Magnetic Resonance Imaging or Endoscopic Ultrasonography for Detection and Surveillance of Pancreatic Neuroendocrine Neoplasms in Patients with Multiple Endocrine Neoplasia Type 1?

Authors

Kosmas Daskalakis[1, 2 *, §], Marina Tsoli[2 *, §], Krystallenia I. Alexandraki[2, §], Anna Angelousi[2, §], Eleftherios Chatzellis[2, §], Apostolos V. Tsolakis[3, 4], Ioannis Karoumpalis[5], Denise Kolomodi[2, §], Evanthia Kassi[2, 6, §], Gregory Kaltsas[2, 7, 8, §]

Affiliations

1 Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
2 1st Department of Propaupedic Internal Medicine, Endocrine Oncology Unit, Laiko Hospital, National and Kapodistrian University of Athens, Athens, Greece
3 Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden
4 Cancer Centre Karolinska, CCK, Karolinska University Hospital, Stockholm, Sweden
5 Department of Gastroenterology, "G. Gennimatas" General Hospital, Athens, Greece
6 Department of Biological Chemistry, Medical School, National and Kapodistrian niversity of Athens, Athens, Greece
7 Clinical Sciences Research Laboratories, Warwick Medical School, University of Warwick, University Hospital, Coventry, UK
8 Centre of Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, UK

Correspondence

Kosmas Daskalakis
1st Department of Propaupedic Internal Medicine,
National and Kapodistrian University of Athens,
Mikras Asias 75,
11527 Athens
Greece
Tel.: + 30/698/8667 113, Fax: + 30/213/2061 794
kosmas.daskalakis@surgsci.uu.se

Key words

multiple endocrine neoplasia type 1, neuroendocrine tumor, magnetic resonance imaging, endoscopic ultrasonography

received 03.03.2019
accepted 15.05.2019

Bibliography

DOI https://doi.org/10.1055/a-0931-7005
Published online: 11.7.2019
Horm Metab Res 2019; 51: 580–585

ISSN 0018-5043

Supplementary Material for this article is available online at http://www.thieme-connect.de/products.

ABSTRACT

Our aim was to compare the clinical utility of Magnetic Resonance Imaging (MRI) and Endoscopic Ultrasonography (EUS) in identifying Pancreatic Neurondocrine Neoplasms (PanNENs) and monitoring size alterations in Multiple Endocrine Neoplasia type 1 (MEN1) patients. Thirty-one MEN1 patients with PanNENs and concurrent screening by EUS and abdominal MRI were included and 129 pancreatic lesions were detected in total. MRI detected fewer lesions than EUS (n = 73 vs. 110, p = 0.006). MRI sensitivity and specificity compared to EUS at 20 and 10 mm cut-offs of maximal lesion diameter were 96 and 88 % (20 mm cut-off) and 90 and 82 %(10 mm cut-off), respectively (concordance rates of 97 and 87 % and Cohen's kappa = 0.912 and 0.718, respectively). Lesions < 1 cm were more often detected with EUS (p = 0.025). Data from sequential concurrent imaging on lesion growth rate [n = 7 (mean ± SD: 2 mm/year ± 3.4 mm vs. 1.9 mm/year ± 3.6 mm)] over a period of at least two years as well as pathology data in connection to preoperative concurrent imaging were available in a small number of patients (n = 7, p = 0.933 for mean differences in maximal lesion diameter). MRI of the pancreas was more readily available and less expensive than EUS in an outpatient setting. In conclusion, MRI performs well compared to EUS for the detection and subsequent surveillance of MEN1-related panNENs larger than 10 mm and seems to be cost-effective. Both modalities could be used at initial assessment and MRI alone could be utilized thereafter in patient surveillance. EUS retains its value in surgical planning and the detection of small mostly functional PanNENs.

* Equal contribution.

§ Institute where the investigations have been carried out: 1st Department of Propaupedic Internal Medicine, Endocrine Oncology Unit, Laiko Hospital, National and Kapodistrian University of Athens, Greece.

Introduction

Multiple Endocrine Neoplasia Type 1 (MEN1) is an autosomal dominant neoplastic disorder caused by germline mutations in the MEN1 gene and characterized by combined occurrence of tumors of the parathyroid glands, the anterior pituitary and the endocrine pancreas [1]. The MEN1 phenotype is extremely diverse with variable expressivity, considerable heterogeneity and a wide age range of penetrance of its different components. Although rare, MEN1-related Pancreatic Neuroendocrine Neoplasms (PanNEN) represent the second most frequent manifestation of MEN1 after primary hyperparathyroidism with a clinical penetrance of 50–70 % [2, 3]. They are characterized by early onset, multifocality and malignant potential with a propensity for development of locoregional and distant metastases depending on the size on the neoplasm. Additionally, PanNENs are one of the leading causes of cancer-related death in MEN1 patients [4]. Thus, prompt initial detection and life-long subsequent imaging monitoring of pancreatic lesions, already from 10 years of age, is crucial in patient management [5, 6].

The majority of MEN1- related PanNENs are nonfunctional (NF), clinically silent tumors, whereas in a subset of MEN-1 patients, they may secrete hormones leading to distinct clinical syndromes [7]. Different imaging modalities are currently available to localize functional PanNENs (F-PanNENs) prior to treatment (mainly surgical), but still their detection may be challenging. On the other hand, the surgical management of MEN1-related NF-PanNEN relies basically on tumor size, as the risk of malignant transformation and metastatic potential rises in larger tumors [8, 9]. However, the cut-off for surgery to minimize the risk of extra-pancreatic extension is still debatable and currently most of the clinical practice guidelines for surgical exploration in MEN1 patients with NF-PanNEN recommend a cut-off size of 2 cm [5, 10, 11]. MEN1 patients with a NF-PanNEN may undergo imaging of the pancreas every 6 to 12 months to assess the growth rate of the tumor [5, 12]. Importantly, as MEN-1 patients are subjected to life-long imaging monitoring, concerns also arise about the radiation risk in younger patients, regarding the routine use of Computed Tomography [13, 14].

To date, Endoscopic Ultrasonography (EUS) and Magnetic Resonance Imaging (MRI) have produced complementary results for detecting MEN1-related PanNENs, concerning both F-PanNEN localization and NF-PanNEN assessment. EUS may be combined with fine needle aspiration and provide information of the neuroendocrine origin of the tumor and grading. However, it is an invasive procedure and may be operator dependent [15, 16]. Additionally, the accuracy of EUS-guided fine needle aspiration compared to biopsy specimens is not great for low ki67 values. Nevertheless, it is still unclear which imaging modality should be routinely implemented at initial assessment and particularly during MEN1 patient follow-up. The main reasons for this are that the most sensitive modality for detecting clinically significant changes in NF-PanNEN has not yet been clearly determined. Moreover, the tumor size cut-off, as well as the least significant change in tumor diameter, that would lead to surgery are still not fully defined [5, 17].

The aim of the present study was to evaluate whether a non-invasive imaging modality, such as MRI of the pancreas could be implemented in MEN1 patient surveillance, as compared to EUS. We also aim to compare the concordance of these two modalities at the size cut-offs of 20 mm, the main indication for surgery, and 10 mm, inconsequential for the management of NF-PanNEN in MEN1 patients, respectively.

Patients and Methods

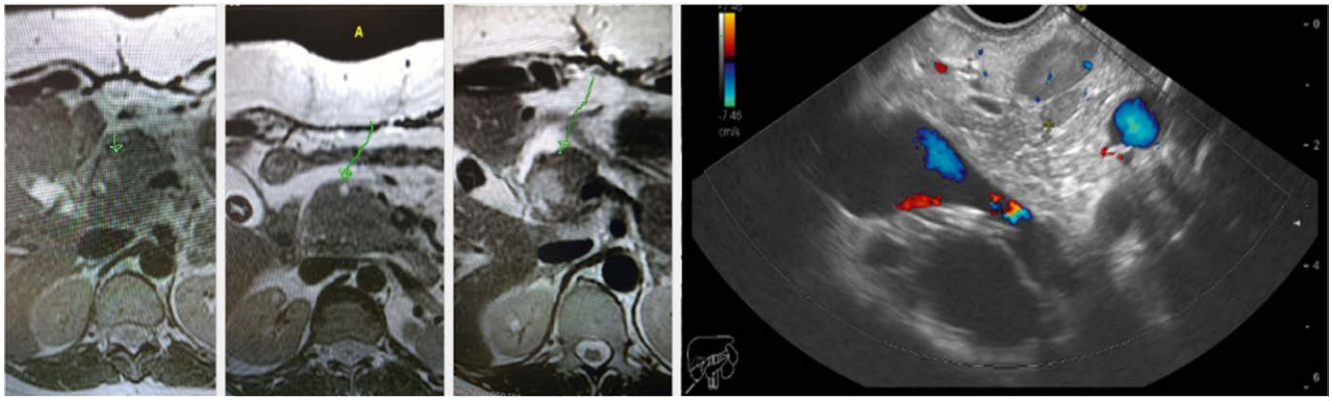
Thirty-one consecutive patients with MEN1-related PanNENs, who had been followed up at the Endocrine Oncology Unit, EKPA-Laiko Hospital, Athens, Greece from January 2005 through August 2018 were included. All patients underwent concurrent evaluation by EUS and MRI of the pancreas with a less than three months interval at initial assessment and/or at follow-up. Data were prospectively collected and retrospectively evaluated. MEN1 patients, who did not have concurrent MRI and EUS imaging were not included in this study.

Ethical approval

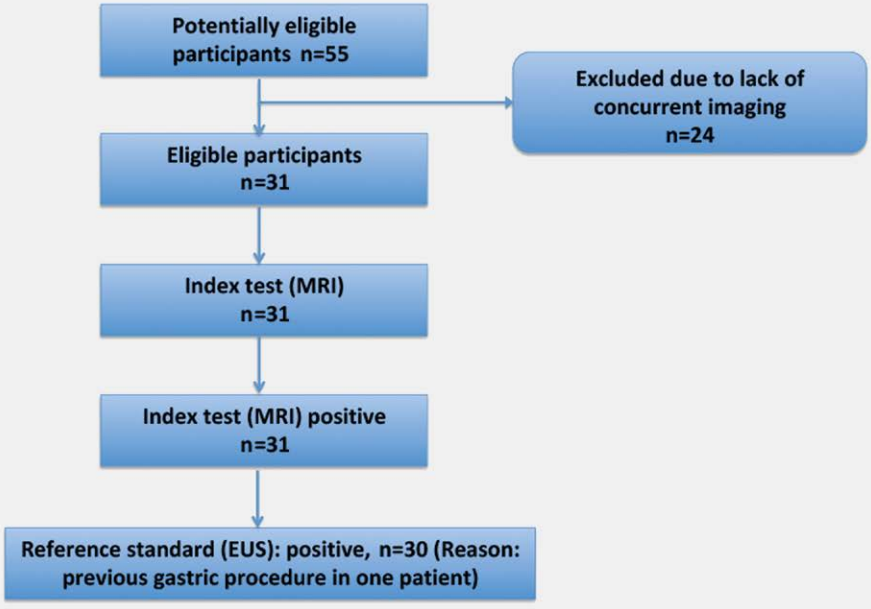
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional Review Board approval was obtained. Informed consent was obtained from all individual participants included in the study.

The diagnosis of MEN1 was confirmed in all patients based on standard international guidelines, including *MEN1* gene mutation detection and/or pathognomonic clinical, biochemical and radiological signs of MEN1–associated tumors [5]. Additionally, all patients had a confirmed radiological diagnosis of PanNEN either on previous Computed Tomography (CT) scan or the modalities (MRI and EUS) assessed in this study (▶ **Fig. 1**). Patient surveillance included the measurement of conventional imaging with MRI every 3–9 months according to existing ENETS guidelines [5]. However, the interval between assessments was increased if the disease was stable (especially for the relatively indolent grade 1, subcentimeter lesions). EUS was used at baseline along with MRI and thereafter upon identification of new pancreatic lesions on MRI at an annual or biannual basis, mainly for functional lesions, in cases demonstrating tumor growth at conventional imaging as well as in the preoperative setting. As computed-tomography is associated with repeated radiation exposure, this modality was not assessed in patient surveillance in our study [13, 14]. Pathology reports were scrutinized for the subset of patients undergoing pancreatic resective surgery (n = 5) after concurrent imaging to assess the validity of these modalities. All patients had biochemical surveillance using standard immunoassays for MEN1 to assess the functional status of PanNENs [5].

Median age at the time of PanNEN evaluation was 44 yrs (range: 16–78). The concurrent PanNEN evaluation with MRI and EUS was conducted in a preoperative setting in 5 patients, whereas 3 patients had previously undergone resective pancreatic surgery at the time of initial evaluation with these modalities. For the five patients who underwent pancreatic resective surgery after concurrent EUS/MRI evaluation, pathology reports were thoroughly reviewed. All cases with available histology/cytology [surgical specimens or EUS-guided fine needle aspirations (FNA)] had well differentiated tumors (18 Grade 1, 8 Grade 2 and 5 tumors of unknown Grade; 24 tumors were NF-PanNENs and seven were F-PanN-



▶ **Fig. 1** Multiple small Pancreatic Neuroendocrine Neoplasms in pancreatic head on axial Magnetic Resonance Imaging and on Endoscopic Ultrasonography.



▶ **Fig. 2** STARD Flow chart for Diagnostic Test Accuracy.

ENs. Eighteen patients had a confirmed MEN1 gene mutation, 6 patients had negative mutational status, whereas the remaining 7 patients were not genetically tested.

MRI (1,5 T GE Signa Explorer 16 channel) was performed according to an axial T1 with and without fat saturation and T2-weighted (with optional T2 with fat saturation), diffusion-weighted imaging (DWI) and axial 3-dimensional volumetric dynamic intravenous gadolinium-enhanced T1 fat-saturated gradient echo sequence protocol. Dedicated high-spatial resolution sequences were used with the reconstruction interval being 4 mm. Patients were fasted for 6 h before the examination. Scans were subsequently scrutinized and reported by a dedicated not blinded radiologist (DK).

EUS was performed under conscious sedation with a linear ultrasonographic endoscope (HV Avious Hitachi console with elastography mode for contrast enhanced technique, compatible to EG3870UTK Pentax Echoendoscope) by the same operator (IK). The scanning frequency varied between 5–10 MHz. The presence of vascularity was assessed with Doppler. EUS-guided fine-needle aspiration (FNA) for cytologic confirmation was performed with a 22 gauge needle (Boston Expect Needle 22 G) on demand by the referring physician or as needed depending on the morphology of the lesion and the judgement of the EUS operator. The pancreas was explored trans-gastrically and trans-duodenally with meticulous peri-pancreatic lymph node exploration/mapping, as well as duodenal exploration in cases of Zollinger–Ellison syndrome.

Finally, we performed a cost-analysis, assessing the costs of a hypothetical routine implementation of MRI of the abdomen versus that of EUS in an outpatient basis for the imaging surveillance

of MEN1 patients in health care systems of different countries (▶ **Supplemetary Table 1S**. To ensure the quality of data reporting, we followed the STARD statement (Standards for Reporting of Diagnostic Accuracy Studies) (▶ **Fig. 2**) [18].

Statistics

Data were described as mean with standard deviation (SD) for parametric data or median with range for non-parametric data, as appropriate. All statistical analyses (frequencies, descriptive statistics, Wilcoxon signed rank sum test, McNemar test, and Cohen's kappa for paired data) were computed with the SPSS 23.0 software package (IBM SPSS Statistics, Armonk, NY, USA). Tests were two-sided and p-value < 0.05 was considered statistically significant.

The frequencies and concordance of EUS and MRI for tumor sizes of ≥ 10 mm and ≥ 20 mm PanNEN, respectively were presented; inter-rater reliability and sensitivity/specificity for MRI compared to EUS for the aforementioned cut-offs were evaluated with Kappa coefficients. PanNEN minimum sizes, multifocality assessment and number of lesions detected per patient were computed with Wilcoxon signed sum rank tests, Fisher exact tests or McNemar test for paired data, as appropriate. Finally, the Bland-Altman plot was used to compare the two imaging techniques. In this graphical method the differences between maximal lesion diameter by MRI and EUS were plotted against the EUS measurements, with the latter being considered the reference or "gold standard" method [19]. The limits of agreement were defined as the mean difference ± 1.96 SD of differences.

Results

In 31 patients, 129 pancreatic lesions were detected in total. MRI detected 73 lesions in 31 patients, whereas EUS detected 110 lesions in 30 patients (p = 0.006). Applying a 20 mm and 10 mm cut-off of maximal lesion diameter, MRI exhibited a concordance of 97 % and 87 % with EUS, respectively. Inter-rater reliability of MRI compared to EUS was deemed excellent for lesion diameter > 20 mm and good for lesions > 10 mm (Cohen's kappa = 0.912 and 0.718, respectively). MRI sensitivity and specificity compared to EUS in this patient cohort for these cut-off values were 96 and 88 % (20 mm cut-off) and 90 and 82 % (10 mm cut-off), respectively. Lesions < 10 mm were detected more often with EUS than MRI (p = 0.025).

Twenty-seven patients exhibited multifocal lesions on either modality. Multifocality assessment did not differ significantly on MRI compared to EUS (p = 0.092), even if more lesions were detected with the latter. In the subset of F-PanNEN (n = 7) in these series, the tumor size was > 10 mm in four cases (EUS localized all four, whereas MRI three F-PanNEN), whereas functional lesions < 10 mm were evident in three cases (EUS identified two lesions, whereas MRI all three). The pathology report review for patients undergoing pancreatic resective surgery (n = 7) showed that both modalities were in 100 % concordance with the pathology findings at the aforementioned cut-offs. Both modalities identified the sequential growth of NF-PanNETs during a minimum two year period in patients subjected to sequential concurrent imaging. Concurrent imaging was applied to assess tumors exhibiting substantial growth rates and also to acquire new fine needle aspirates as necessary for tumor grading [n = 7 (mean ± SD: 2 mm/year ± 3.4 mm vs. 1.9 mm/year ± 3.6 mm)]. Both MRI and EUS did not demonstrate any significant differences in maximal lesion diameter measurements in patients with available pathology report (p = 0.236 for MRI and p = 0.176 for EUS), all of whom had maximal lesion size > 10 mm. Although the number of patients undergoing surgery was indeed small in order to obtain meaningful data, the mean differences between the pathology report and either EUS or MRI, regarding maximal lesion diameter, did not differ significantly (p = 0.933), that is, neither MRI nor EUS seemed to over- or underestimate the tumor size of PanNENs in the few cases with available pathology report.

In Bland–Altman analysis for maximal lesion diameter measurements with the two imaging modalities used (mean of differences ± SD = 0.38 ± 9.56, p = 0.827), the limits of agreement did not exceed differences within the mean ± 1.96 SD in the majority of the patients (two outliers), thus the two methods were considered to be in agreement and may be used interchangeably (▶ **Supplemetary Fig. 1S**).

One patient manifested acute pancreatitis requiring hospitalization secondary to EUS guided FNA. No other procedure-related complications were reported in this series.

Finally, the routine implementation of MRI instead of EUS in MEN1-related PanNEN surveillance would result in variable cost-reduction ranging from 0–67 %, as depicted by the cost of these modalities in the outpatient setting for MEN1 surveillance across different countries (▶ **Supplemetary Table 1S**).

Discussion

In our study, in a single-centre cross-sectional setting we demonstrate that the concordance of MRI compared to EUS in MEN-related PanNENs with tumor size > 10 mm is as high as 87 %. These findings suggest that routine MRI implementation in pancreatic imaging surveillance of MEN1 patients with NF-PanNEN is highly efficient, as smaller NF lesions are considered to be inconsequential for patient management. Additionally, such an implementation in MEN1 patient surveillance would also minimize the risk of potential complications from an invasive procedure as EUS. A subset of patients with NF-PanNEN was subjected to sequential concurrent imaging with EUS and MRI in order to assess tumoral growth rate and potentially acquire new fine needle aspirates, as clinically indicated. This analysis, as well as the assessment of available pathology reports in connection to MRI and EUS maximal lesion measurements, revealed comparable figures, confirming the applicability of MRI in MEN1-related PanNEN surveillance. Finally, cost-analysis of the modalities investigated here, in an outpatient setting and across different countries exhibited a variable cost-reduction ranging from 0–67 % by routinely implementing MRI instead of EUS in the annual imaging surveillance of these patients.

Generally, MRI has the advantage of not using ionizing radiation, being therefore the imaging modality of choice in screening and long-term follow-up of patients, such as these with MEN1. Additionally, it has become more widely available in many countries compared to EUS, and it is a non-invasive procedure with considerable progress in imaging resolution in recent years. On the other hand, EUS still plays a crucial role in the assessment of NENs in the duodeno-pancreatic region and has been the reference examination for accurate preoperative PanNEN assessment with an increase

in PanNEN detection after other modalities are attempted [20]. This is particularly relevant for small functional tumors, which can be challenging to localize [20]. It is also utilized to assess critical surgical details such as the proximity of the main pancreatic duct and vascular structures in this region. Additionally, the use of EUS-guided fine needle aspiration and biopsy of PanNEN and locoregional lymph nodes is indeed of paramount importance in obtaining a cyto/histological confirmation of NEN diagnosis, when necessary. However, a possible disadvantage of EUS, is that it may overestimate the size of MEN1-related PanNENs, especially those with a tumor size < 20 mm [21]. This was not evident in our series in the subset of patients undergoing surgery after concurrent imaging; however, the number of patients who underwent surgery was relatively small to make a strong argument. Nevertheless, the overestimation in size reported by Polenta et al. should probably be taken into consideration for tumors 15–20 mm that approach the currently accepted cut-off of 20 mm necessitating surgical exploration [21].

EUS and MRI have produced complementary results for detecting MEN1-related PanNEN at initial evaluation, according to the largest study to date by the French Endocrine tumor Study Group [15]. Interestingly in this study, EUS missed more PanNEN > 20 mm than MRI [15], whereas in other studies, both EUS and MRI performed well in detecting large size lesions [22–24]. In our study, EUS missed one case only of an 11 mm lesion that was detected by MRI instead; however this single patient had previously undergone a gastric procedure. Previous studies have shown that MRI exhibits high diagnostic performances in PanNEN with reported sensitivities of 74–94 % and specificities of 78–100 % [25]. However, a recent meta-analysis comparing EUS and MRI in MEN1 patients in terms of their sensitivities to localize small F-PanNEN (insulinomas) preoperatively reported a sensitivity of 80 % for EUS and 66 % for MRI, respectively [26]. Hence, EUS seems to be more sensitive than MRI in localizing small F-PanNENs preoperatively and this is also in accordance with the findings of our study, where EUS detected lesions < 10 mm more often than MRI.

The overall reported risk of complications from EUS and EUS-FNA is relatively low and the safety of these procedures appears to be acceptable [27]. However, MEN1 patients are subjected to repeated life-long surveillance and there was one patient in this series manifesting a severe complication (pancreatitis) requiring hospitalization secondary to EUS-FNA.

^{68}Gallium-PET-CT is a further sensitive imaging modality for PanNEN localization as it has a spatial resolution of 0.5–1 cm [28]. There is general consensus that it may be performed in any surgical candidate with PanNEN, as well as patients with advanced and/or disseminated disease to provide a comprehensive staging of the disease extent; however, to date ^{68}Gallium-PET-CT is not used as a surveillance tool in asymptomatic MEN1 patients with or without an established diagnosis of PaNEN [29]. Importantly, regarding functional imaging, the subset of patients with MEN-1 related insulinomas may be in need of special localization with novel modalities, such as ^{68}Gallium DOTA-Exendin PET/CT [30].

Control randomized studies on diagnostic test accuracy are of course the design of choice to determine the benefits of a surveillance protocol to be implemented or compare alternative surveillance strategies. However, the scarcity of MEN1 disease makes such a trial difficult to be conducted. Additionally, the small sample size of our study and the inclusion of MEN1-related PanNEN at different time points in the disease course, when concurrent imaging was available and differences in prior surgical management in a subset of this cohort may all have confounded the results. Another limitation is that final histopathology for tumor size validation in the majority of the patients in this series was not available and therefore EUS was used as the reference modality. Additionally, the raters of MRI as well as the EUS operator were not blinded to patient MEN1 diagnosis and previous panNEN imaging if available; hence, the present study might be limited by recall bias. Nevertheless, observational research on diagnostic test accuracy in MEN1 patients subjected to life-long surveillance, such as the present study is required, to determine which imaging surveillance strategies are most effective for implementation into practice in the field of MEN1.

In conclusion, MRI is a non-invasive modality, which performs equally well as EUS for lesion detection larger than 10 mm and subsequent surveillance of MEN1-related PanNENs, as smaller non-functional lesions are generally considered inconsequential in patient clinical management. Both modalities could be used at initial assessment of MEN1-related PanNENs, as EUS identifies more, smaller than 1 cm neoplasms and therefore has a complementary role. Thereafter, a more conservative and cost-effective surveillance approach with MRI alone may be utilized in MEN1 patient follow-up.

Author Contribution Statement

Drs. Daskalakis and Tsoli contributed equally to this study; had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Kaltsas was the study supervisor.

Funding

Dr. Daskalakis was supported by the Swedish Society of Medicine Post Doctoral Scholarhip and the Lennanders Fund. The other authors of the study have not received any funding.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Thakker RV. Multiple endocrine neoplasia type 1. Endocrinol Metab Clin North Am 2000; 29: 541–567

[2] Trump D, Farren B, Wooding C et al. Clinical studies of multiple endocrine neoplasia type 1 (MEN1). QJM 1996; 89: 653–669

[3] Shepherd JJ. The natural history of multiple endocrine neoplasia type 1. Highly uncommon or highly unrecognized? Arch Surg 1991; 126: 935–952

[4] Ito T, Igarashi H, Uehara H et al. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: A prospective study: Comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine (Baltimore) 2013; 92: 135–181

[5] Falconi M, Eriksson B, Kaltsas G et al. Vienna Consensus Conference p. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology 2016; 103: 153–171

[6] Manoharan J, Raue F, Lopez CL et al. Is Routine screening of young asymptomatic MEN1 patients necessary? World J Surg 2017; 41: 2026–2032

[7] Brandi ML, Gagel RF, Angeli A et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001; 86: 5658–5671

[8] Triponez F, Dosseh D, Goudet P et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Ann Surg 2006; 243: 265–272

[9] Ekeblad S, Skogseid B, Dunder K et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res 2008; 14: 7798–7803

[10] Vinik AI, Woltering EA, Warner RR et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. Pancreas 2010; 39: 713–734

[11] Triponez F, Goudet P, Dosseh D et al. Is surgery beneficial for MEN1 patients with small (< or = 2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. World J Surg 2006; 30: 654–662 discussion 663–654

[12] Thakker RV, Newey PJ, Walls GV et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; 97: 2990–3011

[13] Berrington de Gonzalez A, Mahesh M et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med 2009; 169: 2071–2077

[14] Hall EJ, Brenner DJ. Cancer risks from diagnostic radiology. Br J Radiol 2008; 81: 362–378

[15] Barbe C, Murat A, Dupas B et al. Magnetic resonance imaging vs. endoscopic ultrasonography for the detection of pancreatic tumours in multiple endocrine neoplasia type 1. Dig Liver Dis 2012; 44: 228–234

[16] Camera L, Paoletta S, Mollica C et al. Screening of pancreaticoduodenal endocrine tumours in patients with MEN 1: Multidetector-row computed tomography vs. endoscopic ultrasound. Radiol Med 2011; 116: 595–606

[17] Kann PH, Kann B, Fassbender WJ et al. Small neuroendocrine pancreatic tumors in multiple endocrine neoplasia type 1 (MEN1): Least significant change of tumor diameter as determined by endoscopic ultrasound (EUS) imaging. Exp Clin Endocrinol Diabetes 2006; 114: 361–365

[18] Cohen JF, Korevaar DA, Altman DG et al. STARD 2015 Guidelines for reporting diagnostic accuracy studies: Explanation and elaboration. BMJ Open 2016; 6: e012799

[19] Krouwer JS. Why Bland-Altman plots should use X, not (Y + X)/2 when X is a reference method. Stat Med 2008; 27: 778–780

[20] James PD, Tsolakis AV, Zhang M et al. Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: A meta-analysis. Gastrointest Endosc 2015; 81: 848–856 e841

[21] Polenta V, Slater EP, Kann PH et al. Preoperative imaging overestimates the tumor size in pancreatic neuroendocrine neoplasms associated with multiple endocrine neoplasia type 1. World J Surg 2018; 42: 1440–1447

[22] Lewis MA, Thompson GB, Young WF Jr.. Preoperative assessment of the pancreas in multiple endocrine neoplasia type 1. World J Surg 2012; 36: 1375–1381

[23] Kann PH, Balakina E, Ivan D et al. Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: An endoscopic ultrasound imaging study. Endocr Relat Cancer 2006; 13: 1195–1202

[24] van Asselt SJ, Brouwers AH, van Dullemen HM et al. EUS is superior for detection of pancreatic lesions compared with standard imaging in patients with multiple endocrine neoplasia type 1. Gastrointest Endosc 2015; 81: 159–167 e152

[25] Sahani DV, Bonaffini PA, Fernandez-Del Castillo C et al. Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. Radiology 2013; 266: 38–61

[26] Kann PH. Is endoscopic ultrasonography more sensitive than magnetic resonance imaging in detecting and localizing pancreatic neuroendocrine tumors? Rev Endocr Metab Disord 2018; 19: 133–137

[27] O'Toole D, Palazzo L, Arotcarena R et al. Assessment of complications of EUS-guided fine-needle aspiration. Gastrointest Endosc 2001; 53: 470–474

[28] Deppen SA, Liu E, Blume JD et al. Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med 2016; 57: 708–714

[29] Albers MB, Librizzi D, Lopez CL et al. Limited value of Ga-68-DOTATOC-PET-CT in routine screening of patients with multiple endocrine neoplasia type 1. World J Surg 2017; 41: 1521–1527

[30] Antwi K, Fani M, Heye T et al. Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: Evaluation of diagnostic accuracy in a prospective crossover imaging study. Eur J Nucl Med Mol Imaging 2018; 45: 2318–2327