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Review

Endoscopic Ultrasound in Solid Pancreatic Masses – Current State and Review of the Literature

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A B S T R A C T

Some 25 years ago endoscopic ultrasound (EUS) was introduced in clinical practice for better visualization of pancreas. At the time of introduction EUS was superior to other methods in detection of pancreatic masses allowing tissue diagnosis by later introduced EUS-guided fine needle aspiration (FNA). During the time EUS was improved, electronic probes replaced mechanical probes adding ability of color Doppler, power Doppler, contrast enhanced endosonography as well as EUS elastography analysis. Meanwhile, CT technology has also experienced significant improvements raising the question whether EUS has lost ground in diagnostics of solid pancreatic masses. The aim of this review was to discuss the current evidence of clinical impact of EUS and EUS-FNA in evaluation of solid pancreatic masses with special emphasis on differentiation between benign and malignant pancreatic lesions. According to the literature, the detection of small pancreatic tumors, preoperative localization of pancreatic endocrine tumors and tissue sampling by fine-needle aspiration of pancreatic masses in cases with therapeutic consequences are considered firm indications for EUS. Cytological tissue analysis remains undisputed in differentiation benign from malignant lesions, but the question when FNA is needed is discussed. Color Doppler, power Doppler, contrast enhanced endosonography and especially elastography are also discussed as tools that are bringing additional information in evaluation of pancreatic masses, however insufficient for definitive judgment of the lesion's nature. Pancreatic cancer staging as indication for EUS is discussed controversially, inconsistent results and conflicting evidence in literature making adequate conclusion impossible. However, this indicates that at least the role of EUS is no longer undisputed in this matter. Resuming the role of EUS we can state that despite some controversies EUS is very valuable method in evaluation of solid pancreatic masses and with EUS guided FNA is nowadays by far the best method for obtaining tissue diagnosis.

Key words: *endoscopic ultrasonography, role of EUS, endoscopic ultrasound guided-fine needle aspiration, cytology, pancreatic masses, small tumors, pancreatic malignancy*

Introduction

Some 25 years ago endoscopic ultrasound (EUS) was introduced in clinical practice for better visualization of pancreas. At the time of introduction EUS was superior to other available diagnostic methods for evaluation of pancreatic diseases[1–3]. Transabdominal ultrasound was unable to analyze whole organ due to intervening air in bowels, and computed tomography (CT) scans of that time was obviously inferior in detection of pancreatic tumors[1–3]. EUS evaluates pancreas from very close proximity, and the entire organ can be examined. However, results from early studies[4,5] and studies on missed pancreatic tumors[6] indicate that EUS has lower accuracy for the lesions located in the tail of pancreas. Technology of EUS has improved, electrical probes replaced mechanical probes giving opportunity for better image quality, expanding diagnostic possibilities with color Doppler, po-

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wer Doppler, contrast enhanced endosonography and EUS elastography. In difficult issues such as making differential diagnosis between benign and malignant lesions some papers report power Doppler[7] and contrast enhanced EUS as a good tool[8–10]. Electronic linear probes allowed real time tissue sampling by EUS guided fine needle aspiration (FNA)[11–15] making EUS the method of choice for obtaining tissue diagnosis in regions difficult to reach such as pancreas. Furthermore, elastography, the new and sophisticated ultrasound technology which evaluates tissue hardness is proposed as the method that can differentiate benign from malignant pancreatic lesions without tissue sampling[16–18]. However, during years CT technology has been significantly improved raising question if EUS has lost superiority in diagnostics of pancreatic masses. The aim of this review was to discuss the current evidence of clinical impact of EUS and EUS--FNA in evaluation of solid pancreatic masses with special emphasis on differentiation between benign and malignant pancreatic lesions.

Detection of Pancreatic Masses

From its very beginning EUS was considered very accurate in detection of pancreatic pathology, especially of small pancreatic masses. The rate of detection of pancreatic cancer is considered high[19,20]. Detection rate is lower in patients with chronic pancreatitis, short after acute pancreatitis, in diffuse pancreatic tumors[6] and in low volume centers[21,22]. To obtain maximum yield from EUS it should be preformed after contrast CT and before endoscopic retrograde cholangiopancreatography (ERCP)[23,24]. However, EUS is inadequate for screening for pancreatic masses with exception of special screening programs in patients with familial risk of pancreatic cancer usually after CT and followed with ERCP. Even when conducted under study conditions the yield was relatively low, about 10%, even in patients with high risk for pancreatic cancer[25,26]. Therefore, EUS should not be used as a screening tool in population with small risk of pancreatic cancer. Quite consistent indication for EUS is localization of pancreatic endocrine tumors after laboratorial confirmation of the diagnosis[27,28]. The diagnosis in this case is based on laboratory tests, while imaging the tumor by EUS localizes tumor for easier surgical removal. The other story are non-functional pancreatic endocrine tumors, which are mostly incidental findings detected by other imaging methods. Endosonographic appearance of these lesions is similar to functional tumors, they are typically well demarcated, hypoechoic lesions in the pancreas. However, this morphological appearance is far from sufficient to make diagnosis and FNA should be preformed to obtain tissue diagnosis[29–31]. Conclusion: EUS is still considered the method of choice for detection of small tumors, for localizing pancreatic endocrine tumors and for evaluation of incidental lesions allowing tissue sampling, but it is not suitable to be a screening tool.

Differentiation of Benign from Malignant Lesions: Is FNA Replaceable?

Despite advances in diagnostic imaging techniques, the differentiation between pancreatic cancer and benign lesions is difficult[32–36]. Morphological analysis of endosonographic image in B mode, as well as Doppler analysis, power Doppler analysis and contrast enhanced analysis of pancreatic masses did not fulfilled initial good expectations. Elastographic evaluation of tissue hardness gives additional information about evaluated mass and can differentiate benign masses from malignant in some cases, but in number of cases differentiation is impossible. EUS elastography is superior in differentiation to EUS B mode analysis and can be used as a second line for better characterization of pancreatic masses after negative FNA as well as for targeting which node to evaluate by FNA[37–41].

EUS-FNA is an effective and accurate method for providing tissue diagnosis in patients with suspected pancreatic masses[36,42,43]. Moreover, EUS-FNA has replaced endoscopic retrograde cholangiopancreatography and brush cytology for obtaining tissue since it has a higher success rate and is associated with fewer complications[42]. EUS-FNA differentiates precisely benign and malignant lesions, having high positive predictive value while negative predictive value is lower[44–46]. Not finding malignant cells in aspirated material does not rule out malignancy, so false negative findings emphasized in many studies are problem of this method[35,44–51]. Another problem are indeterminate, suspecious or atypical cytological findings, which occur from 7.8 to 10.9%[46–49]. Some groups of authors, as well as our group, advocate repeated EUS-FNA procedure for enhancing the yield of FNA in negative or suspicious cytological findings[43,46,50]. In experienced hands the technique is quite simple. After the lesion is identified endosonographically the FNA needle is inserted through the working channel of the echoendoscope. Color Doppler sonography is performed in order to avoid vessels in the needle track. The needle is advanced into the targeted lesion under ultrasonographic guidance. The stylet is removed when the tip of the needle is inside the lesion. Constant negative pressure using a syringe attached to the proximal end of FNA needle is applied while doing back-and-forth movements.

In order to get best out of EUS-FNA, attending cytologist should be informed about the patient's clinical status, laboratory findings and imaging studies[46,49,53,54]. The value of direct communication between endosonographist and attending cytologist is priceless for obtaining good samples. For quick assessment of specimen on site evaluation can be done. Direct smears of aspirated material are prepared and based on its macroscopic appearance the selected slide is stained with Hemacolor (Merck KGaA, Germany) for rapid on-site evaluation (ROSE). ROSE enables rapid assessment of sample adequacy[55], and can give preliminary diagnosis[56]. In cases when the needle was clearly seen in lesion, experienced cytologist can asses specimen adequacy by macroscopic specimen

analysis[46,57]. Additional samples for ancillary studies (flow cytometry, immunocytochemistry or molecular studies) can be taken when necessary. For definitive evaluation, slides are air-dried and stained with May-Grünwald--Giemsa. Passes are repeated until a definitive diagnosis is reached, or when the team believes that further sampling would not increase the possibility of obtaining a definitive diagnosis. The most commonly used needles are 22 gauge needles. Newly developed 19 gauge true cut needles that can provide cylinder for a histological assessment did not justify expectations and have not improved sensitivity[58–63].

While performing FNA in iresectable tumors has no adversaries, FNA in resectable tumors is debatable. Some authors advocate avoiding FNA in resectable pancreatic adenocarcinoma since it will not alter management of the patient[64], and other demand cytological diagnoses in this cases[36,42–44]. The fact that management will not be influenced by presumed FNA finding, problem with false negative cytological findings and risk of complications may support a no FNA stand. However, complications are rare and mild, with tumor seeding as most fearful complication[65]. Still, there is only one documented tumor seeding after EUS-FNA of solid pancreatic masses from the beginnings of EUS-FNA world wide[66]. Since there is no way to accurately differentiate benign from malignant lesions by any other method then with tissue diagnosis obtained by EUS-FNA it is hard to say that every detected small solid lesion deserve to be surgically removed. Holding this taught, this group of authors prospectively conducted a study with repeated EUS-FNA procedures in small solid pancreatic masses[46] where in 22 of 46 cases lesions were found to be benign even after repeated EUS-FNA procedures. Follow up period was at least 22 months and there was only one false negative finding. So, EUS-FNA reduced number of unnecessary surgery in patients with small solid pancreatic masses. In conclusion, EUS-FNA is the method of choice for differentiation benign and malignant lesions. However, there is no consensus should EUS-FNA be performed in small solid pancreatic lesions.

Staging of Pancreatic Cancer

Tumor staging is the most debatable indication for EUS in pancreatic cancer patients. At the time of introducing this method, EUS was superior to other methods in detection of pancreatic masses, but even the early studies were not consistent for superiority in staging. Some studies considered EUS inferior[67,68] and other superior to other imaging methods[69–71].

It is difficult to make conclusion in this matter since criteria for resectability used in these studies were different. It is fair to say that the choice of method should be up to personal opinion of clinician and availability of quality equipment and experienced personal.

Resuming the role of EUS we can state that despite some controversies EUS is very valuable method in evaluation of solid pancreatic masses and with guided FNA is nowadays by far the best method for obtaining tissue diagnosis.

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ENDOSKOPSKI ULTRAZVUK U DIJAGNOSTICI SOLIDNIH TVORBI GUŠTERAČE – TRENUTNO STANJE I PREGLED LITERATURE

S A Ž E T A K

Prije otprilike 25 godina endoskopski ultrazvuk (EUS) uveden je u klinički praksu kako bi omogućio bolji pregled promjena u gušterači. U to vrijeme, EUS je bio nadmoćan ostalim metodama u otkrivanju tvorbi u gušterači, a uz kasnije uvedenu citološku punkciju vođenu EUS-om omogućeno je i postavljanje tkivne dijagnoze. Tijekom vremena EUS je tehnološki napredovao. Mehanička sonda zamijenjena je elektroničkom koja je omogućila dodatne analize obojenim Dopplerom i power Dopplerom, te analizu kontrastom pojačanim EUS-om i EUS elastografiju. Istovremeno je znatno napredovala i tehnologija kompjuterizirane tomografije (CT) te neki autori postavljaju pitanje je li EUS izgubio prednost u dijagnostici solidnih tvorbi gušterače. Cilj ovog pregleda je iznijeti najnovije literaturne dokaze o utjecaju EUS-a i EUS-FNA na dijagnostiku promjena u gušterači s posebnim osvrtom na razlikovanje dobroćudnih od zloćudnih promjena. Prema podatcima iz literature, neupitne indikacije za EUS su otkrivanje malih tumora gušterače, preoperativna lokalizacija endokrinih tumora te dobivanje uzoraka za tkivnu dijagnozu u slučajevima kad to ima utjecaj na daljnji postupak s bolesnikom. Citološka tkivna dijagnoza je i dalje neupitna za razlikovanje malignog od benignog, međutim postavlja se pitanje kad je tkivna dijagnoza i citološka punkcija neophodna. Prema literaturnim podatcima obojeni Doppler, power Doppler, EUS pojačan kontrastom i EUS elastografija su se pokazali kao metode koje nude dodatne informacije u evaluaciji solidnih promjena gušterače, ali nedovoljno da bi otkrile definitivnu prirodu lezije. Uloga EUS-a u procjeni proširenosti tumora gušterače je prema literaturnim podatcima kontroverzna, a kako neki upućuju na superiornost EUS-a a drugi na superiornost CT-a nije moguće dati kvalitetan zaključak. Međutim, to ukazuje da EUS nije neprikosnoven u procjeni proširenosti tumora.