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## Value of Somatostatin Receptor PET/CT in Patients With MEN1 at Various Stages of Their Disease

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**Short Title:** <sup>68</sup>Ga-DOTATOC in MEN1

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48 **Value of somatostatin receptor PET/CT in MEN1 patients at various stages of their**  
49 **disease**

50

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92 **Short Title:** <sup>68</sup>Ga-DOTATOC in MEN1

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96

97 **Abstract**

98 **Context.** Despite the growing evidence of the clinical value of somatostatin receptor (SSTR)  
99 PET in the evaluation of neuroendocrine tumors/NET, its role remains to be clarified at  
100 different time points in the MEN1 patient journey. The rareness of the disease is however a  
101 significant impediment to prospective clinical trials.

102 **Objectives.** The goals of the study were to assess the indications and value of SSTR PET/CT  
103 in MEN1 patients.

104 **Methods.** We retrospectively included patients from 7 French expert centres for whom data  
105 on SSTR PET/CT and morphological imaging performed at the same period were available.  
106 Detection rates of PET study were analysed.

107 **Results.** One hundred eight patients were included. SSTR PET/CT was performed at  
108 screening (n=33), staging (n=34), restaging (n=37) and for PRRT selection (n=4). PET  
109 detected positive pancreatic lesions in 91% of cases at screening, with comparable results to  
110 MRI but superiority to CT (P=0.049). Metastases (mostly LN) were present at the screening  
111 phase in 28% of cases, possibly due to the suboptimal value of screening morphological  
112 imaging in the assesement of nodal metastases and/or a long delay between imaging studies.  
113 SSTR PET/CT was considered as superior or complementary to the reference standard in the  
114 assessment of LN or distant metastases in the vast majority of cases and regardless of the  
115 clinical scenario.

116 **Conclusion:** This study shows the potential added value of SSTR PET in the assessment of  
117 MEN1-associated NETs and provides a great impetus towards its implementation in the  
118 evaluation of MEN1 patients.

119

## 120 **Introduction**

121 Multiple endocrine neoplasia type 1 (MEN1) is an inherited autosomal dominant  
122 disease due to germline mutation in the tumor suppressor *MEN1* gene that encodes for menin.  
123 The population frequency is approximately 1 in 30,000 individuals. MEN1 predisposes to the  
124 development of multiglandular parathyroid disease, pituitary tumors, duodeno-pancreatic  
125 neuroendocrine tumors (NETs) as well as other less frequent tumors, such as adrenocortical  
126 tumors, bronchial/thymic NETs and lipomas (1).

127 Until present, MEN1 patients continue to have decreased life expectancy primarily due  
128 to the malignant course of NETs, particularly pancreatic and thymic NETs (1-6). It is  
129 therefore of major importance to perform an accurate diagnosis at the earliest stage of  
130 development and to identify tumors with aggressive behavior that would require a tailored  
131 treatment. A personalized approach to each patient is recommended: « The right treatment, for  
132 the right patient, at the right time ».

133 In a large cohort of patients, 23% of patients <21yrs had pancreatic NET (9% non-  
134 functional PanNET, 12% insulinomas, and 2% gastrinomas) (7). Due to the suboptimal  
135 sensitivity of serum tumor markers (8,9), imaging is the cornerstone of this screening strategy  
136 (10). At screening, the existing guidelines recommend to use imaging studies without  
137 ionization for depicting duodeno-pancreatic NET, such as MRI and/or EUS (up to yearly)  
138 (11). The optimum methods for screening for thymic and bronchial tumors have been less  
139 established but mostly rely on MRI or CT.

140 In recent years, somatostatin receptor (SSTR) PET/CT using [<sup>68</sup>Ga]-labeled  
141 somatostatin analogs has proven to be effective in the diagnostic evaluation of various NETs,  
142 and is also mandatory when selecting candidates for targeted radiotherapy (PRRT) in patients  
143 with inoperable and progressive metastatic NETs (11). SSTR PET has progressively replaced  
144 somatostatin receptor scintigraphy (SRS) due to its many advantages (i.e., greater image

145 resolution, shorter imaging times, lower radiation exposure, cheaper costs in properly  
146 equipped departments). At present, the value of SSTR PET/CT in MEN1-associated NETs  
147 has been evaluated in six studies with very promising results in terms of lesion detection and  
148 impact on patient management (12-18). Overall, SSTR PET often detects more primary NETs  
149 (except thymic carcinoids) and metastases than morphological imaging, with very few false  
150 positives. The literature is however hampered by frequent mixing of various clinical scenarios  
151 (screening at initial diagnosis, disease staging, restaging or prior to PRRT) and the limited  
152 number of cases (19).

153         The primary aim of the study was to describe the indications and the value of SSTR  
154 PET/CT in the setting of a retrospective study that assembles a large cohort of MEN1 patients  
155 evaluated in seven reference centres.

156

157



158 **Patients and Methods**

159

160 **Study Design**

161 We performed a retrospective, multicentre study conducted in seven reference centres.  
162 Each centre provided anonymised data from their MEN1 patients that were obtained as part of  
163 their routine management and that were collected from their institutional medical datafiles.  
164 Regarding imaging findings, no central reading was performed in the setting of this study, but  
165 all images were analyzed on-site by experienced radiologists and nuclear imaging physicians  
166 in the setting of institutional multidisciplinary team meetings. The potential added value of  
167 SSTR PET compared to other imaging investigations was left to the judgement of the  
168 investigators. The precise anatomical location of each lesion within a target organ as well as  
169 their size were not collected, making impossible any head-to-head comparison between  
170 modalities at each individual level.

171

172 **Patients**

173 A total of 108 MEN1 patients were included in this study (Nantes University Hospital:  
174 36 patients, Marseille University Hospital: 17 patients, Beaujon University Hospital: 15  
175 patients, Lyon University Hospital: 15 patients, Strasbourg University Hospital: 11 patients  
176 Bordeaux University Hospital: 7 patients and Clermont-Ferrand: 7 patients). The diagnosis of  
177 MEN1 was defined by the presence of at least two MEN1-related lesions or one MEN1-  
178 related lesions and a family history of MEN1, or a positive MEN1 genetic screening test (20).  
179 Genetic analysis was performed after obtaining informed consent in one of the TENgen  
180 network laboratories (21). All patients underwent SSTR PET/CT (i.e., [<sup>68</sup>Ga]-Ga-DOTA-TOC  
181 PET/CT) at various stages of their disease: screening (No prior-knowledge of any duodeno-

182 pancreatic or thymic NET), staging (follow-up of untreated NET), restaging (patients treated  
183 for NET in ,at least, one anatomic site) and in the selection stage for PRRT.

184 The study was approved by the Assistance Publique-Hôpitaux de Marseille ethics  
185 advisory committee (N°PADS21-159). Waiver of patient consent was granted by the ethics  
186 committee, given the retrospective nature of the study.

187

### 188 **Imaging techniques**

189 [<sup>68</sup>Ga]-Ga-DOTA-TOC was used in all centers in accordance with market authorization.  
190 PET/CT acquisition protocols were performed according to each institutional guidelines.  
191 Images were captured from the vertex to mid thigh at approximately 60 min post-injection.  
192 The CT data were used for attenuation correction and fusion imaging. Images were  
193 reconstructed in a standard display including transaxial, sagittal and coronal projections. The  
194 delay between PET studies and other imaging modalities was less than 3 months. In patients  
195 that were evaluated more than once by SSTR PET, the PET study that was temporally closer  
196 to the morphological imaging study was selected for analysis. Morphological imaging  
197 protocols (CT, MRI and EUS) were also performed according to the institutional guidelines.  
198 All examinations were locally interpreted and reviewed by experienced physicians.

199

### 200 **Analysis of PET/CT data**

201 PET/CT studies were locally interpreted by experienced nuclear physicians as either  
202 positive or negative. A positive PET/CT was defined when at least one focal area of  
203 pathologically increased radiotracer uptake was detected, when compared to the surrounding  
204 tissue and physiological biodistribution. For regional analysis, the following regions were  
205 analysed separately: pancreas, duodenum, stomach, lungs, lymph nodes (LN), liver and bone.  
206 A region was considered positive when it contained at least one focal area of pathologically

207 increased radiotracer uptake, regardless of the number of positive foci. For lesional analysis in  
208 the pancreas, the total number of lesions was recorded. If the number of lesions exceeded 5,  
209 the count was scored as >5.

210

### 211 **Gold Standard**

212 At a patient level, the neuroendocrine nature of the lesions was confirmed by  
213 pathological analysis following surgery or biopsy. In non-operated cases, the diagnosis was  
214 based in each center by a multidisciplinary consensus that integrated all imaging studies and  
215 follow-up data.

216

### 217 **Clinical management following SSTR PET study**

218 The clinical management of patients following SSTR PET/CT was described as either:  
219 active surveillance, surgery or other therapeutic options (e.g., chemotherapy, somatostatin  
220 analogue, targeted therapy or PRRT, liver-directed therapy).

221

### 222 **Genotype-phenotype correlation analysis**

223 In order to study the potential relationships between genotype and development of  
224 metastases, *MEN1* variants were regrouped into two groups: those with null mutations (i.e.  
225 start loss, entire gene or exon deletions, non-sense variants, frameshift variants or variant  
226 affecting splicing), and those with non-truncating variations (i.e. synonymous or missense  
227 variants). Variants were reclassified according to the guidelines (22) and proposed  
228 adjustments for *MEN1* variants (23). Only pathogenic and likely pathogenic variants were  
229 considered in the analysis.

230

231

232 **Statistical analysis**

233 Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).  
234 Categorical variables are reported as frequencies and percentages. Comparison between  
235 PET/CT and CT/MRI findings for the pancreas, duodenum and lymph nodes according to the  
236 different groups, were performed using Chi-Square test or Fisher's exact test, as appropriate.  
237 Addressing issues of separability and small sample sizes, Firth's penalized likelihood  
238 approach was performed in logistic regression models to estimate risk factors associated with  
239 PET positivity for PanNET, LN and distant metastases in the screening group according to the  
240 age of the patient when performing the PET/CT. Odds-ratios were expressed with 95%  
241 confidence intervals. All the tests were two-sided. The association between germline *MEN1*  
242 variants and development of metastases was studied using a Fisher's exact test. The statistical  
243 significance was defined as  $p < 0.05$ .

244

245 **Results**

246

247 **Patients**

248 Among the 108 included cases, SSTR PET/CT was performed at various disease stages:  
249 33 at screening, 34 at staging, 37 at re-staging and 4 for PRRT selection. Related cases were  
250 younger than index cases at the time of PET study ( $p=0.098$ ). Primary Hyperparathyroidism  
251 (PHPT), pituitary adenoma, adrenocortical adenoma and lipoma were the most frequent  
252 manifestations. At staging and restaging, 5.9% and 16.2% had distant metastases respectively,  
253 regardless of the primary NET (**Table 1**).

254

255 **SSTR PET/CT findings: patient and region-level analysis**

256 On per-patient analysis, SSTR-PET/CT showed NET lesions in 90.9% (30/33) of cases  
257 at screening, 100% at staging (34/34), 97.3% at restaging (36/37) and 100% at pre-PRRT  
258 evaluation (4/4). The pancreas was the most frequent site for primary NET and was detected  
259 by SSTR PET in more than 90% of cases regardless of the context. Two different anatomical  
260 regions (including lymph nodes) were positive on PET in 37% of cases. The vast majority  
261 (86.8%) of positive LN were abdominal (celiac and superior mesenteric or retroperitoneal).  
262 The percentage of patients with liver and bone metastases were 15.7% and 0.9%, respectively  
263 **(Table 2)**.

264 Regarding patients found to have PanNET at screening, only 5% harbored  
265 simulatenously an extrapancreatic neuroendocrine primary on SSTR PET. LN metastases of  
266 duodeno-pancreatic origin were found in 20% and 47% of the screening and staging groups,  
267 respectively. Among patients evaluated at the restaging phase, 30% had distant metastases.

268 On per-organ analysis and regarding pancreatic involvement, PET was positive in  
269 90.9% of cases at screening vs 71.4% for CT (p=0.049) and 92.3% for MRI; it was positive in  
270 97% of cases at staging vs 93.1% for CT and 83.3% for MRI; and 86.5% at restaging vs  
271 54.5% for CT (p=0.003) and 63.6% for MRI (p=0.055). For LN metastasis detection, PET  
272 performed better than the other imaging modalities, regardless of the clinical scenario, in  
273 particular, at staging, PET was positive in 47.1% of cases vs 13.8% for MRI (p=0.016), and at  
274 restaging in 40.5% of cases vs 13.6% for MRI (p=0.03) **(Table 3)**. The percentage of regions  
275 with SSTR-positive foci on PET/CT imaging is described in Figure 1.

276

### 277 **Head-to-head comparison between SSTR PET/CT and morphological imaging at lesion** 278 **level**

279 Comparison between PET and MRI has been compared for pancreatic lesions and  
280 metastases in all cases that have been evaluated by both modalities (72 cases). PET frequently

281 reported involved regions that were missed by MRI (3.8 to 16.7% depending on the context)  
282 while the opposite rarely occurred (0-4.6%) (**Table 4**). When compared to conventional  
283 imaging (MRI and CT), tumor multifocality was frequently detected by all modalities (**Figure**  
284 **2**).

285

### 286 **Clinical management following SSTR PET study**

287 Overall, SSTR PET/CT was considered by investigators as superior to conventional  
288 imaging (MRI and/or CT) in terms of lesion detection in 51.5% of cases (17/33) at screening,  
289 44.1% (15/34) at staging and 56.1% (23/41) at restaging+pre-PRRT stage. In the same  
290 scenarios, PET was considered as either equal and/or complementary to conventional imaging  
291 in respectively 39.4% (13/33), 38.2% (13/34) and 36.6% (15/41). In the remaining cases, PET  
292 was considered as inferior to conventional imaging (9%, 17.6% and 7.3%, respectively).

293 Surgical treatment was performed after PET in 39.4% (13/33), 26.8% (9/34) and 8.1%  
294 (3/37) in the screening, staging and restaging subgroups, respectively. Active surveillance was  
295 decided in 51.5%, 58.8% and 64.9% across the same subgroups. In the remaining cases,  
296 patients were treated medically with the use of SSA in respectively 6%, 14.7% and 10.8% in  
297 the same respective subgroups. Three out of the 4 cases were eligible for PRRT and  
298 subsequently treated.

299

### 300 **Clinical and genetic factors affecting the value of SSTR PET**

301 At the screening phase, multivariate analysis taking into account age at the time of PET  
302 study, sex, time interval between initial diagnosis and PET, index vs non-index status; only  
303 age at the time of PET was found to be weakly positively associated with positive PET  
304 findings for pancreatic NET, although non significantly (OR, 1.13;95% CI, 0.99-1.29;  
305  $p=0.071$ ). Importantly, there was no statistical difference across decades regarding PET

306 positivity for PanNET. Finally, at screening, no statistical difference was observed between  
307 age at the time of PET and PET positivity for lymph nodes (OR, 0.22, 95% CI 0.002-21.906;  
308  $p=0.520$ ) and distant metastases (OR, 0.02, 95% CI 0.001-8.712;  $p=0.212$ ) as well as between  
309 index vs non-index status and PET positivity for lymph nodes (OR, 0.40, 95% CI 0.17-0.95;  
310  $p=0.390$ ) and distant metastases (OR, 0.68, 95% CI 0.30-1.53;  $p=0.353$ ), as well as between  
311 index vs non-index status and PET positivity for lymph nodes (OR, 0.40, 95% CI 0.17-0.95;  
312  $p=0.390$ ) and distant metastases (OR, 0.68, 95% CI 0.30-1.53;  $p=0.353$ ).

313 All but 3 patients carried a germline variant in the *MEN1* gene (**Supplemental Table 1**,  
314 [https://figshare.com/articles/online\\_resource/MENNETREY\\_Supplemental\\_Tables\\_docx/166](https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070)  
315 [44070](https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070)) (24). Variants were available for 97 patients and corresponded to frameshift deletion,  
316 insertion or insertion-deletion in 34 cases (35%), non-sense mutations in 10 cases (10%),  
317 missense variants in 26 cases (27%), large deletion of the gene in 5 cases (5%), start loss in 3  
318 cases (3%), in frame deletion or duplication in 2 cases (2%), variants affected splice junction  
319 in the latter 17 cases (18%). Among the variants identified in the 97 patients, 2 variants were  
320 classified as uncertain significance.

321 Twelve new variants have been identified. No significant statistical association was observed  
322 between genotype (null vs non-truncating variants) and the presence of metastatic lymph  
323 nodes (OR, 2, 95% CI 0.77-5.05;  $p=0.24$ ), distant metastases (OR, 1.47, 95% CI 0.48-3.98;  
324  $p=0.6$ ) or both (OR, 1.4, 95% IC 0.43-4.13;  $p=0.77$ ) (**Supplemental Table 2**,  
325 [https://figshare.com/articles/online\\_resource/MENNETREY\\_Supplemental\\_Tables\\_docx/166](https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070)  
326 [44070](https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070))(24). Although not statistically significant, there was a trend towards decreased risk for  
327 nodal or distant metastasis in patients with non-truncating variants (OR, 0.47, 95% CI 0.18-  
328 1.7;  $p=0.17$ ).

329

330 **Discussion**

331 To the best of our knowledge, this is the largest study that evaluates SSTR PET/CT in  
332 the real life setting of patients with MEN1 at various stages of their disease (screening,  
333 staging, restaging and pre-PRRT). Although the present non-interventional study is limited by  
334 important biases, it provides some important insights regarding the utilization of SSTR PET  
335 in MEN1 patients. The principal conclusions that can be drawn from this study include:  
336 Firstly, most of MEN1 patients in our cohort harbor SSTR positive pancreatic NETs.  
337 Secondly, NETs metastases can be detected in a large proportion of cases by SSTR PET.  
338 Thirdly, SSTR can be considered as superior or complementary to conventional imaging in  
339 the vast majority of cases, regardless of the disease stage.

340 Despite the potential added value of SSTR PET in MEN1, there is still a concern from  
341 physicians and patients regarding diagnostic radiation exposure that can be illustrated by the  
342 relatively advanced age of patients at the time of PET study in the screening group. This  
343 strong reservation to use ionizing radiation also exists for other patients with an underlying  
344 genetic susceptibility syndrome towards certain cancers. This is even more valid in MEN1  
345 patients because fundamental studies demonstrate that menin is involved in DNA repair and  
346 mutated cells are more sensitive to injury from radiation, however, this merits further studies  
347 (25). The psychological impact, acceptability of repeated imaging studies, their availability  
348 and cost are also important factors to consider. Overall, these controversies exist and are  
349 important but the under-use of SSTR PET/CT or PET/MR must be balanced against the  
350 potential risk of delayed diagnosis of NET (25). Our study shows that more than 90% of  
351 patients belonging to this group harbor SSTR-positive pancreatic NET with an important  
352 trend towards multifocality within the pancreatic gland. The identification that 91% of  
353 patients with MEN1 in the screening group have a pancreatic NET is important and consistent  
354 with the data from pathological studies (26,27). These studies report that more than 90% of  
355 pancreases from MEN1 patients had neuroendocrine microtumors and/or NET. We



356 acknowledge that it is somewhat surprising that these patients were considered as negative on  
357 previous imaging investigations but this may illustrate some possible drawbacks or limits of  
358 the current imaging strategy or possible practical difficulties in the implementation of  
359 guidelines. Nevertheless, MRI and CT performed at the same period of the SSTR PET were  
360 found to accurately depict duodeno-pancreatic NETs. Of note, it is widely accepted that the  
361 highly elevated tumor-to-background uptake greatly facilitates their detection on SSTR  
362 PET/CT. Our study was not designed to provide any recommendation regarding the use of  
363 SSTR PET/CT in the screening of duodeno-pancreatic NET in MEN1 patients. We also  
364 support the use of imaging studies without ionization such as MRI in the first two decades of  
365 patients' lives but strongly encourage paying more attention to SSTR PET and discussing the  
366 optimal time frame for offering it to patients in the future guidelines. Furthermore, newer PET  
367 technology can dramatically decrease patients' exposure to radiation.

368         The diagnosis of metastases (mainly LN) remains a critical problem for morphological  
369 imaging due to its limited sensitivity and specificity, especially in the diagnosis of tiny nodes.  
370 We found a high proportion of patients with regional and distant metastases that were  
371 considered as occult on CT, while the opposite situation was rarely observed. In particular, for  
372 disease staging and restaging, the added value provided by SSTR PET/CT clearly promotes  
373 its use prior any surgical intervention. Our results are in accordance with other studies that  
374 found a very good sensitivity of SSTR PET in the staging/restaging of duodeno-pancreatic  
375 NETs, which can be higher than that of the recommended imaging modalities. We also show  
376 that SSTR provides complementary information to conventional imaging in the vast majority  
377 of cases, regardless of the disease stage that could significantly impact the management of  
378 patients. At present, the value of SSTR PET/CT in MEN1-associated NETs has been  
379 evaluated in the setting of five studies which showed very promising results. Froeling *et al.*,  
380 pioneered the evaluation of the impact of [<sup>68</sup>Ga]-Ga-DOTA-TOC PET/CT in the diagnosis

381 and management of MEN1 patients (12). This retrospective, single-centre study included a  
382 series of 19 MEN1 patients. A total of 78 lesions were detected with a sensitivity and  
383 specificity of [<sup>68</sup>Ga]-Ga-DOTA-TOC PET/CT of 91.7% and 93.5% respectively, regardless of  
384 tumor origin. PET performed better than CT alone (43.3% sensitivity and 61.3% specificity),  
385 especially in the diagnosis of LN metastases. A change in patient management was observed  
386 in 50% cases, most of which related to indications for pancreatic surgery. Sadowski *et al.*,  
387 have prospectively evaluated 26 MEN1 patients with [<sup>68</sup>Ga]-Ga-DOTA-TATE PET/CT, SRS  
388 and CT (13). A total of 107, 33 and 48 lesions were detected by [<sup>68</sup>Ga]-Ga-DOTA-TATE,  
389 SRS and CT, respectively. All the lesions observed by SRS and CT scan were found on  
390 [<sup>68</sup>Ga]-Ga-DOTA-TATE. A change in therapeutic management was induced by PET in 31%  
391 of cases (8/26), mostly due to surgical indications. Lastoria *et al.*, have prospectively  
392 evaluated 18 MEN1 patients with [<sup>68</sup>Ga]-Ga-DOTA-TATE PET/CT (14). A pathological gold  
393 standard was obtained in 9 cases. Sensitivity and specificity of [<sup>68</sup>Ga]-Ga-DOTA-TATE were  
394 both 100% for PanNET. Morgat *et al.*, has prospectively compared [<sup>68</sup>Ga]-Ga-DOTA-TOC,  
395 SRS and CECT in the detection of duodeno-pancreatic NET in a series of 19 MEN1 patients  
396 (15). [<sup>68</sup>Ga]-Ga-DOTA-TOC was found to perform better than SRS and CECT (detection rates  
397 76%, 20% and 60%, respectively p<0.0001), as well as have a higher specificity. [<sup>68</sup>Ga]-Ga-  
398 DOTA-TOC detected 15 of 25 subcentimetric duodenopancreatic lesions that were not  
399 visualised by CECT. Finally, Patil *et al.*, have reported their experience from a retrospective  
400 analysis of 34 MEN1 patients evaluated by either [<sup>68</sup>Ga]-Ga-DOTA-TATE or NOC and CT  
401 (16). PET was found to detect more lesions than CT (per-lesion: 74.1% vs 63.7%, p=0.23 and  
402 per-patient: 89.2% vs 71.4%, p=0.09), with a PPV of 100% for both modalities. The  
403 combination of the two imaging modalities provided the highest detection rates. [<sup>68</sup>Ga]-Ga-  
404 DOTA-TATE or NOC PET/CT was particularly superior to CECT in the detection of  
405 gastrinoma (90% vs 10%, p=0.0003) and metastases (85% vs 47.5%, p<0.00001), especially

406 small LN metastases. [<sup>68</sup>Ga]-Ga-DOTA-TATE was inferior to CT for thymic carcinoids (85.7%  
407 vs. 100%). We could not evaluate this latter finding in our study since none of our patients  
408 harbored a thymic NET at the time of the study. Cuthbertson *et al.*, have assessed the value of  
409 SSTR PET/CT in a series of 183 cases with PanNET (36 MEN1, 141 sporadic, 6 other).  
410 Overall, PET provided additional informations to other imaging findings in 54% of patients  
411 and influenced management in 39% of cases (18).

412 The identification of predictors of tumor aggressiveness is of main importance in order  
413 to guide physicians towards a more personalized risk-stratified follow-up. In our study, we  
414 failed to identify a relationship between the nature of the variants (i.e. null variants: non-sense  
415 variants, frameshift variants, entire gene or exon deletions, variants affecting start codon or  
416 splicing *vs* non-truncating variants: missense or synonymous) and LN and/or distant  
417 metastases. Missense variants were slightly associated with a less aggressive clinical  
418 phenotype but more patients would be necessary to achieve a statistical significance.  
419 Nevertheless, in our analysis, patients' age was not considered due to the lack of reliable  
420 information regarding the age of onset of metastatic disease.

421 We acknowledge several important limitations of the present study: its retrospective  
422 nature, the limited sample size per-subgroup, and the absence of pathologically proof for all  
423 SSTR positive foci. The latter point is often lacking in imaging studies because of ethical and  
424 practical reasons, it is often not possible to obtain pathological confirmation of each lesion. Of  
425 note, there are limited false positive findings in the evaluation of duodeno-pancreatic NETs  
426 and experienced nuclear physicians are aware of potential variants, caveats, and pitfalls that  
427 are commonly encountered on SSTR PET imaging (28).

428 In conclusion, our retrospective study of 108 MEN1 patients shows that SSTR-based  
429 imaging is superior and complementary to conventional imaging in the vast majority of cases  
430 in the assessment of LN or distant metastases, regardless of the disease stage. This study gives

431 new evidence-based data illustrating the steadily growing role of SSTR PET in the evaluation  
432 of adult patients with MEN1. Its role warrants to be clarified in the upcoming future clinical  
433 practice guidelines for MEN1.

434

#### 435 **Data Availability Statement**

436 Supplemental data can be uploaded using the following link:

437 [https://figshare.com/articles/online\\_resource/MENNETREY\\_Supplemental\\_Tables\\_docx/166](https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070)  
438 [44070](https://figshare.com/articles/online_resource/MENNETREY_Supplemental_Tables_docx/16644070)

439

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562 **Tables and Figures' legends**

563 **Table 1. Patients and tumors' characteristics at the time of SSTR PET/CT study**

564 (\*) percentage metastatic at the time of PET study.

565 Abbreviations :

566 PET : positron emission tomography

567 SSTR : somatostatin receptor

568 PRRT : peptide receptor targeted radiotherapy

569 NET : neuroendocrine tumours

570 MEN 1 : multiple endocrine neoplasia type 1

571

572 **Table 2. Positive results on SSTR PET/CT on per Patient and per Region analysis across**  
573 **disease stage subgroups**

574 \*Previous history of pancreatectomy for duodeno-pancreatic NET

575

576 **Table 3. Imaging positivity on SSTR PET/CT, CT, MRI and EUS (per-region analysis)**

577 Abbreviations:

578 NET : neuroendocrine tumours

579 SSTR : somatostatin receptor

580 PET : positron emission tomography

581 CT : CT scan

582 MRI : magnetic resonance imaging

583 EUS : endoscopic ultrasound

584

585 **Table 4. Head-to-head comparison between SSSTR PET/CT and MRI or CT for**  
586 **detection of pancreatic NET and metastases (LN and distant met)**

587

588 **Figure 1. Percentage of regions with SSSTR-positive foci on PET/CT imaging**

589 **Figure 2. Number of pancreatic NET on SSSTR PET/CT and conventional imaging-CI**

590 **(CT or MRI)**

591 Number of patients in ordinate

592

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595

596 **Tables and Figures**

597  
598  
599  
600

**Table 1.**

	<b>Screening</b>	<b>Staging</b>	<b>Restaging</b>	<b>Pre PRRT</b>
<b>N</b>	33	34	37	4
<b>Index Case in the MEN1 family (%)</b>	45.5	41.2	32.4	75
<b>Male/female sex (%)</b>	54.5/45.5	41.2/58.8	43.2/56.8	50/50
<b>Average age at the time of PET study (min-max). median (IQR)</b>				
Index Cases	54 (18-77)	55.5 (22-69)	56 (37-78)	56 (49-66)
Related cases	38.5 (22-72)	49.5 (20-77)	50 (22-71)	42 (42-42)
<b>Positive genetic test (%)</b>	96.9	97	100	75
<b>Primary hyperparathyroidism (%)</b>	90.9	97	97.2	50
<b>Pituitary Adenoma (%) (Secreting %)</b>	45.4 (60)	50 (58.8)	62.1 (60.8)	50 (100)
<b>Adrenocortical adenoma (%)</b>	15.1	52.9	48.6	25
<b>Lipoma (%)</b>	21.2	26.4	21.6	50
<b>Previous personal history of NET</b>				
Duodenum (%)	0	20.6	18.9	50
Pancreas (%)	0	76.4	86.4	50
Thymus (%)	0	0	16.2	0
Lung (%)	0	11.8	10.8	25
<b>Delay between SSTR PET and diagnosis of MEN1 (Years), median (IQR)</b>	1	4	11	7
<b>Metastatic disease of NET at the time of PET study (regardless of the primary): % regional/% distant</b>	0	5.9/5.9	35.1/16.2	25/100

601  
602

603 **Table 2.**  
604

	<b>Screening</b>	<b>Staging</b>	<b>Restaging</b>	<b>Pre-PRRT</b>
<b>N</b>	33	34	37	4
<b>Per Patient</b>	30/33 (90.9%)	34/34 (100%)	36/37 (97.3%)	4/4 (100%)
<b>Per organ (primary tumor)</b>				
Pancreas	30/33 (90.9%)	33/34 (97.0%)	32/37 (86.5%)	3/4* (75%)
Duodenum	1/33 (3.0%)	3/34 (8.8%)	4/37 (10.8%)	0/4
Stomach	0/33	2/34 (5.9%)	3/37 (8.1%)	0/4
Lung	0/33	2/34 (5.9%)	1/37 (2.7%)	0/4
<b>Per organ (metastases)</b>				
Lymph Node	7/33 (21.2%)	16/34 (47.0%)	15/37 (40.5%)	0/4
Lung	1/33 (3.0%)	2/34 (5.9%)	4/37 (10.8%)	0/4
Liver	2/33 (6.0%)	5/34 (14.7%)	6/37 (16.2%)	4/4 (100%)
Bone	0/33	0/34	1/37 (2.7%)	0/4

605

606

607 **Table 3.**  
608

	Screening				Staging				Restaging				Pre-PRRT			
	PET	CT	MRI	EUS	PET	CT	MRI	EUS	PET	CT	MRI	EUS	PET	CT	MRI	EUS
<b>N</b>	33	28	26	15	34	29	24	15	37	33	22	10	4	3	3	
<b>Primary NET</b>																
<b>Pancreas</b>	30 (90.9%)	20 (71.4%)	24 (92.3%)	11 (73%)	33 (97.0%)	27 (93.1%)	20 (83.3%)	15 (100%)	32 (86.5%)	18 (54.5%)	14 (63.6%)	10 (100%)	3 (75%)	2 (66.7)	1 (33.3%)	
<b>Duodenum</b>	1 (3.0%)	0 (0%)	1 (3.8%)	0 (0%)	3 (8.8%)	2 (6.9%)	2 (8.3%)	0 (0%)	4 (10.8%)	1 (3.0%)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
<b>Stomach</b>	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.9%)	1 (3.4%)	1 (3.4%)	0 (0%)	3 (8.1%)	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
<b>Lungs</b>	0 (0%)	0 (0%)			2 (5.9%)	2 (6.9%)			1 (2.7%)	1 (3.0%)			0 (0%)	0 (0%)		
<b>Thymus</b>	0 (0%)	0 (0%)			0 (0%)	0 (0%)			0 (0%)	0 (0%)			0 (0%)	0 (0%)		
<b>NET metastases</b>																
<b>Lymph Node</b>	7 (21.2%)	4 (14.3%)	4 (15.4%)	0 (0%)	16 (47.1%)	8 (27.6%)	4 (13.8%)	1 (6.7%)	15 (40.5%)	10 (30.3%)	3 (13.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
<b>Lung</b>	1 (3.0%)	1 (3.6%)			2 (5.9%)	3 (10.3%)			4 (10.8%)	3 (9.0%)			0 (0%)	0 (0%)		
<b>Liver</b>	2 (6.0%)	0 (0%)	1 (3.8%)	0 (0%)	5 (14.7%)	4 (13.7%)	3 (10.3%)	0 (0%)	6 (16.2%)	6 (18.1%)	3 (13.6%)	0 (0%)	4 (100%)	3 (100%)	3 (100%)	
<b>Bone</b>	0 (0%)	0 (0%)			0 (0%)	0 (0%)			1 (2.7%)	1 (3.0%)			0 (0%)	0 (0%)		

609

610 **Table 4.**

611

612

	Screening		Staging		Restaging	
Patients (N)	26		24		22	
<b>Pancreatic NET</b>	MRI +	MRI -	MRI +	MRI -	MRI +	MRI -
PET +	24 (92.3)	<b>1 (3.8)</b>	20 (83.3)	<b>4 (16.7)</b>	13 (59)	<b>3 (13.7)</b>
PET -	0	1 (3.8)	0	0	1 (4.6)	5 (22.7)
Patients (N)	15		15		9	
<b>Pancreatic NET</b>	EUS +	EUS -	EUS +	EUS -	EUS +	EUS -
PET +	11 (73.3)	<b>3 (20)</b>	15 (100)	0	7 (77.8)	0
PET -	0	1 (6.7)	0	0	2 (22.2)	0
Patients (N)	28		29		33	
<b>Lymph Node</b>	CT +	CT -	CT +	CT -	CT +	CT -
PET +	3 (10.8)	<b>4 (14.3)</b>	7 (24.1)	<b>7 (24.1)</b>	10 (30.3)	<b>4 (12.1)</b>
PET -	1 (3.5)	20 (71.4)	1 (3.5)	14 (48.3)	0	19 (57.6)
<b>Distant metastases</b>	CT +	CT -	CT +	CT -	CT +	CT -
PET +	1 (3.5)	<b>2 (7.2)</b>	5 (17.2)	<b>2 (6.9)</b>	8 (24.2)	<b>2 (6.1)</b>
PET -	0	25 (89.3)	1 (3.5)	21 (72.4)	0	23 (69.7)

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