RESEARCH LETTER

Impact of endosonography-guided fine-needle aspiration and biopsy on the management of patients with suspected pancreatic neuroendocrine tumors

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Introduction The incidence rate of pancreatic neuroendocrine tumors (PNETs) shows an increasing tendency globally.[1] Most accidentally detected PNETs (up to 90%) are well-differentiated and nonsecreting tumors, with asymptomatic presentation and usually slow growth rate.[2]

Endosonography-guided sampling from solid pancreatic tumors is recommended as the first-choice diagnostic procedure, when pathological diagnosis is required.[3] The current standard of care for pancreatic tissue sampling is based on linear-array endosonography combined with fine-needle aspiration (FNA) biopsy. Recently, a new generation of fine-needle biopsy (FNB) has been offered for use in endosonography. Nevertheless, the superiority of FNB over FNA in the diagnosis and pathomorphological evaluation of PNETs has not yet been clearly shown.[4]

The positive impact of endosonography-guided sampling on the management of patients with solid pancreatic lesions was previously reported in retrospective and prospective studies.[5,6] However, most available evidence concerns patients with suspected pancreatic adenocarcinoma, and knowledge on the influence of endosonography with or without sampling in the case of PNET suspicion is scarce.[7,8] Importantly, management strategies substantially differ between PNET and pancreatic adenocarcinoma in terms of pharmacotherapy, surgical intervention, and local therapy (alcohol and thermal ablation) in patients ineligible for either surgery or surveillance in the case of small-sized, well-differentiated, and nonfunctional PNETs.[2] The role of endosonography as a tool for clinical decision making when dealing with a suspicion of PNET is emphasized in guidelines; however, the diagnostic algorithm mentions it only as one of the available options.[9]

Our study aimed to evaluate the safety and clinical impact of performing endosonography on clinical decision making in patients with a suspicion of PNET and to compare the influence of various needle types on the outcomes of endosonography-guided biopsy.

Patients and methods We retrospectively analyzed data of 59 patients with suspected PNET who were hospitalized in our center for endosonography performance in the years 2017 to 2019. All patients were referred to our unit from the Department of Endocrinology and Neuroendocrine Tumors (Medical University of Silesia, Katowice, Poland), appointed the Center of Excellence by the European Neuroendocrine Tumor Society (ENETS).

Criteria for endosonography-guided biopsy in the case of pancreatic lesions, established by the neuroendocrine tumor board, included: 1) pancreatic lesion of unclear characteristic, measuring 2 cm or less; 2) uncertain result of previous biopsy; 3) no exact grading before patients' eligibility evaluation for further treatment options; 4) radiological or clinical features suggesting a different malignant or benign lesion; and 5) other, depending on individual cases.

All patients underwent preliminary diagnostic imaging including computed tomography (CT) and/or magnetic resonance imaging (MRI) before

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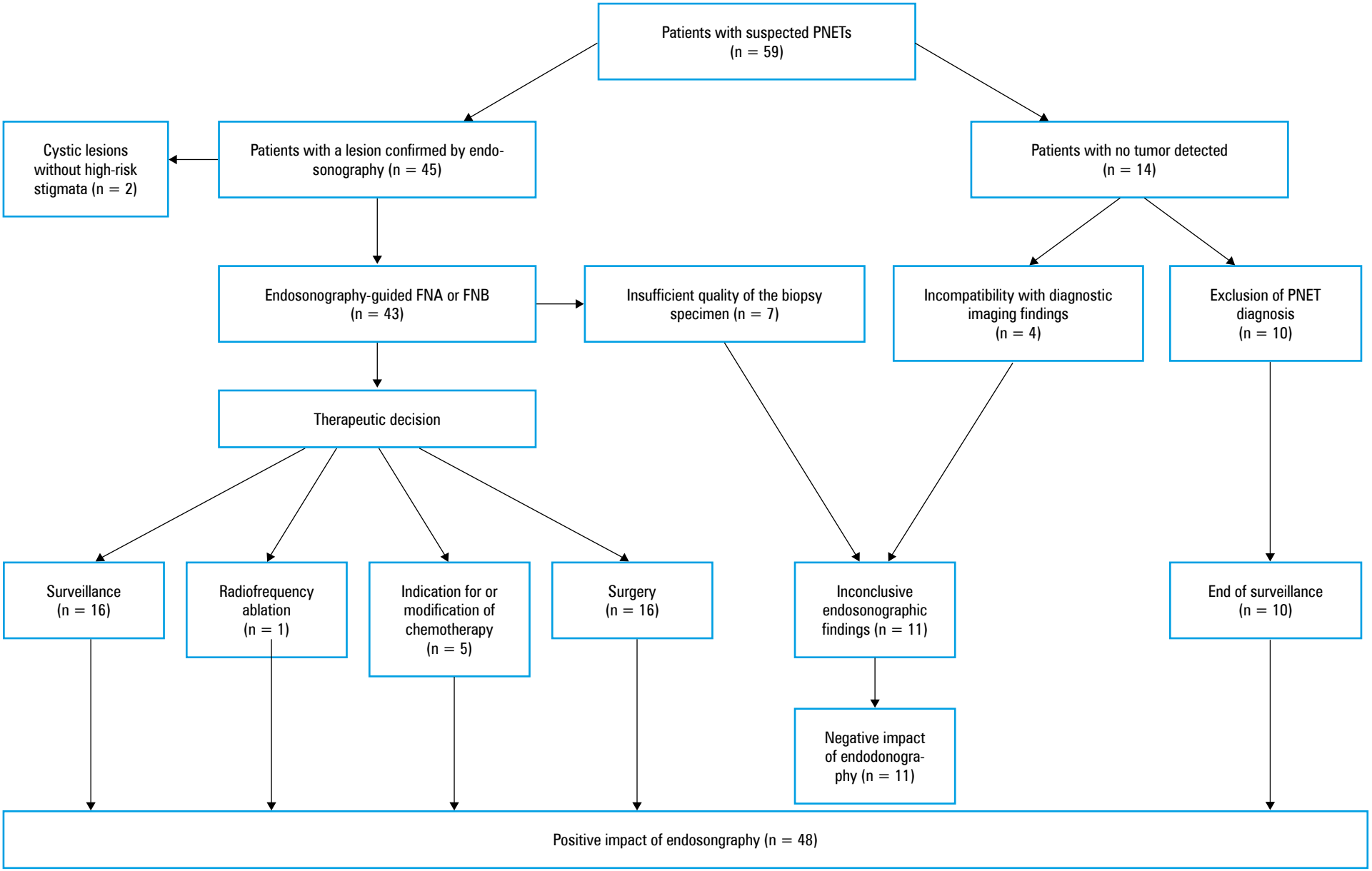

FIGURE 1 Flowchart of patients with a suspicion of pancreatic neuroendocrine tumor (PNET) showing the impact of endosonography-guided fine-needle aspiration (FNA) and fine-needle biopsy (FNB) on the management strategy

being deemed eligible for endosonography. In that group, 8 out of 59 patients were diagnosed with disseminated neuroendocrine cancer, and the role of endosonography was to examine the pancreas as a possible location of the primary lesion. In 2 out of 59 patients undergoing diagnostic workup because of a suspicion of insulinoma, the decision was made upon an inconclusive result of a 72-hour fasting test.

Endosonography-guided biopsy Endosonography-guided biopsies were performed under sedoanalgesia. The Olympus GF-UCT180 linear echoendoscope (Tokio, Japan) was applied for examinations. In all cases, color Doppler imaging was used to exclude large, interposing vascular structures, which was a contraindication to puncture. Fine-needle aspiration biopsies were performed with 19, 22, or 25-gauge aspiration needles (Olympus, Tokyo, Japan) and nonaspiration FNBs, with 20, 22, 25-gauge needles (ProCore, Cook Medical, Bloomington, Indiana, United States and Acquire, Boston Scientific, Marlborough, Massachusetts, United States) according to operators' preference. There was no on-site cytopathological study. The acquired material was considered diagnostic when its quality allowed us to perform immunohistochemical staining (synaptophysin, chromogranin, and CD56) and to evaluate the cell proliferation marker (Ki67%) in at least 100 cells.

Impact of endosonography on decision making The clinical decision-making process proceeded according to the current ENETS Consensus Guidelines for the management of PNETs.[9] Histopathological records (where applicable) with endosonographic documentation were referred to the ENETS center tumor board—a multidisciplinary staff composed of endocrinologists, radiologists, oncologists, and surgeons. Depending on that decision, the impact of endosonography was considered "positive" if it led to well-defined therapy (surgery, start or modification of chemotherapy) or active surveillance. The impact of endosonography was considered "negative" when the biopsy result was inconclusive, leading to additional diagnostic procedures (CT, MRI, positron emission tomography–CT).

Statistical analysis Data were presented as mean (SD) or median and interquartile range for quantitative variables and percentages for qualitative variables. The Fisher exact test was used to assess differences between FNB and FNA groups. The Spearman rank correlation coefficient was used to evaluate the relation between the needle size and specimen length. All analyses were performed with the Statistica software, version 13 (TIBCO Software, Inc., Palo Alto, California, United States).

Ethics Due to the retrospective, data-based design of the study, the approval of a local ethics committee nor patient informed consent were necessary.

Results A total number of 59 patients who underwent endosonography were included in the analysis. The study patients' mean age was 58 years (range, 28–83 years), and women constituted the majority of participants (n [%] = 35 [59.3]). Endosonography confirmed the presence of a nodule in 45 out of 59 patients (76.3%). In the remaining cases (n = 14), the presence of tumors previously found on CT or MRI was not confirmed by endosonography, and further careful re-evaluation of contrast imaging techniques by the tumor board excluded PNET in 10 out of 14 patients (71.4%). In the remaining 4 patients, further in-depth diagnostic workup was continued. During the performance of additional procedures (which included repeated endosonography, CT, MRI, or positron emission tomography–CT), solid pancreatic lesions missed during the initial endosonographic examination were confirmed in 3 cases (5% of the total number of patients included). A single patient was diagnosed with accessory spleen.

The median size of lesions detected by endosonography was 14 (16) mm (range, 6–43 mm). In almost half of the cases, tumors were localized in the head of the pancreas (48.2%). In 12 cases (26.6%), lesions were found in the body, in 10 (20%) in the uncinate process, and 2 (4.2%) in the tail of the pancreas.

Performing endosonography had a positive clinical impact on final decisions made by the tumor board in 48 of 59 patients (81%). Most of the patients in whom endosonography positively influenced therapy were deemed eligible for further surveillance (16 of 48 patients [31%]). In 11 of 59 patients (19%), the result of endosonography was inconclusive and further diagnostic procedures were scheduled. Among those patients, the decision of the tumor board to expand the diagnostic workup was made because of unequivocal imaging findings (4 patients) or insufficient quality of biopsy specimens (7 patients).

Biopsy was performed in 43 of 45 patients (95.6%). In 2 individuals, small (below 10 mm) cystic lesions with no high-risk stigmata were found. Adenocarcinoma was diagnosed in a single patient who underwent endosonography-guided FNB.

Histopathological diagnosis was established more frequently when FNB was used compared with FNA (100% vs 74%; $P = 0.01$). We confirmed a positive correlation between the needle size and length of the specimen for both types of needles (FNA: $R = 0.3$; FNB: $R = 0.33$; $P = 0.02$); however, the mean length of the tissue specimen did not differ between FNA and FNB needles (median, 5 [5] mm vs 5 [6] mm).

We noted only a single case of mild endosonography-related pancreatitis, which prolonged hospital stay without long-term complications at 6-month follow-up.

Discussion The survival of patients with PNETs has dramatically improved in the last decade, and several therapeutic strategies are available nowadays.[10] The recent ENETS Consensus Guidelines emphasized the importance of histopathological evaluation for prognosis in PNET and various classification and grading systems were proposed for these patients.[9] According to the current guidelines,[9] a conservative approach is a safe practice in nonfunctional and asymptomatic PNETSs measuring 2 cm or less. This applies to G1 and G2 tumors with a low Ki-67 index assessed on histopathological examination.

In 81% of our study patients, performing endosonography allowed us to start an appropriate therapy or follow-up strategy. Moreover, endosonography led to the exclusion of PNET in 20% of patients when such lesion was detected on CT or MRI (10 patients) or it was a small intraductal papillary mucinous neoplasm. This finding confirms the superiority of endosonography over CT and MRI, the methods that may lead to a false diagnosis in the case of 10% to 40% of small pancreatic focal lesions suggestive of PNET.[11] Our data complement previous studies exploring the influence of endosonography-guided sampling in patients with a suspicion of adenocarcinoma.[5,6] Our research letter is, to date, one of few reports focused on the clinical impact of endosonography in selected subgroups of patients with PNET.[7]

The role of a decent quality of specimens is crucial for the decision-making process when dealing with a suspicion of PNET owing to the significant predictive value of the proliferation index and its effect on treatment approaches. In our study, FNB was significantly more effective than FNA, with 100% diagnostic biopsies in 16 patients. We also showed that a positive correlation between the needle size and sample size is stronger when using FNB needles.

To date, only a few studies have compared the diagnostic performance of FNA and FNB in the diagnosis of PNETs. Ayres et al[12] indicated that FNB might be more efficacious in neuroendocrine tumors. However, that retrospective analysis included patients with solid pancreatic tumors, and the authors emphasized that the overall number of 16 cases of PNET was too small to draw robust conclusions. Our study is one of the first to prove the clinical usefulness of endosonography in the decision-making process in patients with suspected PNET. This study also demonstrated the high diagnostic efficacy of FNB, which was superior to FNA.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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