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Imaging in multiple endocrine neoplasia type 1: recent studies show enhanced sensitivities but increased controversies

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Abstract

In multiple endocrine neoplasia type 1 (MEN1) patients, a number of recent studies compare the ability of different, new imaging modalities to existing modalities to localize the important neuroendocrine tumors (NETs) that contribute to their decreased life expectancy (pancreatic NETs [pNETs] and thymic carcinoids). These included the use of ⁶⁸Ga-DOTATOC-PET/CT, endoscopic ultrasound and MRI. The current paper analyzes these results in light of current guidelines and controversies involved in the treatment/management of MEN1 patients. Particular attention is paid to results in these studies with thymic carcinoids and nonfunctional pNETs/gastrinomas, which recent studies show are particularly important in determining long-term survival. These studies show a number of promising imaging results but also raise a number of controversies, which will need to be addressed both in their use initially and for serial studies in these patients.

Keywords

endoscopic ultrasound; hyperparathyroidism; insulinoma; MEN1; MRI; pancreatic neuroendocrine tumor; somatostatin-receptor scintigraphy; thymic carcinoid; Zollinger–Ellison syndrome

Before reviewing the recent studies in multiple endocrine neoplasia type 1 (MEN1) patients that are the basis for this article, a review of a few aspects of the current management/treatment of MEN1 patients is needed to understand both these articles' promise and the controversies that arise from these studies. In all guidelines for MEN1 patients, neuroendocrine tumor (NET) localization is an essential step in all aspects of their management [1–3]. In general, cross-sectional imaging studies (computed tomography [CT], MRI and ultrasound) are the standard modalities recommended [1–10], and more recently for nonparathyroid lesions, the use of ¹¹¹In-DTPA-octreotide (octreoscan), and in addition, for evaluation of pancreatic NETs (pNETs), the endoscopic ultrasound (EUS) in selected

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patients [1–3,6,7,9–12]. In general, data from prospective studies are lacking, and in most cases the use or order of use of these imaging modalities has been proposed in consensus statements or in detailed studies of a few of these imaging modalities. The result of this is that there is not a well-established consensus on which imaging studies should be performed at what stage of evaluation the MEN1 patient is in: during initial evaluation (either in patients detected by genetic screening or with symptomatic presentation), for follow-up after no intervention or after an intervention (surgery, etc.) or even in patients with advanced disease. Whereas some recent imaging studies in MEN1 patients (which will be reviewed below) have provided some important insights in this area, but they have also raised new questions. This has occurred because of the unique features of the natural history of MEN1 patients revealed from recent studies, the unique features of the treatment of these NETs in MEN1 patients and because of the limitations of current approaches.

Current natural history of MEN1 & improvements needed

Despite all of the advances in treatment of MEN1 patients, particularly for the functional syndromes associated with parathyroid disease, gastrinomas/insulinomas, pituitary tumors; the life expectancy of MEN patients is still only 55 years, shortened from a normal population [13,14]. The principal cause of death has changed dramatically, from the complications of hormone-excess states, particularly gastrinomas, to the malignant course of the NETs, particularly, for pNETs and thymic carcinoids [13–16]. Numerous studies show that in general, other tumors that occur with increased frequency in MEN1 patients usually pursue an indolent course and are an uncommon cause of death at present. These include other carcinoid tumors (pulmonary and gastric) and tumors of the adrenal, pituitary, skin (neurofibromas, collagenomas, etc.), smooth muscle or CNS (meningioma, ependymomas, etc.) [6,13–15,17–21]. These results demonstrate that to further extend survival in MEN1 patients not only will effective treatment of the hormone-excess states be needed but also enhanced methods to identify malignant NETs and develop effective early treatments are essential, in addition to developing effective treatments for patients where early treatment is not effective and they develop, or they present with, advanced metastatic disease from a malignant NET [6]. This earlier diagnosis and tailored treatment/diagnosis will need to be particularly directed at identifying aggressive pNETs (which now causes 40–50% of deaths) and thymic carcinoids (currently causing 12–24% of deaths, almost entirely in males) [13–15,22].

Importance of early treatment of pNETs & thymic carcinoids in MEN1 patients

The principal limitation of the current approaches to pNETs is the general inability to identify early which patient harbors a tumor that will pursue an aggressive course and the inability to cure the patient early, in most cases without aggressive surgery. This is a significant problem in all MEN1 patients because pathology studies reveal that 95–100% of MEN1 patients possess nonfunctional pNETs (NF-pNETs), in most cases they are microscopic and multiple, and it is estimated that in only up to 13% do they cause symptomatic disease [5,6,13]. By the second decade of life, the penetrance of pNETs is already in 42% of patients [12]. Furthermore, 20–61% of MEN1 patients develop at some

point Zollinger–Ellison syndrome (ZES), due primarily to a duodenal gastrinoma (85–95%) which is invariably multiple, frequently small (<0.5 cm) and metastasize early to lymph nodes (40–50%) [23–27]. Another 10–31% of MEN1 patients develop insulinomas, which also may be small, multiple, although less frequently malignant, and need to be distinguished from NF-pNETs to allow resection [5,28]. The remaining functional pNETs (F-pNETs) (glucagonomas, VIPomas, SSomas, GRFomas, etc.) are present in <1–3% of MEN1 patients and thus are uncommonly a cause of death [5,13]. A prospective study in MEN1/ZES patients [29] demonstrated that in 15% of the patients the pNETs pursue an aggressive course, which, although lower than the 25% seen in patients with sporadic ZES [30,31], the ZES presents an earlier time ($\approx$ 10 years earlier in MEN1 patients), and therefore MEN1 patients have a potentially longer course [32]. In patients with thymic carcinoids, which are the most aggressive NETs that MEN1 patients develop [5,13,16,19,33,34], the principal problem in improving treatment is their early identification so they can be resected, because in most series, many appear to pursue a relatively aggressive course with metastases to lymph nodes, encasement of vital mediastinal structures and invasion of adjacent tissues [5,13,16,19,33,34].

Limitations of current approaches for pNETs in MEN1 patients

The currently approaches used in most MEN1 patients have significant limitations to accomplish the above goals of earlier diagnosis and treatment for particularly pNETs and thymic carcinoids. To identify pNETs in MEN1 patients, recent studies demonstrate that the commonly used serum tumor markers (chromogranin A, pancreatic polypeptide and glucagon) are relatively insensitive (sensitivity 33–58%) for NF-NETs [35]. Therefore, at present except for F-pNETs that leaves imaging as the primary method to diagnose early pNETs and thymic carcinoids, which are almost all not associated with a hormone-excess state in MEN1 patients [16,36–39]. Cross-sectional imaging is generally limited by pNETs size and will miss more than 50% of those less than 1.5 cm in some studies; however, ^{111}In -DPTA-octreotide (octreoscan) has greater sensitivity but still misses 35–50% of pNETs less than 1 cm [5,6,40,41]. In contrast, the EUS which will be discussed in greater detail below, has greater sensitivity, frequently detecting pNETs down to 0.5 cm; however, it is an invasive procedure, operator-dependent and less sensitive in the pancreatic tail region [6,11,42–46]. In addition to the sensitivity of older imaging methods, even when the pNETs are identified, there are current limitations. First, the prognostic factors available are of very limited use and have not been systematically studied. Whereas numerous studies demonstrate the prognostic value of grading/TNM classifications of sporadic NETs and pNETs proposed by the WHO/ENETS/AJCC with the grading based on Ki67 and mitotic indexes [47–49], these have not been systematically applied to MEN1 patients. Furthermore, this approach is limited because pNETs are frequently small in size (<1 cm) and are frequently multiple in MEN1 patients complicating the use of endoscopic approaches which are generally used for serial assessments after obtaining tissue by fine-needle aspiration, which may not accurately identify the true grade or may be difficult because of the small size of many of the pNETs limiting the ability to obtain sufficient material [50]. Second, various pathological features of the sporadic pNETs such as presence of cytokeratin19/c-Kit immunoreactivity or necrosis, loss of tumor-suppressor genes *ATRX/DAXX* [51–53], as well as the type of MEN1

mutation (presence of mutations involving CHES1 interacting domain [54], mutations of Jun-D interacting domain area [55]) all have been reported to have prognostic value but are generally not used and have not been studied prospectively. Similarly, the lack of genotype–phenotype correlations with the development of the different NETs that MEN1 patients develop is a major limitation [1,6,56]. Third, even if a pNET is identified, without criteria available at present to use for predicting prognosis and separating patients into different risk categories to tailor aggressiveness of treatment, there is considerable controversy on the role of surgery, the only method of potentially curing the patient at present. Whereas all guidelines/investigators agree that if a nongastrinoma F-pNETs is found (insulinomas, vipoma, glucagonoma, etc.), the patient should undergo surgical exploration if resectable and there are no medical contraindications [1–3,57–59]. However, in the case of NF-pNETs or gastrinomas, significant controversy exists [3,5,23,24,60–63]. This occurs for a number of reasons. First, these occur frequently in young patients with a potentially long-life expectancy and without aggressive resection, neither patients with ZES/MEN1 or NF-pNETs are cured [3,5,23,24,60–63]. Tumor enucleation does not result in cure of ZES/MEN1 patients [5,23,64]; and although a proximal pancreaticoduodenotomy (Whipple resection) will cure the ZES in MEN1 patients [59,65–67], it is not routinely recommended in patients with MEN1 because of the long-term potential complications [3,5,57,60,65]. Also, in patients with NF-pNETs, because of the multiplicity of small adenomas, a total pancreatectomy [68] would be required, which because of its morbidity, is not recommended [5,63]. Furthermore, studies show that MEN1 patients with small NF-pNETs (<2 cm) have no increased mortality [69]; in another study involving 14 MEN1 patients with NF-pNETs over an average follow-up of 6.5 years, no growth in the pNETs was seen [70] and in patients with MEN1/ZES with pNETs imaged less than 1.5–2 cm in diameter, at 15 years of follow-up, survival was 100% without any treatment of the pNET [13,65]. This has led to the consensus/expert opinion statements of both the ENETS [3,63,71] and NANETS [57] to not recommend routine surgery for patients with MEN1 with NF-pNETs or MEN1/ZES with imaged pNETs less than 1.5–2 cm in diameter.

Limitations of current approaches for thymic carcinoids in MEN1 patients

For thymic carcinoids, current guidelines recommend screening begin at aged 15 years and that a CT or MRI be repeated every 1–2 years [1]. It is particularly important that these tumors are systematically screened for in MEN1 patients because, in contrast to sporadic thymic carcinoids, many are asymptomatic when detected by screening without an accompanying hormone-excess state as often seen in patients with sporadic thymic carcinoids (i.e., Cushing's syndrome, carcinoid syndrome, acromegaly present in up to 40% sporadic, very rare-MEN1 thymic carcinoid patients) [13,16,19,20,33]. Unfortunately, it was hoped that prophylactic partial thymectomy carried out at the time of parathyroid surgery, would be protective, but in a number of reports this has not proven to be the case, and therefore it is recommended all patients are systematically screened. Thymic carcinoids occur more than 90% in males in MEN1 [5,16,19,20,33]; however, so far, this marked gender selection has not been factored into existing guidelines [13]. Unfortunately in many series, patients with thymic carcinoids are uncommonly cured; however, this may be due in large part to the fact that thymic carcinoids were only recognized as part of the MEN1

syndrome in the 1980s and they have not been as carefully screened for as pNETs, parathyroid or pituitary disease [16,19,36–38] and are therefore often diagnosed late in their course. In one prospective study [16], 40% of the patients with MEN1 and thymic carcinoid did not have recurrence after surgery, although the followup was relatively short, which is consistent with reported surgical cures of some patients in other series [19,20,33,36], raising the possibility that early surgical intervention can be curative in patients with MEN1 and thymic carcinoids.

Recent pNET MEN1 imaging studies

Recent pNET imaging studies: overall

Recently, a number of prospective imaging studies in MEN1 patients have provided important insights that will affect a number of the management considerations discussed above, both by providing support for some approaches, but also by raising additional controversies. These included for the first time prospective [72–74] and nonprospective studies [75,76] reporting the enhanced sensitivity/specificity for localizing NETs, including pNETs, in MEN1 patients, using ^{68}Ga -DOTATOC positron-emission tomographic/CT imaging (^{68}Ga -DOTATOC-PET/CT); a prospective study of the comparative value of MRI scanning and the EUS in MEN1 patients for localizing pNETs [77] and a cross-sectional study [46] reporting the superiority of EUS to cross-sectional imaging (CT/MRI), somatostatin-receptor scintigraphy (SRS) with ^{111}In -DPTA-octreotide and PET scanning with ^{11}C -5-HTP.

Recent MEN1 pNET imaging studies

In well-differentiated pNETs (G1, G2 grade), as well as NETs in other locations, found in both MEN1 patients as well as occurring sporadically, over-/ectopic-expression of one of the somatostatin-receptor subtypes (sst1-5) occurs in 80–95% of cases [78,79]. This occurrence has allowed widespread use of ^{111}In -DPTA-octreotide (octreoscan; which localizes sst2-5 primarily) combined with SPECT imaging to localize pNETs/NETs in both MEN1 patients and sporadic tumors [72,78,80]. In a number of studies of patients with abdominal NETs, ^{111}In -DPTA-octreotide has a sensitivity of 46–100% (pNETs-46–93%) with an overall sensitivity of 78% and in a number of studies in patients with both MEN1 and sporadic NETs, it is more sensitive than cross-sectional imaging [41,65,78,81–83]. Nevertheless, it frequently does not detect small lesions, missing 35–50% of NETs less than 1 cm in diameter [5,6,40,41,78].

Recently, ^{68}Ga -DOTATOC-PET/CT is being increasingly used to image NETs and is now generally recommended over ^{111}In -DPTA-octreotide in Europe for imaging of pNETs (F-pNETs/NF-pNETs)/GI-NETs/pulmonary carcinoids [84–87], however, it is not yet approved or widely available in the USA. Until recently, ^{68}Ga -DOTATOC-PET/CT had not been assessed in MEN1 patients, however, it has been widely assessed in patients with sporadic pNETs/NETs where it is shown to have greater sensitivity (93%) than ^{111}In -DPTA-octreotide and cross-sectional imaging studies [88], excellent specificity (85%) [88] and furthermore its addition to an evaluation results in a change in management of 21–60% of sporadic NET patients [84,89–95]. This occurs because ^{68}Ga -DOTATOC-PET/CT has

greater resolution imaging lesions down to 2–5 mm, and it also has the advantage of allowing shorter imaging times, lower radiation exposure, cheaper cost and can be readily made from a generator [88,92].

Recently, the use of ^{68}Ga -DOTATOC-PET/CT in MEN1 has been reported in both prospective studies [72,74] and retrospective study [73]. In one recent prospective study involving 26 MEN1 patients [72], ^{68}Ga -DOTATOC-PET/CT detected more than twice as many lesions as CT or ^{111}In -DPTA-octreotide; it was positive in 27% of patients (6/26), negative on the other two imaging studies, and it resulted in a change in management in 31% of patients. In the second prospective study involving 18 MEN1 patients [74], ^{68}Ga -DOTATOC-PET/CT had a sensitivity/specificity for pNETs (100/100%), pituitary adenomas (75/83%), parathyroid (28/100%) and adrenal adenomas (75/83%). In this study, these did not differ from results with combined conventional results (CT, ultrasound and MRI) for localizing pNETs, pituitary or adrenal lesions, however, conventional imaging had greater sensitivity for pituitary lesions. It was concluded that ^{68}Ga -DOTATOC-PET/CT had the advance of giving a panoramic view of MEN1-related lesions at one assessment that could be obtained only from a combination of different conventional imaging studies [74]. In a retrospective study of 21 MEN patients (19 MEN1), ^{68}Ga -DOTATOC-PET/CT had a sensitivity/specificity of 92/94% for detecting any NET lesion; its sensitivity was significantly better than CT (with or without contrast) and it influenced therapeutic management in almost a half the patients [73].

These above recent data support the conclusion that, similar to sporadic pNETs/NETs, the use of ^{68}Ga -DOTATOC-PET/CT in MEN1 patients will result in enhanced detection of NETs including both pNETs and other MEN1 NETs, except parathyroid lesions.

Recent MEN1 pNET imaging studies: EUS studies

Numerous recent studies support the conclusion that EUS, in both MEN1 patients and those with sporadic disease, is the most sensitive modality for detecting intrapancreatic pNETs, including both F-pNETs and NF-pNETs [46,96–98]. This includes EUS being more sensitive than cross-sectional imaging studies (MRI, CT and ultrasound) and SRS with ^{111}In -DPTA-octreotide (octreoscan); however, data from prospective comparisons with ^{68}Ga -DOTATOC-PET/CT are not yet available. This increased sensitivity of EUS is illustrated well by results from a recent study [46] of 41 patients with proven MEN1, in which EUS identified 101 pNETs in 83% of the patients (34/41), whereas CT/MRI identified 35 pNETs in 32 patients, SRS with ^{111}In -DPTA-octreotide identified 32 pNETs in 18 patients and ^{11}C -5-HTP PET identified 35 pNETs in 19 patients. EUS has sufficient sensitivity to identify pNETs less than 0.5 cm in diameter in a number of studies [42,43,45]. EUS has additional added advantages over both ^{68}Ga -DOTATOC-PET/CT and ^{111}In -DPTA-octreotide because it also allows accurate assessment of pNETs size, can be used to assess serial changes in pNETs size and fine-needle aspiration can be used to assess grade and other tumoral characteristics [43,46,96,97]. Serial studies with EUS to assess changes in pNET size are possible because serial EUS assessments are reliable with a study showing repeated EUS measurement had a variation of only $5.5 \pm 4.6\%$ overall, with a $7.1 \pm 6.3\%$ in pNETs <5 mm, variation of $4.4 \pm 2.6\%$ in pNETs >5 mm, allowing calculation of a

significant changes as 15.4% overall, for pNETs <5 mm a 19.9% change and >5 mm in size as 12.3% change [43]. Serial EUS studies show that most pancreatic microadenomas and even pNETs <2 cm in diameter in MEN1 patients are generally relatively stable and uncommonly increase rapidly in size [11]. In one recent serial study in MEN1 patients [11] with a mean followup of 6.5 years in 11 patients with 18 pNETs with a mean size of 1 cm (range: 0.5–2.4 cm), the mean growth rate was 1.32 mm/year, with 11/18 (61%) showing stability or a decrease in pNET size. Newer lesions developed in 7/11 (64%) of the MEN1 patients and they had a faster growth rate averaging 3.0 mm/year [11]. A second study over a 2-year period in 20 patients with MEN1 serially assessing 20 pNETs <1.5 cm in diameter (mean: 5.9 mm) found an average change of 1.32% increase in pNET diameter, the appearance of 0.62 new lesions per year and in 1/20 patients, a rapidly growing lesion was seen [97], concluding small pNETs (<1.5 cm) are slow growing, risk for metastatic disease is low, however, occasional small, asymptomatic pNET in MEN1 patients can be rapidly growing [97]. These studies [11,97] highlight the need for routine follow-up (at least yearly) and assessment in MEN1 patients of possible growth of small asymptomatic pNETs (<2 cm), which are not surgically treated, which is the current recommendation by the ENETS, NANETS and GTE for the treatment of these patients [5,57,63].

In patients with ZES/MEN1 or sporadic ZES which both have duodenal gastrinomas in more than 80% of patients, which are frequently small (<0.5 cm) [23,26,27,30,99,100], invariably multiple in the case of MEN1 patients [26,27,64], the role of EUS is much more limited because it misses the duodenal gastrinomas in approximately a half the cases [65,101,102]. However, in MEN1/ZES patients, some investigators advocated using EUS prior to surgery because it will exclude the presence of a larger pancreatic lesion [44,45,101,103]. Generally, in these patients' cross-sectional imaging studies (CT, MRI and ultrasound), SRS with ¹¹¹In-DTPA-octreotide or ⁶⁸Ga-DOTATOC-PET/CT and in a rare patient, gastrin venous sampling is recommended to image pNETs preoperatively as well as specific intraoperative methods to localize duodenal tumors [3,60,64,65,77,100,104–109].

Insulinomas in both MEN1 patients and sporadic cases are almost invariably (>99.5%) intrapancreatic in location and EUS is highly sensitive for their localization as it is for other intrapancreatic pNETs [58,65,110,111]. The difficulty in insulinomas in MEN1 patients is that they are multiple in 8–82% of cases [28,58,112] and the EUS, while frequently identifying multiple lesions [58], does not localize which is actually secreting insulin (although fine needle aspiration [FNA] may be suggestive). In this particular case, some recommend the use of regional intraarterial calcium injections and hepatic venous insulin sampling to localize the insulinoma(s) [65,113–117] and/or the use of insulin or glucose sampling intraoperatively [58,118].

Recent MEN1 pNET imaging studies: MRI (MEN1) studies

Because serial imaging is needed in most MEN1 patients for pNETs and other NETs, there is increased interest in the ability to use cross-sectional, noninvasive imaging for this, particularly MRI, and a number of recent studies have examined this issue. As outlined in the previous section, at present EUS has the greatest sensitivity for detecting small pNETs, however, almost all MEN1 patients required regular surveillance for the progression of

small NF-pNETs (<2 cm) not resected or the development of additional NF-pNETs postresection [1]. Therefore, repetitive imaging is required, and EUS, while highly effective for this purpose, is a invasive procedure, and therefore other imaging modalities that can serial assess changes in pNET size would be of clinical useful, such as repeated cross-sectional imaging studies. Although such imaging may miss small pNETs less than 1.5–2 cm in diameter in a proportion of cases with the existing guidelines and the results of the studies outlined above, which show no increased mortality from pNETs of this size, the failure to detect small NF-pNETs (<2 cm) on repetitive imaging in an asymptomatic MEN1 patient would not change management [1,3,6,69,77].

A recent multicenter, prospective study [77] of cross-sectional imaging, involving 90 MEN1 patients attempted to begin to address this question by first evaluating the sensitivity of MRI and EUS in detecting pNETs of differing sizes in these patients [1,3,57]. In this study [77], EUS detected 268 pNETs in 75 MEN1 patients and MRI detected 158 pNETs in 67 patients. For pNETs 10 mm or 20 mm (criteria for monitoring frequency/treatment used by different groups), EUS detected 86 and 13 lesions in 48 and 13 patients, respectively, whereas MRI found 67 and 20 pNETs in 42 and 17 patients, respectively. EUS and MRI showed a moderate agreement for detecting pNETs 10 mm with a Kappa coefficient of 0.55. For pNETs 20 mm, EUS failed to detect 11/24 lesions and MRI 4/21 lesions. For patients with pNETs 10 mm, EUS failed to identify 9/57 (16%) patients and MRI 11/57 (19%) of patients. This study concludes that MRI and EUS are complementary for detecting pNETs in MEN1 patients and both should be performed at the initial evaluation. Although these data did not prospectively evaluate follow-up, the fact that both MRI and EUS miss a proportion of patients with pNETs 20 mm raises the possibility that performing both studies should be considered on follow-up evaluations until perspective studies demonstrate only the most sensitive modality in a given patient might suffice.

The results of the above study [77] have both similarities and differences from previous studies of MRI-localizing pNETs, which were primarily performed in patients with sporadic pNETs. In a previous study [119] in patients with sporadic pNETs 2cm, MRI had an 85% sensitivity; however, MRI's detection rate for pNETs is size dependent [96,120] with detection rates less than 10% for pNETs 1 cm in diameter, 50% when 2 cm in diameter and 80–100% when at least 3 cm in diameter [96,119,120].

This size dependence of MRI, similar to seen with CT scanning, is of particular relevance to MEN1, both because the gastrinomas are characteristically small, located in the duodenum and are multiple, as are many of the NF-pNETs and insulinomas [25–28,64]. Missing the small NF-pNETs (<2 cm) will not generally affect the management in MEN1 patients according to present guidelines [1,63,69]. However, the missing of small insulinomas, which invariable are managed surgically, can directly affect management [1,5,28], as can the missing of multiple gastrinomas, if surgery is planned for some reason in that MEN1/ZES patient, even though current guidelines would also recommend surgery not routinely be performed in ZES/MEN1 if there are no imaged lesions 2 cm [3,5,60]. In contrast, the failure to identify pNETs 2 cm in MEN1 patient can have a marked effect on management in determining the need for surgery and affecting follow-up [1,3,5,69]. The above data suggest that even with contrast enhancement and other improvements, current MRI scanners

will miss up to 20% of patients who have pNETs ≥ 2 cm in diameter, the cutoff size used in most guidelines for conservative follow-up, and thus this could prove a major liability for the use of MRI alone in following MEN1 patients for growth of pNETs.

One of the unproven but prominent potential concerns in patients with MEN1 is the possible detrimental effects of repeated doses of ionizing radiation from imaging studies, such as CT scans, with SRS with either ^{68}Ga -DOTATOC-PET/CT or ^{111}In -DPTA-octreotide or rarely with angiography [6,77,121]. This will be discussed in more detail in the paragraphs below on queries/controversies. MRI has the advantage of not delivering radiation, so there is a particular interest in this imaging modality in MEN1 patients requiring frequent serial imaging tumor assessments.

Recent MEN1 pNET imaging studies: queries/controversies

MEN1-pNETs: when should ^{68}Ga -DOTATOC-PET/CT be used in patients with MEN1 for pNET detection?

The above studies in MEN1 patients, as well as numerous studies in patients with sporadic pNETs, establish that ^{68}Ga -DOTATOC-PET/CT has enhanced sensitivity for detecting pNETs over the currently used imaging studies recommended in various MEN1 treatment guidelines (cross-sectional imaging [CT and MRI] and ^{111}In -DPTA-octreotide scanning), although it is not established whether it is more sensitive than EUS. Furthermore, in two studies, ^{68}Ga -DOTATOC-PET/CT's use is reported to change clinical management in 31–47% of the MEN1 patients [72,73]. In one study [73], the principal reason for changing management was an additional indication for surgery; and in the other [72], the principal reason for changing management was also an influence on the recommendation for surgery of a primary or metastatic lesion.

The current MEN1 guidelines principally recommend the use of serial cross-sectional imaging studies (MRI and CT) annually to detect pNETs [1,3,57,63]; and the Endocrine Society in their 2012 guidelines recommends that screening for NF-pNETs starts at 10 years, biochemical screening for insulinomas at 5-year old and gas-trinomas at 20-year old [1]. In MEN1 patients, gastrinomas and insulinomas are almost invariably initially identified by biochemical-screening studies, and the localization studies are used after the diagnosis to assess primary location and extent of disease. Therefore, ^{68}Ga -DOTATOC-PET/CT's principal use in MEN1 patients with gastrinomas/insulinomas is not for diagnosis but for tumor localization after the diagnosis is established. In a recent study [122] on patients with sporadic insulinomas, ^{68}Ga -DOTA-Nal³-PET/CT's detection rate was only 23% likely because of the low/absence of somatostatin receptors on insulinomas, which is a lower sensitivity than cross-sectional imaging or EUS in many studies [28,65,118]. Furthermore, ^{68}Ga -DOTATOC-PET/CT, because of its enhanced sensitivity for NF-pNETs, will likely detect in MEN1 patients additional pancreatic lesions, while perhaps missing the insulinomas(s), and it does not distinguish which of the lesions detected could be the insulinomas(s). Therefore, it is likely that ^{68}Ga -DOTATOC-PET/CT will have limited utility in MEN1 insulinoma patients.

In patients with NF-pNETs or gastrinomas, ^{68}Ga -DOTATOC-PET/CT will be very useful for staging the location and extent of metastatic disease, especially in a patient with advanced disease or prior to surgery in a patient with imaged lesions more than 2 cm in diameter. However, current guidelines recommend surgery for MEN1 patients only with NF-PETs/gastrinomas with an imaged tumor more than 2 cm in most cases. Therefore, the enhanced detection of small pNETs (<2 cm) due to ^{68}Ga -DOTATOC-PET/CT's will not change generally the management of these patients.

MEN1-thymic carcinoid: when should ^{68}Ga -DOTATOC-PET/CT be used in patients with MEN1 for thymic carcinoid detection?

Thymic carcinoids are the most aggressive NET, MEN1 patients develop and only by early detection and surgery can these patients be cured. Current guidelines recommend CT or MRI screening every 1–2 years starting at aged 15 years [1]. At present, it is not established that ^{68}Ga -DOTATOC-PET/CT will detect thymic carcinoids earlier, enhance their cure rate or even whether most MEN1 thymic carcinoids can be detected by ^{68}Ga -DOTATOC-PET/CT. Furthermore, these lesions can develop rapidly in less than 6 months going from undetectable to significant size [16], so it raises the question that even if ^{68}Ga -DOTATOC-PET/CT has enhanced sensitivity for detecting MEN1 thymic carcinoids, how should it be used in serial studies. At present, it is not established whether the guidelines suggested with serial cross-sectional imaging are adequate to detect most thymic carcinoids early and allow the MEN1 patients to be surgically, when used in serial follow-up, and therefore whether additional more sensitive imaging methods are needed.

MEN1: role of ^{68}Ga -Dotatoc-PET/CT in serial monitoring for NETs & in younger patients with MEN1

As stated above, present guidelines recommend up to annual use of CT scanning (or MRI if available) for detection of pNET/thymic carcinoids/adrenal tumors in MEN1 patients beginning in some cases as young as 15 years of age [1]. Now that studies are beginning to establish that ^{68}Ga -DOTATOC-PET/CT in MEN1 patients is more sensitive than the recommended imaging modalities for many of these NETs, how often should ^{68}Ga -DOTATOC-PET/CT be recommended for serial use, what age to start and in which MEN1 patients in these two categories, is currently unclear.

Although most reviews and guidelines point out that ionizing radiation whether from ^{68}Ga -DOTATOC-PET/CT or CT scanning should be a consideration in selecting serial imaging studies in patients with MEN1, this issue has never been studied and there are no data on it. This may be a particular issue with time in MEN1 patients because basic science studies demonstrate that menin, the protein altered in patients with MEN1, is involved in DNA repair, cell cycle control and transcriptional regulation, and when there is a loss of menin activity as occurs in MEN1 patients, cells become more sensitive to the effects of ionizing radiation as well as other cell-damaging injuries [123–125]. With ionizing radiation, the cells with inactivated menin show defects in DNA repair, alterations in cell cycle checkpoint regulation and failure of upregulation of DNA damage-response proteins such as p21 after the injury [123,124]. In a series of patients with sporadic thymic carcinoids [126], it was proposed that smoking, as well as radiation, might constitute risk factors. There is no

evidence in series of MEN1 patients at present that radiation was a risk factor in the patients who developed thymic carcinoids; however, smoking has been proposed as such [16,37,38]. Numerous studies have raised concerns of the use of imaging studies involving radiation in younger patients (without MEN1) [127–129], and whether younger MEN1 patients are at increased risk is unclear. The possible increased risk of cell injury from ionizing radiation in MEN1 patients, combined with the needed for serial imaging (up to yearly), also combined with the observations that pNETs and other NETs occur in MEN1 patients in the second decade [12,130], leading to guidelines proposing serial monitoring at earlier ages, all raise controversies about when and how frequent these studies should be used. These concerns support the increased use of imaging studies without ionization such as MRI.

MEN1-NETs: should MRI be used in patients with MEN1 for NET detection more often?

As stated above, the use of either CT scanning or MRI is listed in most guidelines as the standard imaging studies to be used in patients with MEN1, especially for serial studies. In MEN1 patients, for the different malignant NETs they develop, there is little information of the comparative value of the two studies. The comparative study of MRI versus EUS for the detection of pNETs in MEN1 patients reviewed above [77] is one of the few prospective studies of MRI scanning in MEN1 to other modalities. This study although demonstrating that MRI will detect approximately 85% of pNETs ≥ 2 cm, the recommended cutoff for surgery in most guidelines for MEN1 patients with NF-pNETs/gastrinomas, it is still missing 15% of patients. Only when combined with EUS is all pNETs ≥ 2 cm detected. These data lead to the conclusion that at least for pNETs with the use of existing MRI techniques, it may not have sufficient sensitivity and be adequate alone, for serial imaging. There is almost no information on the comparative value of MRI versus other imaging studies for other NETs MEN1 patients develop.

Whole-body MRI would be of value in patients with MEN1 because of their developing NETs in different locations. Recently, whole-body MRI in non- MEN1 patients, primarily with advanced disease, has been compared with ^{68}Ga -DOTATOC-PET/CT [131] and the effect of whole-body MRI on these patient's management. In this study [131], whole-body MRI and ^{68}Ga -DOTATOC-PET/CT showed comparable overall lesion-based detection rates for metastatic involvement in different NETs but differed in their organ-based detection rates. Whole-body MRI was superior for detecting metastatic in liver and bone, whereas ^{68}Ga -DOTATOC-PET/CT was superior for detecting pulmonary lesions and metastases in lymph nodes [131]. It was concluded that in a given patient, they generally benefited from the complementary information from both whole-body MRI and ^{68}Ga -DOTATOC-PET/CT. However, similar studies need to be performed in MEN1 patients before this approach can be recommended in these patients.

MEN1-EUS: what is the role of EUS in management of MEN1 patients?

EUS's potential role in MEN1 patients is principally in detecting and grading NF-pNETs, localizing other F-pNETs when the diagnosis is established and ruling out pancreatic gastrinomas in patients with MEN1/ZES. As reviewed above, most studies demonstrate that EUS is more sensitive than cross-sectional imaging in detecting NF-pNETs, but is this increased sensitivity clinically useful? As discussed above for ^{68}Ga -DOTATOC-PET/CT,

under current guidelines only the detection of NF-pNETs ≥ 2 cm will lead to a surgical recommendation. EUS, similar to MRI, in the prospective study reviewed above [77] missed a proportion of these patients (11/24), primarily in those with NF-pNETs in the pancreatic tail area, and therefore alone is not sufficient for this purpose. EUS has the advantage of allowing careful assessment of the growth of pNETs and therefore has the promise of being very useful for serial assessment of pNET growth in MEN1 patients initially found to have small pNETs ≥ 2 cm and being treated conservatively. However, EUS is an invasive procedure, operator dependent, available in primarily specialty centers and in some cases performed under general anesthesia, so this limits its availability/widespread use. At present, it is not clearly defined from prospective studies the role of EUS in MEN1 patients or the usefulness of EUS-guided fine-needle aspiration to assess NET grade.

Conclusion

A number of recent studies, some prospective in nature, evaluate in MEN1 patients the ability of ^{68}Ga -DOTATOC-PET/CT, EUS and MRI to visualize pNETs as well as other NETs. The current paper analyzes these results in light of current guidelines and controversies involved in the treatment of MEN1 patients. Particular attention is paid to the results in these studies in regard to thymic carcinoids and NF-pNETs/gastrinomas, which recent studies show are particularly important in determining long-term survival.

Future perspective

The results of the recent imaging studies for NETs reviewed in this article show important promising results as well as experimental approaches that will help define the management of these patients in the future and lead the way to planning new studies. The use of prospective studies, as was done in a number of these studies, to define the initial value of the various imaging modalities as well as to define their value in serial usage in these patients is essential for future studies. The assessment of how the use of a given modality changes the management is needed to evaluate their roles in these patients and this requires a prospective study. For the future studies to be clinically pertinent in the management of the MEN1 patients, they need to concentrate on identifying patients with NETs that are most important in determining long-term survival (aggressive pNETs and thymic carcinoids). Also the long-term potential risks of various serial imaging studies need to be assessed.

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EXECUTIVE SUMMARY

- Important findings/controversies raised by recent imaging papers in multiple endocrine neoplasia type 1 (MEN1) are reviewed and discussed.
- Results related to neuroendocrine tumors (NETs) determining survival are concentrated on (pancreatic [p]NETs and thymic carcinoids).
- Generally unclear from prospective studies at present what imaging studies for pNETs, thymic carcinoids should be performed initially and on serial follow-up in MEN1 patients.
- Current recommendations for imaging initially and for follow-up of pNETs, thymic carcinoids in MEN1 patients have limitations.
- Recent prospective/retrospective studies in MEN1 patients show that ^{68}Ga -DOTATOC-PET/CT has enhanced sensitivity over conventional cross-sectional imaging studies for pNETs and its use changes management in up to 30% of patients.
- It is controversial and currently unclear at what age ^{68}Ga -DOTATOC-PET/CT should initially be used and what is its place in follow-up of MEN1 patients with pNETs or thymic carcinoids.
- Recent prospective/retrospective studies in MEN1 patients show that MRI has promise for initial/serial studies, but it misses a proportion of clinically important nonfunctional pNETs (NF-pNETs).
- Numerous studies how endoscopic ultrasound is the most sensitive modality for detecting pNETs, but its exact role initially and in serial studies of patients with NF-pNETs is unclear.
- In experimental studies, a defect in menin (protein encoded by the *MEN1* gene) leads to increased susceptibility to injury and injury repair from radiation. The effect of repeated imaging involving radiation in younger patients with MEN1 needs to be considered and studied.