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Is endoscopic ultrasonography more sensitive than magnetic resonance imaging in detecting and localizing pancreatic neuroendocrine tumors?

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Abstract
To compare endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) in terms of their sensitivities to localize pancreatic neuroendocrine tumors (pNET) preoperatively. Systematic analysis of the literature; sensitivity of EUS and MRI in insulinomas and pancreaticoduodenal NETs in multiple endocrine neoplasia type 1 (MEN1) in series of at least 20 subjects referring to tumors confirmed by surgery and histopathology. Other imaging methods reported were also assessed. Eighteen publications on insulinomas (782 cases) could be analyzed, no study in MEN1 fulfilled the inclusion criteria and compared EUS to MRI. Data quality was moderate: all publications referred to case series. Mean correct detection / localization rates (sensitivity) were calculated: EUS 80%, MRI 66%, computed tomography 63%, angiography 52%, somatostatin receptor scintigraphy 42%, ultrasonography 23%; arterial calcium stimulation with hepatic venous sampling regionalized correctly in 80%. EUS seems to be more sensitive than MRI in localizing pancreatic neuroendocrine tumors. If a specialized endosonographist is available, EUS is the preferable imaging procedure. Otherwise, MRI is a suitable alternative.

Keywords Endoscopic ultrasonography · EUS · Magnetic resonance imaging · MRI · Neuroendocrine tumor · NET · Insulinoma

1 Introduction

At first sight, it seems to be an easy task to just compare two different methods of imaging of pancreatic neuroendocrine tumors (pNET). However, one has to keep in mind that there is an important difference between magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS): MRI is a highly standardized imaging technique. Of course, there are some technical differences between imaging devices, for instance resolution, slice thickness and signal characteristics. Nevertheless, pictures generated by those machines all look quite similar. It is primarily the challenge for the radiologist to view these pictures which have been generated by a technician, analyze them and come to a precise interpretation.

On the contrary, EUS is a highly subjective imaging procedure. Its significance strongly depends on the individual skill set of the endosonographist. This does not only refer to her/his experience in EUS imaging, but also to her/his individual experience in the imaging of pNETs. In other words: An endosonographist who really is experienced in staging esophageal and rectal cancer by EUS does not necessarily produce reliable results when looking for insulinoma. This has been impressively shown by the study of Fendrich et al. [5] which presented a low correct localization rate of insulinomas by EUS because of the inclusion of EUS findings obtained in a decentralized fashion in hospitals with endosonographists with probably little experience in imaging pNETs.

The task for the endosonographist is to be sure to have seen the whole pancreas from all possible perspectives out of stomach and duodenum at the end of the procedure. This sounds easy, but in fact is not. Furthermore, it is up to her/him to decide whether to her/him a radial or a longitudinal scanner seems to be more appropriate. Analyzing the literature on the value of EUS in detecting pNETs is probably biased by the fact that available publications on that issue derive from centres/endosonographists with a high level of individual experience. However, this may also be the case in papers published by specialists in radiology or nuclear medicine focusing on their favorite imaging procedures.

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2 Methods

In order to compare the reliability of EUS and MRI in localizing pNETs, this study systematically analyzes literature available on this issue concerning insulinomas and pancreaticoduodenal NENs in multiple endocrine neoplasia type 1 (MEN1) in series referring to at least 20 subjects with documented diagnosis (insulinoma, MEN1) and EUS performed.

A standardized Pubmed search has been performed by May 26th, 2017, on original studies published in English combining the keywords "[EUS or endosonography or endoscopic ultrasound or endoscopic ultrasonography] and [insulinoma or multiple endocrine neoplasia type 1 or MEN1]" published since the year 2000.

The data in these papers were analyzed systematically. Scientific analysis has been performed in five steps:

1. Only studies referring to tumors confirmed by surgery and histopathology in all patients were accepted.
2. Given correct EUS detection / localization rates (sensitivity) were assessed. If this information was not exactly given in the paper, it has been excluded from the study. The arithmetic mean of the EUS detection / localization rates (sensitivity) as given in the respective publications was calculated.
3. If MRI data were available, these data were included into a comparative analysis. The arithmetic mean of the MRI detection / localization rates (sensitivity) as given in the respective publications was calculated.
4. Additional information on other modalities of preoperative localization in these publications was analyzed. The arithmetic mean of the respective detection / localization rates (sensitivity) as given in the respective publications was calculated.
5. It was assessed whether there is a trend in diagnostic accuracy over time in EUS and MRI by identifying the two studies with the lowest detection / localization rates.

It has to be kept in mind that tumor detection rates by different imaging modalities were not in all manuscripts the primary endpoint of the papers included in this systematic analysis. Thus, information concerning detection and localization rates were extracted from these publications as far as possible.

3 Results

Concerning insulinomas, 18 publications could be included into the analysis (Table 1). These papers report on a total of 782 cases. However, looking at the author groups, is has to be suspected that a subset of patients have been reported more than once.

The mean correct EUS detection / localization rates (sensitivity) was found to be 80%. For MRI, 66% were calculated, and for US 23%, CT 63%, angiography 52%, and SRS 42%, respectively. Correct regionalization by ASVS was reported in 80%.

The two studies with the lowest correct EUS detection / localization rates (sensitivity) have been published in 2001 and 2002, for MRI in 2001 and 2016.

In MEN1, numerous studies have been published. However, almost all studies compare detection rates of different imaging methods to the total of lesions found by every method, thus did not fulfill the inclusion criteria that tumors had to be confirmed by surgery and histopathology in all patients.

Just one study fulfilled the inclusion criteria for this systematic analysis which reports a 100% sensitivity of EUS, however does not provide MRI data ([15]; Table 2).

4 Discussion

I feel it is mandatory that the discussion of this study starts with its limitations. All the publications that could be included into this study were case series, not prospective studies. Imaging strategy differed between patients within the study: not all imaging procedures reported in the studies were performed in all patients. Details on technical equipment are frequently not given, for instance for EUS whether a longitudinal or radial scanner had been used. Usually, information is missing about whether EUS pancreatic imaging has been performed by positioning the patient on her/his left side or in supine position. EUS in left side position may be associated with a low sensitivity of detecting lesions in the pancreatic tail which might explain a respective statement in the paper of Sotoudehmanesh et al. [19]. There is usually no information available on the personal experience of the endosonographist in the imaging of pNETs (compare: "methods", [5]) which, however, seems to be a highly relevant factor for diagnostic precision of EUS in this context. Reporting on a large number of patients does not necessarily mean that the endosonographist has an extensive experience since endosonographists may have changed over time. Such information is usually not available from the publications. It may be suspected that the earlier the manuscript has been published and the more patients have been enrolled, the older the technical equipment might have been. Mean tumor sizes differ between studies. It may be suspected that the larger the mean tumor diameter, the better MRI might have been in comparison to EUS [1, 12]. Furthermore, it seems to be likely that there is a multiple reporting of patients in different settings and publications. Concering MEN1, no study could be identified that compared EUS and MRI in patients in whom all tumors had been confirmed by surgery and histopathology. Assessing ASVS was not the primary endpoint of this study, but has been analyzed as secondary endpoint and information on its sensitivity is listed in Table 1. In this context, it has to be stated that ASVS just regionalizes, but not localizes

Table 1 Correct detection/localization rates (sensitivity) in insulinomas

First author journal year	Patients analyzed in the study	Correct localization by EUS	Correct localization by MRI	Correct localization by other modalities
Anderson Am J Gastroenterol 2000 [2]	33	88%	–	
Machado Hepatogastroenterology 2001 [16]	59	27%	17%	US: 30% CT: 25% angiography: 54% ASVS: 94%
Chen Hepatobiliary Pancreat Dis Int 2002 [3]	74	33%	64%	US: 30% CT: 63% ASVS: 90%
Gouya Am J Roentgenol 2003 [7]	30	94%	–	CT: 69%
Kaczirek Wien Klin Wochenschr 2004 [10]	67	71%	85%	CT: 50% angiography: 65%
Queiroz Almeida J Endocrinol Invest 2006 [18]	64	75%	65%	US: 23% CT: 28% angiography: 38% ASVS: 67%
Kann Eur J Endocrinol 2007 [13]	29	90%	–	
Sotoudehmanesh Endocrine 2007 [19]	52	90%	–	CT: 84%
Fernandez-Cruz World J Surg 2008 [6]	23 (in a cohort of 49 pNET patients)	95%	80%	CT: 70%
Morganstein Eur Radiol 2009 [17]	28	86%	71%	CT: 44% SRS: 33% ASVS: 100%
Druce Eur J Endocrinol 2010 [4]	36	65%	64%	CT: 75% SRS: 50% ASVS: 63%
Varma Dig Surg 2011 [22]	40	94%	82%	CT: 62%
Grygiel Pol Przegl Chir 2012 [8]	45	80%	67%	US: 9% CT: 69%
Tellez-Avila Endosc Ultrasound 2015 [20]	24	100%	–	CT: 60%
Jyotsna Indian J Med Res 2016 [9]	66	95%	85%	CT: 79%
Tsang ANZ J Surg 2016 [21]	32	90%	42%	CT: 90% ASVS: 63%
Wei Langenbecks Arg Surg 2016 [23]	33	80%	75%	US: 22% CT: 72%
Kann Endocrine 2017 [14]	47	94%	–	

insulinomas and may thus not be considered suitable for planning minimal invasive surgery.

Thus, the message to be taken from this paper has to be handled carefully.

Table 2 Correct detection/localization rates (sensitivity) in MEN1

First author journal year	Patients analyzed in the study	Correct localization by EUS	Correct localization by MRI	Correct localization by other modalities
Lewis World J Surg 2012 [15]	52	100%	–	CT: 81% SRS: 84%

Comparing EUS and MRI to other imaging methods such as US, CT, angiography and SRS, EUS and MRI seem to be the favorite ones. In comparison to MRI, EUS has been reported to be more sensitive. As indicated by the fact that the two studies with the lowest sensitivity of EUS have been published early in 2001 and 2002, this method seems to have undergone a learning curve and/or a process of relevant technical evolution.

It has furthermore to be kept in mind that EUS not only enables tumor localization with a high sensitivity, but also may be highly relevant in planning minimal invasive surgery as anatomical relations to critical structures in the neighborhood can precisely be assessed [11]. Nevertheless, it has to be stated again, that the relevance of EUS strongly depends on the personal experience of the endosonographist in imaging pancreatic pNETs. If such an experienced endosonographist is not available, MRI may be the preferable procedure in individual settings / hospitals.

5 Conclusion

In conclusion, EUS has been reported to be more sensitive than MRI in localizing pancreatic neuroendocrine tumors. However, quality of EUS imaging strongly depends on the endosonographist's individual experience, thus should be performed in specialized centres by a specialist. If a specialized endosonographist is not available, MRI may be the preferable alternative procedure.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest or whatever conflict there might be perceived.

Abbreviations *ASVS,* arterial calcium stimulation with hepatic venous sampling; *CT,* computed tomography; *EUS,* endoscopic ultrasonography; *MRI,* magnetic resonance imaging; *NEN,* neuroendocrine neoplasia; *pNET,* pancreatic neuroendocrine tumor(s); *SRS,* somatostatin receptor scintigraphy; *US,* ultrasound

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