature of the lesion (solid, fluid, mixed);

therefore, the choice of biopsy monitoring method depends on the size, location, and morphology of the lesion. Of course, the experience of the researcher is significant here. In the case of accompanying post-inflammatory changes, altered anatomical relations, difficulties in inserting the endoscope, or other potential limitations of EUS, it may be difficult to perform.

However, needles used in fine needle aspiration (FNA) and fine needle biopsy (FNB) are only 0.5-1 mm in diameter (25-20 G). Obtaining cytological material (FNA) provides no reliable base for proliferative factors and mitotic activity assessment. Even if we get a tissue sample (FNB), its volume might be insufficient to assess all required histopathological features. In addition, the technique of obtaining a tissue sample in FNB may cause architectural distortion, making it impossible to correctly assess proliferative factors and mitotic activity, whereas core needle biopsy (CNB) by using needles of 20-14 G (1-1.5 mm) with a cutting chamber provides a thicker tissue sample (scrap) and undisturbed architecture of the collected tissue.

The aim of this study was to analyse the usefulness of a core biopsy in the diagnosis of malignant neoplasms of the pancreas, including sensitivity and accuracy of diagnosis, safety of the procedure, and indication of factors that may increase the risk of complications after biopsy.

Material and methods

A retrospective analysis of data was performed in a group of 100 patients diagnosed with a focal lesion of the pancreas, qualified for a core biopsy.

Required data were collected: sex and age of patients, initial clinical diagnosis, tumour size and location, and tumour morphology. The following features were also noted: thickness of the needle used, the quality of tissue sample in macroscopic evaluation, the number of scraps taken, histopathological diagnosis and results of immunohistochemical assessment, and occurrence of complications with an assessment of their severity (according to Clavien-Dindo classification).

The study population comprised 42 women and 58 men, aged 42-93 years. The biopsy procedure was performed under the guidance of ultrasound (US). All patients included in the study showed the presence of a focal lesion in the pancreas (initial diagnosis: pancreatic tumour) by computed tomography (CT) or US. When qualifying for biopsy, the results of laboratory tests (coagulation parameters) were taken into account, and the necessity to fast for up to 5 hours before the procedure was emphasized.

After the patient was qualified for biopsy the skin and peritoneum in the puncture pathway were locally anaesthetized with 1% lignocaine at the site of the lesion in the pancreas shown in the imaging examination. After the skin incision, the needle was inserted into the lesion and 1-3 samples were taken (needle diameter 16-20 G, section

length 0.8-2 cm, the number of biopsy repetitions depended on the macroscopic evaluation of the material; as a rule, one sampling was performed if the material was rich. After biopsy the patient was assessed by US/CT for the presence of bleeding. In our centre, core biopsy is an in-hospital procedure; therefore, the patient remained under clinical observation for 24 hours.

All statistical calculations were performed using the STATISTICA version 12.0 statistical package (StatSoft Inc. www.statsoft.com) and an Excel spreadsheet.

Quantitative variables were characterized by the arithmetic mean, standard deviation, median, minimum and maximum value (range), and 95% CI (confidence interval). Qualitative variables are presented in terms of counts and percentages.

The Shapiro-Wilk W test was used to check whether the quantitative variable came from a normally distributed population. The Leven (Brown-Forsythe) test was used to test the hypothesis of equal variances. To establish a relationship and its strength and direction between the variables, a correlation analysis was used to calculate the Pearson and/or Spearman correlation coefficients. In all calculations, $p = 0.05$ was adopted as the level of significance.

Results

Our own material comprised 100 percutaneous core biopsies in patients with focal lesions in the pancreas. The size of the tumours was 2-4 cm on average (the smallest change in size was 1 cm, the largest up to 7 cm), the location was predominantly the head of the pancreas (69 cases, the remaining 24 in the body, and 7 in the tail of the pancreas), the number of samples taken (number of punctures during the procedure) was 1-4 (mostly 1), the most common needle gauge is 18 G, and in the majority the tissue samples were rated as good.

The analysis included needle thickness, number of punctures, and sample quality, and the correlations between these variables were assessed. Interestingly, there was no statistically significant correlation between the thickness of the needle and the quality of the samples collected (correlation coefficient $R = 0.01$, $p = 0.6763$).

Another factor analysed was the accuracy of diagnosis, and the usefulness of the collected material to determine further management. The studied group was selected from patients qualified for biopsy in the years 2011-2018, so there is a verification of diagnosis in at least 3 years of clinical observation. The obtained results are a sensitivity of 92%, a specificity of 100%, and an accuracy of 93.3%.

In 79 patients (79% of the group studied) it was possible to confirm a diagnosis of neoplasm. In other patients no neoplasm was found, and in one patient we were unable to set the diagnosis.

Complications were assessed according to the Clavien-Dindo scale as well as correlation with needle thickness, quality of samples, and number of punctures (Table 1).

There was no statistically significant correlation between the needle thickness and the severity of complications (correlation coefficient $R = -0.07$, $p = 0.5074$), while a statistically significant positive correlation (correlation coefficient $R = 0.22$, $p = 0.0242$) was found between the number of samples taken and the severity of complications, i.e. the degree of complications increased with the number of punctures.

Severe complications (Clavien-Dindo II-IV) constitute 1% of cases (retroperitoneal haematoma); pain at the puncture site classified as a minor complication requiring no further treatment appeared in 9% of cases.

Discussion

The aim of the study was to evaluate the effectiveness of a core biopsy of pancreatic tumours as a method to confirm the diagnosis, which is necessary for treatment planning and prognosis, with an analysis of complications.

Until recently, this topic was not widely studied, and for some time there have been further studies in the literature comparing different techniques of collecting material to determine the optimal procedure, i.e. to ascertain which of the available methods allows the most reliable material to be obtained with the lowest possible risk of complications.

The needles used for biopsy can provide cellular or tissue material, depending on needle size and biopsy technique.

Different needle sizes mean different diagnostic possibilities. FNA/FNB is performed with 25-20 G needles (0.5-1 mm), while for CNB it is 20-14 G (1-1.5 mm). Some authors point out that despite the better quality of the material obtained by core biopsy (tissue material, larger volume), there is no significant difference in the detection of malignant lesions [5-8], and others emphasize that CNB is more sensitive than FNA in the diagnosis of pancreatic lesions [9,10]. So far, no uniform comparison of these 2 techniques has been described, but the literature has compared their sensitivity, which on average is estimated at 93% for CNB [6,11-15] and 67-99% for FNA [13,16-22], other studies report a sensitivity of 91% for core biopsy and 80% for collecting only cellular material.

The technique of collecting the material using FNA is puncture of the lesion, moving the needle to loosen the

Table 1. Incidence of complications in the studied group

Complications	N = 100 n (%)
No complications	90 (90)
Grade 1	9 (9)
Grade 2	0 (0)
Grade 3	1 (1)
Grade 4	0 (0)

tissue structure, and aspiration of the cellular material, without preserving the original architecture of the tissue.

In the case of FNB the needle is inserted into the lesion and cuts out a block (cylinder-shaped fragment) from it. An anterior-posterior movement is often used to ensure the sample is correctly inserted into the needle, which can also disrupt the original architecture of the tissue.

CNB with a needle equipped in the cutting chamber allows removal of a tissue fragment without the under-pressure. Because the key to determining the degree of tumour differentiation and planning further treatment is assessment of the Ki67 proliferation index and the number of partition figures, a removed tissue fragment must allow evaluation of these features. The material collected correctly during core biopsy preserves the architecture, and the immunohistochemical staining performed on it allows appropriate evaluation. In the case of FNA, fixation of the material with the cell block method allows immunohistochemical staining, but the architecture of tissues is disturbed, which may result in an incorrect assessment of proliferative activity [23].

The problem of spreading cancer cells along the puncture canal, raised by some researchers, in the case of CNB can be easily solved by using appropriate biopsy techniques, i.e. a coaxial needle, where the cutting needle enters through the cannula/sheath, preventing the implantation of neoplastic cells into the biopsy canal [24].

The oldest study found dealing with the topic of percutaneous biopsy in the diagnosis of pancreatic lesions is an article from 1989 [25], in which material was developed from 33 ultrasound-guided punctures (results in the Table 2). Subsequent reports from later years on larger groups of patients allow the sensitivity, specificity, and accuracy of the procedure to be established at the levels of 94%, 98%, and 95%, respectively. The authors analyse the advantages and disadvantages of the method, its predictive value, and possible complications with the assessment of their severity [26]. There is an opinion that percutaneous access is more invasive than endoscopic access, while at the same time core biopsy (allowing to assess the architecture of tissues) is more useful (due to better quality of material) than cytology itself, determining its accuracy at the level of 91% in the case of core biopsy and 80% if only cellular material is collected.

In both procedures (both percutaneous and endoscopic access) complications mainly concern grades I/II in the Clavien-Dindo classification, so it is usually pain at the puncture site, and sometimes moderate bleeding. Complications requiring radiological, surgical, or endoscopic intervention (grade III/IV) are rare; in the studied material there was one case, but no death was reported due to complications after biopsy (one case in the literature [27]).

Papers discussing the usefulness of sectional biopsy have been selected from the available literature.

The size of the studied groups varied between 33 [25] (the oldest work from 1989) and 250 [28]. In our own material, the data of 100 patients were assessed. The age structure of the group in the study with the highest population [28] is those aged 16-88 years, and in the case of the remaining authors 20-87 years. In our material, patients between 42 and 93 years of age were examined. The needle thicknesses used by other authors are 22-18 G. For the punctures analysed in this study, needle sizes 14-20 G were used, most often (80%) 18 G.

The number of punctures during a single procedure by other authors (where data was available) is 1-4. The number of punctures in our own material is also 1-4. The method of biopsy monitoring in other authors was US, also in the material of this work 100 punctures were performed under US control. The sensitivity, specificity, and accuracy of sectional biopsy according to data published by other authors are, respectively, 90-100%, 95-100%, and 91-100%, and in our work 92%, 100% and 93.3%.

The assessment of the severity of complications based on the Clavien-Dindo scale also gave results similar to those from the literature; in the work of Klassen [29], discussing more severe complications after biopsy (grade II-IV) based on the results of a large group of 426 patients, they were reported in 2.8% of cases, and in smaller studies [27,28,30,31] these values are 1.6-2%. In our own analysis, the frequency of more severe complications is 1%.

The Table 2 illustrates the results of the authors of several papers on ultrasound-guided sectional biopsies of the pancreas, followed by our own results.

Taking into account the high accuracy and sensitivity of the method, the low percentage of serious complications is another factor that classifies percutaneous biopsy as a method of great usefulness in the diagnosis of pan-

Table 2. Usefulness of core needle biopsy (CNB)

Author	Number of biopsies (n)	Sensitivity (%)	Specificity (%)	NPV (%)	Accuracy (%)
Bhatti <i>et al.</i> [27]	153	90	95	42	91
Kahriman <i>et al.</i> [28]	250	99	94.7	94.7	98.4
Wei <i>et al.</i> [31]	53	90.48	100	84.6	96.08
Yang <i>et al.</i> [15]	88	92.6	100	60	93.3
Mitchel <i>et al.</i> [25]	33	100	100	100	100
Own results	100	92	100	95.2	93.3

creatic tumours. Like any invasive procedure, it is not completely risk-free, but the obtained data allow for the implementation of appropriate procedures, sometimes targeted therapy, which, apart from the assessment of the stage of advancement, is of fundamental importance in the treatment of pancreatic neoplastic disease.

In a study comparing the effects of puncture of pancreatic tumours with 25 G EUS-FNA and percutaneous 18 G CNB [32], the authors did not describe significant differences in the accuracy, sensitivity, or specificity of these methods, but they showed a significantly higher diagnostic potential of CNB (86%) compared to EUS-FNA (66%).

Tissue material is more reliable for the assessment of proliferation indicators than a cytological aspirate; good quality tissue material allows for full histopathological diagnosis and differentiation by immunohistochemistry, with the assessment of the expression of the neuroendocrine markers (chromogranin A and synaptophysin) and the proliferation index Ki-67 (determination of the degree of proliferation). It also allows the assessment of prognostic microscopic features, such as clots of neoplastic cells in the lumen of the vessels (angio-invasiveness) [3]. It can therefore be said that in the case of CNB, the probability of obtaining sufficient information to make a diagnosis is higher than in the case of FNA [33].

In our material of 100 patients, 11 were diagnosed with neuroendocrine neoplasm, and appropriate therapy was implemented on the basis of the Ki67 index.

In the studied material, the frequency of more severe complications (stages II-IV according to Clavien-Dindo) was 1%. In works of other authors, the percentage rates of complications were 0-6%. There was a statistically significant correlation between the number of samples taken and the severity of complications; the degree of complications increased with the number of scraps, which in practice translates into the number of punctures. A similar

correlation was also found in other authors (in the comparison by Tian *et al.* [1]). So, it seems essential to achieve satisfactory sample quality from one puncture, which requires experience; the procedure is easy, but only in experienced hands.

The estimated cost analysis compares the valuation of the procedure itself along with the necessary equipment. The cost of EUS with biopsy is about 5 times higher than the cost of an ultrasound-guided core biopsy. In addition, in the case of EUS, the cost of general anaesthesia must often be added. Therefore, core biopsy can be defined as a cheaper and less invasive procedure than EUS, while obtaining material with probably better diagnostic value, based on data from the literature.

Conclusions

Despite the risk of transabdominal puncture, a core biopsy is a valuable source of information necessary for treatment planning. Tissue material is more reliable for the assessment of proliferation indicators than a cytological aspirate. The choice of the type of biopsy (percutaneous or endoscopic) depends on several factors and requires analysis each time. In cases where EUS is not a good solution (size/location of the lesion), percutaneous puncture will provide answers necessary for further management. The time of the procedure is also important; CNB is a short procedure lasting several minutes, while during EUS-FNA/FNB anaesthesia is often used, and the examination time is longer. The cost of transabdominal core biopsy is several times lower than that of endoscopic biopsy. Due to the low percentage of severe complications, CNB can be described as effective, accurate, and safe.

Conflict of interest

The authors report no conflict of interest.

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