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Review

Endoscopic ultrasound in pediatric population: a comprehensive review of the literature

Barbara Bizzarri[1], Giorgio Nervi[1], Alessia Ghiselli[1], Elisabetta Manzali[1], Francesco Di Mario[1], Gioacchino Leandro[2], Federica Gaiani[1], Stefano Kayali[1], Gian Luigi de'Angelis[1]

[1] Gastroenterology and Endoscopy Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; [2] National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. *Background and aim:* Endoscopic ultrasonography (EUS) with or without fine needle aspiration/biopsy (FNA/B) is a well-established diagnostic tool in adults for the evaluation and management of gastrointestinal (GI) tract disorders. Its use in children is still limited as well as literature in pediatric age is limited, although the application of EUS is now increasing. The present article aims to review the current literature about EUS indication, accuracy and safety in pediatric age. *Methods:* Electronic literature searches were conducted using Pubmed, Medline, Embase, and the Cochrane Central Register of Controlled Trials using the word pediatric endoscopic ultrasound, pediatric pancreaticobiliary AND/OR EUS, pediatric EUS technique. Main patients and procedures characteristics were analyzed. The primary endpoint was the indication of EUS. Secondary endpoints were the accuracy of the technique and the incidence of complications. *Results:* Data were extracted from 19 articles. A total of 571 patients were investigated, with a median age of 12,7 years. A total of 634 EUS procedures were performed. The majority of EUS procedures investigated the pancreaticobiliary tract (77,7%). Most studies showed a high positive impact on management with a median value of 81,7%. No major complications were reported. Five studies reported minor complications with a median value of 2%. *Conclusions:* EUS is safe and has a significant role in the diagnosis of pancreaticobiliary and GI diseases even in children, with a high therapeutic success. An increasing EUS utilization by pediatric gastroenterologists is expected and offering dedicated EUS training to some selected pediatric gastroenterologists might be indicated. (www.actabiomedica.it)

Key words: indication, accuracy, safety of EUS in children

Background and aim

Available since the 1980s, endoscopic ultrasound (EUS) allows detailed anatomical visualization of structures around the gastrointestinal (GI) tract, including the individual layers of the GI tract (1). However, EUS has not had a relevant role in Gastroenterology, until the advent of the fine needle aspiration (FNA) in 1991 (2). After the introduction of FNA, EUS has increasingly been applied in the field of Gastroenterology and nowadays EUS use in adults is well established and widespread.

Although the application of endoscopic ultrasound in children is increasing, EUS and EUS-FNA in children are supported by limited number of studies. This is mainly because of the lower incidence of pancreaticobiliary and GI neoplasms, presumptive size limitations of EUS equipment for pediatric patients, the need for sedation or anesthesia, the lack of skilled pediatric endosonographers and limited awareness among pediatricians of EUS diagnostic and therapeutic capabilities (3).

Benefits include absence of ionized radiation exposure, excellent axial resolution providing detailed

real-time imaging of structures and wall layers, and the capacity to sample tissue and fluid collections via FNA and fine needle biopsy (FNB) (4).

The aim of this paper is to review the current literature for EUS indication, accuracy and safety in pediatric age.

Equipment

EUS is composed of different instruments: the echoendoscopes in which US transducer is placed on the tip and a water-filled balloon surrounding the transducer, the miniprobes that can be inserted inside the biopsy channel of a standard endoscope.

Although the application of traditional linear echo-endoscopes may be feasible in patients weighing at least 15-25 kg, data evaluating EUS in patients of this size are limited (4, 5). This limit can be overcome by using smaller (6.3-6.9 mm outer diameter) endobronchial ultrasound equipment in the GI tract. With this equipment, EUS can successfully be performed in children as young as 2 months of age (6). In alternative, EUS can be performed using miniprobes through the working channel of a standard pediatric endoscope.

Radial EUS scopes provide a 360° sonographic view, which is perpendicular to the tip of the endoscope. Radial scope is generally used to study the upper digestive system because it allows complete and simple anatomical orientation and faster exploration of large areas of the gastro-intestinal tract and adjacent organs (7). Linear EUS scopes provide a 150° sector view, which is parallel to the long axis of the endoscope. It shows the gastrointestinal wall worse than the radial one, but it is in general used for the organs outside the gastrointestinal tract (e.g. pancreas), and it is indispensable for FNA (8). Both endoscopes operate a frequency between 5 and 10 MegaHz.,

Methods

Data sources

Electronic literature searches were conducted using Pubmed, Medline, Embase and the Cochrane, Scopus from 1 January 1993 to 1 September 2018.

Search Mesh terms included: "pediatric endoscopic ultrasound", "pediatric pancreaticobiliary AND/OR EUS", "pediatric EUS technique". Additional articles were selected reviewing the references of the papers identified using these key words. No attempt was made to locate unpublished material.

Study selection (inclusion/exclusion criteria)

Published studies were included if they met the following criteria:

(1) the indications of EUS in children were investigated, (2) studies involving only patients in pediatric age, (3) no gender restrictions, (4) final diagnosis was indicated (5) complication were reported, and (6) publication in English. We excluded (1) systematic reviews, abstracts, and guidelines; (2) studies involving adult patients; (3) studies not in English; (4) animal and ex vivo studies.

Data extraction

Data extraction was conducted independently by 2 investigators (B.B. and G.L.de'A.), with the discrepancies resolved by the consensus of these 2 investigators. The publications were manually screened and reviewed to identify reports for pediatric EUS.

This study did not require ethical approval as all the used data have been published previously.

The following details were recorded: Patients (the total number of patients enrolled in each study indication of EUS, mean age); Intervention (with or without FNA, Therapeutic procedures); Outcomes (diagnosis, treatment, clinical impact, complications).

Results

After removal of duplicates and screening for inclusion and exclusion criteria a total of 19 studies (3, 9-26) from 1998 and 2018 were included. Eleven studies were performed in the USA (11, 12, 15-20, 23, 25-26), 4 in Europe (3, 9, 14, 22) and 4 in Asia (10, 13, 21, 24).

Patients and procedures characteristics

The main findings are reported in Table 1. A total of 571 patients were investigated with EUS. The patients age ranged between 0,5 and 21 years old, with a median age among the studies of 12,7 years old. A total of 634 EUS procedures were performed. In 21,2% of cases a EUS-FNA or a Tru-Cut Biopsy (TCB) was performed. A 16,4% of operative EUS including drainage of pseudocyst, celiac plexus block, cyst gastrostomy with stents placement, transluminal biliary drainage following failed Endoscopic Retrograde Cholangio-Pancreatography (ERCP) cannulation were reported.

Indications and impact

Details of the indications and impacts are presented in Table 2. The majority of EUS investigated the pancreaticobiliary tract (77,7%), followed by the upper GI tract, including the evaluation of the esophagus, stomach and duodenum (15,4%), rectum (4%), and other indication (such as evaluation of lymph-nodes, mediastinal/abdominal mass) (2,9%).

Most studies about EUS in children showed a high positive impact on management ranging from 35,5 % to 100 % (media=81,7%).

Complications

There were no reported main complications in the included studies (Table 3). Five studies reported minor complications from 2 to 22% with a mean value of 2%. The reported minor complications included self-limited bleeding without need for intervention or hospitalization (19, 21) during FNA/TCB, late bleeding (19th day) after pseudocyst drainage (3), mild pancreatitis (20), transient desaturation after conscious sedation (21), postprocedural fever after cystogastrostomy (21) and after pseudocyst drainage (26), intra-procedural anesthesia-related complications (laryngospasm and hypoxemia (26).

Table 1. Patients and procedures characteristics

Studies	No patients	No procedures	Age yrs	FNA/TCB%	Therapetic procedures %
Roseau et al 1998	18	23	4-16(12)	0	0
Usui et al 2002	2	2	0,5-4 (2,25)	0	0
Nadler et al 2002	1	1	13 (13)	100	0
Varadarajulu et al. 2005	14	15	5-17 (13)	FNA (20)	0
Cohen et al 2008	32	32	1,5-18 (12)	FNA (21,9)	0
Bjerring et al. 2008	18	18	0,5-15 (12)	0	0
Attila et al. 2009	38	40	3-17 (13,5)	FNA (30)	5,2
Rosen et al 2010	25	42	NA (14)	0	0
Al-Rashdan et al. 2010	56	58	4-18 (16)	FNA (25,9)	8,9
Jazrawi et al 2011	10	10	4-17 (11,8)	FNA (20)	80
Larissa et al 2012	9	9	9-18 (13,6)	FNA/TCB 100	0
Scheers et al. 2015	48	52	2-17 (12)	FNA (25)	8,3
Gordon et al. 2015	43	51	4-18 (14,5)	FNA (25,5)	0
Mahajan et al. 2016	121	125	3-18 (15,2)	FNA (5,6)	0
Fugazza et al 2017	40	47	3-18 (15,1)	FNA (6,4)	2,5
Law et al 2018	1	1	8 (8)	0	100
Singh et al 2018	32	32	8-18 (14)	0	0
Jia et al 2018	5	6	6-17 (13)	0	100
Raina et al 2018	58	70	6-21 (18)	FNA (22,4)	6,9
Total	571	634			
Mean			12,7	21,2	16,4

Table 2. Main indications and impact of EUS procedures

Studies	Indication %				Impact%
	PB	Upper GI	Rectum	Other	
Roseau et al 1998	34,8	34,7	26,1	4,3	NA
Usui et al 2002	0	100	0	0	100
Nadler et al 2002	100	0	0	0	100
Varadarajulu et al. 2005	100	0	0	0	93
Cohen et al 2008	59,4	34,4	6,3	0	44
Bjerring et al. 2008	61,1	16,7	0	22,2	78
Attila et al. 2009	62,5	17,5	2,5	17,5	NA
Rosen et al 2010	100	0	0	0	NA
Al-Rashdan et al. 2010	72,4	3,4	6,9	0	86
Jazrawi et al 2011	100	0	0	0	86
Larissa et al 2012	100	0	0	0	86
Scheers et al. 2015	100	0	0	0	98
Gordon et al. 2015	66,7	11,8	1,9	0	80
Mahajan et al. 2016	94,4	1,6	0	0	35,5
Fugazza et al 2017	59,6	47,3	31,9	0	87,2
Law et al 2018	100	0	0	0	NA
Singh et al 2018	100	0	0	0	NA
Jia et al 2018	100	0	0	0	Na
Raina et al 2018	65,6	24,1	0	10,3	88
Mean	77,7	15,4	4	2,9	81,7

Table 3. Complications

Studies	Minor complications %	Major complications %
Roseau et al 1998	nil	nil
Usui et al 2002	nil	nil
Nadler et al 2002	nil	nil
Varadarajulu et al. 2005	nil	nil
Cohen et al 2008	nil	nil
Bjerring et al. 2008	nil	nil
Attila et al. 2009	nil	nil
Rosen et al 2010	NA	NA
Al-Rashdan et al. 2010	nil	nil
Jazrawi et al 2011	nil	nil
Larissa et al 2012	22	nil
Scheers et al. 2015	2	Nil
Gordon et al. 2015	2,3	Nil
Mahajan et al. 2016	2,4	Nil
Fugazza et al 2017	nil	Nil
Law et al 2018	nil	Nil
Singh et al 2018	nil	Nil
Jia et al 2018	nil	Nil
Raina et al 2018	8,6	Nil
Total	2	0

Discussion

Compared to the firmly established role of EUS/EUS-FNA in adults, data in pediatric patients are still scarce. Moreover, most studies focus on diagnostic indication for EUS and only few provide information on its therapeutic role in this population (12, 17). A limit of EUS in pediatrics is the presumptive size of EUS equipment, especially when therapeutic EUS procedures are required. Although literature showed that the application of linear echo-endoscopes may be feasible in patients weighing at least 15-25 kg, data regarding this modality are still limited (27). More limits are due to the lack of experience of operators as well as the rarity of diseases that require EUS evaluation in children. Even though studies in pediatrics described that only 21,2% of patients underwent FNA/TCB, currently available literature suggest that EUS-guided pancreatic tissue sampling can be performed with technical and clinical results corresponding to the procedures in adults for similar indications (3, 9, 12, 14, 17). Literature suggests that EUS-FNA is technically

successful in more than 95% of cases if carried out by an experienced endosonographer with a sensitivity of 87% and a specificity close to 100% (28). The most recurrent scenario in which EUS-FNA is reported in children include pancreatic tissue sampling in the setting of pancreatic mass or suspected Acute Idiopathic Pancreatitis (AIP) (4).

Regarding the indications, pancreaticobiliary disease is the most common reason for EUS referrals in the pediatric population. Various pancreaticobiliary diseases may require EUS evaluation also in pediatric age such as inflammatory conditions (suspected choledocholithiasis/microlithiasis, recurrent/chronic/autoimmune pancreatitis), congenital conditions (choledochal cyst, anomalous pancreaticobiliary junction, pancreas divisum, duodenal duplication, ectopic pancreas), cystic lesions (pancreatic pseudocyst, mucinous/serous cystic neoplasms), neoplastic conditions (neuroendocrine tumors, solid pseudopapillary tumor, lymphoma) (5).

EUS is known to be a sensitive procedure to evaluate both biliopancreatic diseases and gastrointestinal diseases, due to the peculiar ability to visualize early pathological changes in the pancreatic gland and to differentiate the 5 GI layers (29).

In acute pancreatitis, EUS is not indicated in the evaluation of the extension of the inflammatory process, where CT remains the gold standard, nevertheless, EUS is indicated to study the etiology of pancreatitis, being choledocholithiasis the most common cause of acute pancreatitis (78.9%) (16).

In lithiasis EUS has been shown to be 95% to 100% accurate for diagnosing such diseases as suspected choledocholithiasis and microlithiasis (13). EUS has a higher resolution and is more sensitive especially for microlithiasis (less than 3 mm in size) when compared to magnetic resonance cholangiopancreatography, or CT (30, 31). Moreover, children with EUS showing no evidence of microlithiasis can potentially avoid unnecessary cholecystectomy or ERCP (5). Therefore, EUS can identify patients with biliary pancreatitis in which the ERCP will be useful and replace diagnostic ERCP which is more invasive and associated with more risks (12). Actually, one study demonstrated that ERCP was avoided in 13 out of 17 children due to findings noted on EUS (32).

Pancreas divisum is the most common pancreatic congenital anomaly and it may play a role in "idiopathic" acute and chronic pancreatitis (33).

EUS can be performed to exclude pancreas divisum with a sensitivity of 100% and specificity of 96%, avoiding the risks associated with ERCP (5).

Pseudocyst is the most common pancreatic cystic lesion in childhood, about 75% of all cases (18). The common causes of pancreatic fluid collections (PFCs) in children worldwide are trauma (leading cause up to 50% of cases), gallstone, idiopathic, hereditary, viral, or toxin-mediated pancreatitis (34).

The rates of technical success were significantly better for the EUS-guided approach with even minor complications compared to gastrostomy (18), a success rate of 94% and with long-term pseudocyst resolution in 85% of cases (18). One recent study demonstrated successful pediatric therapeutic EUS procedures in a 6 years old child weighting 18,5 kg (25). But data in pediatric population are still limited, as reported in this review with a 16,4% of therapeutic procedures, compared to adult population (65,6% of pseudocyst requires percutaneous/endoscopic or EUS drainage) (35). Pancreatic neoplasms are rare in children. Pancreatic necrosis, solid pseudopapillary tumor, neuroendocrine tumor, insulinoma and gastrinoma, and lymphoma are the most frequent in pediatric patients (4,5). EUS has proven to be sensitive and specific in diagnosing pancreatic masses in pediatric population. Contrast-enhanced harmonic EUS and EUS elastography can be helpful to improve the accuracy of EUS (36, 37).

This review reveals that EUS played a significant role in establishing a definitive diagnosis and managing pediatric disorders with an important clinical impact ranging from 35,5-100%, with a median value of 81,7%. The authors explain that the possible reason for the low impact factor (35,5) are the lack of follow up in recurrent acute pancreatitis, the largest subgroup (59%) (21), the avoidance of ERCP by EUS in previous studies was taken as a positive impact in management and the less stringent criteria to define a positive impact in some studies (12-14, 17).

The main complications reported in children are related to therapeutic procedures (19-21, 26). Complications rates regarding perforation are similar compared with standard endoscopy. The risk of iatro-

genic pancreatitis as a result of EUS-FNA arises in patients undergoing FNA of pancreatic masses, cysts or the pancreatic duct, involving direct passage of needle through pancreatic tissue (38). Despite the use of Doppler, bleeding is reported with an incidence of 1-4,4% as intraluminal hemorrhage, and 1,3% as extraluminal hemorrhage (39). Other complications are anesthesia-related ones, since in pediatric age these procedures need sedation or general anesthesia.

Conclusions

EUS is an emerging modality even in pediatric age that provides detailed evaluation of the pancreatic parenchyma and GI system due to its high sensitivity and accuracy (5). Until now, EUS has been performed in a relatively small number of pediatric patients and the majority of endosonographers are adult gastroenterologist who usually work with instruments for adults.

Moreover, EUS enables to obtain FNA/FNB sampling or larger core tissue biopsies that may be beneficial in the diagnosis of certain pathologies such as neoplasms or AIP. Compared to ERCP, it is a safe modality with minimal risk (40-42) and diagnostic ERCP can be therefore avoided. EUS is a safe and useful outpatient procedure with minimal morbidity, although requires sedation preferably with anesthesiologic support, especially for pediatric patients. Therefore, the complex management required for the pediatric patients may limit the use of EUS in children to highly trained experts and to tertiary care centers.

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Correspondence:
Barbara Bizzarri,
Gastroenterology and Endoscopy Unit,
Department of Medicine and Surgery, University of Parma,
Via Gramsci 14, 43126, Italy
Tel. +39 3484119789
E-mail: babizzarri@yahoo.it