

Impact of ⁶⁸Ga-DOTATATE PET/CT on the Management of Neuroendocrine Tumors:

The Referring Physician's Perspective

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Abstract

Somatostatin receptor imaging with ^{68}Ga -DOTATATE-PET/CT (DOTATATE) is increasingly used for managing patients with neuroendocrine tumors. The objective of this study was to determine referring physicians' perspectives on the impact of DOTATATE on the management of neuroendocrine tumors.

Methods: A set of 2 questionnaires (pre-PET and post PET) was sent to the referring physicians of 100 consecutive patients with known or suspected neuroendocrine tumors, who were evaluated with DOTATATE. Questionnaires on 88 patients were returned (response rate: 88%). Referring physicians categorized the DOTATATE findings on the basis of the written PET reports as negative, positive or equivocal for disease. The likelihood for metastatic disease was scored as low, moderate or high. Intended management prior to and changes as a consequence of the PET study were indicated.

Results: The indications for PET/CT were initial and subsequent treatment strategy assessments in 14% and 86% of patients, respectively. Referring physicians reported that DOTATATE led to a change in suspicion for metastatic disease in 21 patients (24%; increased and decreased suspicion in 9 (10%) and 12 (14%) patients, respectively). Intended management changes were reported in 53/88 (60%) patients. Twenty patients (23%) scheduled to undergo chemotherapy were switched to treatments without chemotherapy and six (7%) were switched from watch and wait to other treatment strategies. Conversely, five patients (6%) were switched from their initial treatment strategy to watch and wait.

Conclusions: This survey of referring physicians demonstrates a substantial impact of ^{68}Ga -DOTATATE PET/CT on the intended management of patients with neuroendocrine tumors.

Key words: NET, neuroendocrine tumors, somatostatin receptor, PET, DOTATATE

INTRODUCTION

Imaging somatostatin receptor (SSTR) expression using ^{68}Ga labelled somatostatin receptor (SSTR) agonists represents the diagnostic arm of the $^{68}\text{Ga}/^{90}\text{Y}/^{177}\text{Lu}$ theranostic pair used for managing neuroendocrine tumors (NETs). Epidemiologic data demonstrate that the prevalence and incidence of NETs is increasing (1973: 1.09/100,000: 2004: 5.25/100,000) (1). As metastases at the time of diagnosis are present in around 20-50% (2, 3) and tumors recur in 40-60% of patients (4, 5) there is a clinical need for an imaging assay that allows for precise staging and restaging of the disease while at the same time serving as a predictive biomarker for treatment response.

Assessing the expression of SSTRs has been the domain of ^{111}In - DTPA-octreotide which preferentially binds to SSTR 2 (6) and detects gastroenteropancreatic NETs with a median sensitivity of 84% (7). Hybrid SPECT/CT scanners have not improved the detection of lesions smaller than 1.5 cm (8). More recently, ^{68}Ga -labelled SSTR-agonists such as ^{68}Ga -DOTATOC, ^{68}Ga -DOTANOC and ^{68}Ga -DOTATATE were introduced for PET imaging (9, 10) and have been shown to detect and phenotype neuroendocrine tumors with a high accuracy (11).

However, high accuracy of a diagnostic test does not necessarily translate into an impact on patient management. We were recently granted an Investigational New Drug (IND) application by the FDA to prospectively determine whether and how gallium-68-tetraazacyclodecane tetraacetic acid-octreotate (^{68}Ga -DOTATATE) imaging affects the management of patients with neuroendocrine tumors.

MATERIALS AND METHODS

The DOTATATE IND allowed 100 neuroendocrine tumor patients to be studied in a Phase 1. Patients of all ages were enrolled with suspected or histologically proven neuroendocrine tumors referred to us for a clinical ^{68}Ga -DOTATATE PET/CT (DOTATATE) between June 2013 and July 2014. The prospective questionnaire of referring physicians was approved by the University of California, Los Angeles Institutional Review Board (IRB). Because referring physicians were surveyed on the impact of this diagnostic test on patient management the informed consent requirements were waived by the IRB.

Patient Preparation And Image Acquisition

Patients fasted for 4 hours prior to the PET/CT study. Patients on somatostatin receptor blockade were scanned prior to the scheduled monthly dose of long-acting octreotide (12).

DOTATATE was synthesized using the fractionated method as described before (13). It was injected intravenously at a dose of 5.1 ± 0.5 mCi (range: 3.3 – 5.7 mCi). A tracer uptake time of 60 minutes (mean 63 ± 8 min) was allowed before imaging with a 64 detector PET/CT system commenced (Biograph True Point 64 or Biograph mCT, Siemens). No adverse events occurred during the tracer uptake period and the scanning procedure. Furthermore, no subsequent adverse events were brought to our attention by patients or referring physicians. Scanning time per bed position varied between 2 and 5 minutes depending upon patient weight (14).

PET images were reconstructed with an iterative algorithm (OSEM; 2 iterations, 8 subsets). The CT acquisition parameters were 130 kV, 0.5-second tube rotation, 4-mm slice collimation, and a bed speed of 8 mm/s. The CT images were reconstructed using filtered back projection at 3.4

mm axial intervals to match the slice separation of the PET data. A previously published CT-based algorithm was used for attenuation correction and lesion localization (15). Intravenous contrast was administered in 81/88 patients (92%) using 90–115 mL Omnipaque 350 (GE Healthcare) with an injection speed of 2 ml/s.

Image Interpretation

DOTATATE PET/CT studies were interpreted qualitatively during a clinical readout session. Scans were classified as positive if focally increased tracer uptake not attributable to normal physiological uptake was seen and as negative if no increased tracer uptake was identified. Scans were interpreted as equivocal if focally increased tracer uptake was not clearly physiological or pathological. Pertinent clinical information such as patient history, biopsy results and reports from previous imaging tests were available at the time of image interpretation. The written reports of the imaging studies were used by the referring physicians to classify PET interpretations as positive, negative or equivocal.

Survey

Eighteen referring physicians participated in the survey. A set of two questionnaires per patient was mailed to the referring physicians as follows: A *pre-PET* questionnaire inquired about the indications for the study (initial versus subsequent treatment strategy), tumor characteristics such as grade, primary location and stage, the level of clinical suspicion for metastases, previous imaging and therapy, the planned treatment approach and whether additional imaging was intended. The second, *post PET* questionnaire required referring physicians to categorize the

DOTATATE findings on the basis of the written PET reports as negative, positive or equivocal for disease. They were asked to score the likelihood for metastatic disease as low, moderate or high. Furthermore, the survey inquired about any unexpected metastases and the need for additional biopsies. Finally, Referring physicians were queried about intended management changes as a consequence of the PET study.

Statistical Analysis

Suspicion for metastatic disease based on written PET reports was scored by referring physicians as 0=low; 1=moderate or 2=high on the pre- and post-PET questionnaires. Changes in the level of suspicion were classified as increasing, decreasing or unchanged. The intended treatment plan was recorded before and after the scan, and changes in treatment were determined for each patient. The treatment options were watch and wait, radiation, chemotherapy, somatostatin analogs, surgery, peptide receptor radiotherapy (PRRT), and other. Changes from one modality to another or the addition of a different modality were classified as change in treatment plan. Selection of the same modality before and after the scan was categorized as no change. To simplify the analysis we focused on changes from/to watch and wait; from/to surgery; and from/to chemotherapy.

RESULTS

Referring Physicians And Questionnaires

A total of 100 patients were referred by 18 physicians. Referring physicians returned 88/100 complete sets of pre-and post-PET questionnaires (response rate, 88%). Pre-and post-PET questionnaires were completed within a median of 9.0 days (mean: 12.9±14.9 days) and 13.5 days after the scan (mean: 30.8±37.1 days), respectively.

Patient Population and Treatment History

The patient population consisted of 38 males and 50 females with a mean age of 59 ± 12 years (range: 27–84 years). Primary tumor location, tumor grades and tumor stages are listed in Table 1. Twelve patients (13.6%) were referred for initial while the remaining 76 patients (86.4%) underwent subsequent treatment strategy assessments.

Twelve/88 patients (13.6%) had no prior treatment. Of the remaining 76 patients, 6 (7.9%) had only chemotherapy, 26 (34.2%) only surgery, 8 (10.5%) only sandostatin, whereas 5 (6.6%) had chemotherapy and surgery, 2 (2.6%) chemotherapy and sandostatin, and 1 (1.3%) chemotherapy and PRRT). Two patients (2.6%) had surgery and PRRT, and 19 (25.0%) surgery and sandostatin. The remaining seven patients had prior surgery, sandostatin and either chemotherapy (n=4; 5.3%), PRRT (n=2; 2.6%) or both (n=1; 1.3%).

Referring Physicians' Interpretation Of Clinical PET Reports

DOTATATE reports were interpreted by the referring physicians as negative in 28 (31.8%), positive in 55 (62.5%) and equivocal in 5 (5.7%) patients. In addition, metastases unknown by the referring physician prior to PET were found in 38 patients (43.2%) (supplemental Table 1).

Level Of Suspicion For Metastatic Disease

Responding physicians reported that the *pre-PET suspicion* for metastatic disease was low in 24 patients (27.3%), intermediate in 13 patients (14.8%), and high in 51 patients (58.0%), respectively. Following PET the suspicion level remained unchanged in 67 patients (76.1%), decreased in 12 (13.6%) and increased in 9 (10.2%) patients (Figures 1 and 2), respectively (supplemental Table 1). Thus, the level of suspicion for metastatic disease changed in 23.9% of the patients.

Clinical Assessment After PET And Impact Of DOTATATE On Patient Management

Referring physicians interpreted all available clinical information including PET and concluded that there was no evidence for disease in 25 patients (28.4%); evidence for primary tumor without regional or distant metastases in 6 patients (6.8%); lymph node involvement in 3 patients (3.4%) and distant metastases in 54 patients (61.4%) (supplemental Table 1).

The intended treatment for each patient prior to PET/CT is listed in supplemental Table 2. The most frequent intended treatment strategies prior to PET included watch and wait (20/88; 23%), sandostatin (9/88; 10%), surgery (7/88; 8%) and chemotherapy + sandostatin (11/88; 13%). DOTATATE imaging resulted in intended management changes in 53/88 (60.2%) patients (Figure 3). All intended treatment changes as a consequence of PET are listed in supplemental Table 3.

The most relevant intended management changes are depicted in Table 3: Twenty patients (22.7%) scheduled to undergo chemotherapy were switched to treatments without chemotherapy (Figure 4), whereas 3 patients were switched to a chemotherapy-including treatment plan. In 6 (6.8%) patients watch and wait was changed to other treatment strategies. Conversely, in five patients (5.7%) the initial treatment strategy was replaced by watch and wait. Three patients initially planned to undergo surgery only were switched to surgery + sandostatin (2/88) or watch and wait (1/88). In contrast, one (1/88) patient was switched from a multi-modality approach to surgery alone.

In addition to patient management, patient safety was also observed for adverse reactions during administration of DOTATATE and for one hour after its administration. At approximately 24 hours after administration of DOTATATE, patients were questioned about any signs or symptoms of a drug reaction and any adverse reactions. The results indicated no discomfort or adverse events associated with DOTATATE.

DISCUSSION

This prospective survey of treating physician's perspective demonstrates a substantial impact of DOTATATE on the intended management of patients with neuroendocrine tumors. DOTATATE changed intended management in 60% of the patients. Importantly, the intent to treat with chemotherapy was changed to intended strategies without chemotherapy in more than 20% of the population.

Intended management changes occurred in 60% of the patients. Forty-three percent of PET reports were interpreted by referring physicians as showing evidence for unexpected metastases. However, the level of suspicion for metastatic disease changed only in 24% of the patients. This difference is explained by additional lesions detected by DOTATATE in patients with already known metastatic disease as illustrated in Figure 5. Previous retrospective studies in patients with NETs had reported a comparable impact of DOTATATE or DOTATOC on patient management (16, 17). Another study (18) in 64 patients reported a switch to or from chemotherapy in 16% of the patients. Interestingly, this study also identified a need for contrast-enhanced PET/CT studies as 21% of the management changes were based on CT findings. This justifies the use of intravenous contrast in more than 90% of the current patients.

Thirty-two percent of DOTATATE reports were interpreted by referring physicians as negative for disease. However, their overall *clinical* assessment concluded that only 28% of the patients were disease free. Thus, in 3 patients the DOTATATE scan was considered false negative. Two of these patients had aggressive, dedifferentiated disease indicated by proliferation indexes of 25% and 95%, respectively, likely associated with loss of SSTR expression (19). In both patients the anatomically evident lesions were considered true positive for metastatic disease. The third

patient had sclerotic, DOTATATE negative bone lesions and a prior history of prostate cancer. No biopsy was available and the referring physician attributed the bone metastases to the NET rather than the prostate cancer. Intended management changes occurred much more frequently than changes in the level of suspicion for metastatic disease. One explanation is that confirmation of SSTR expression of metastatic lesions led to changes from chemotherapy to sandostatin based treatments (Table 3) (Figure 4). In other patients DOTATATE ruled out or confirmed disease leading to changes to/ from watch and wait. Most likely DOTATATE increased the confidence of intended treatment plans or helped to decide among multiple available treatment-modalities.

It is important to mention that the current study has some limitations. First, the surveyed physicians were all users of PET. The reported impact on management may therefore by study design favor PET. Second, this study only evaluated intended changes of treatment strategy. It was beyond the scope of this study to analyze implementation of intended management changes as well as the impact of PET on patient outcome. Third, we investigated a very heterogeneous group of patients including staging and restaging, previously known metastases as well as patients with a low probability of metastatic disease. However, we believe that this heterogeneity represents a realistic clinical scenario for DOTATATE imaging.

DOTATATE and DOTATOC PET/CT are the diagnostic standard of care in patients with neuroendocrine tumors in most parts of the world. However, since DOTATATE is not approved in the US, the current study required an IND granted by the FDA.

CONCLUSION

The major impact of DOTATATE or DOTATOC on the management of patients with NETs established retrospectively (16-18) and now prospectively emphasizes the need for professional organizations and patient advocacy groups to collaborate and petition the FDA for rapid approval of DOTATATE PET/CT without the need for large scale randomized trials. It appears ethically questionable to conduct trials between two diagnostic modalities when one of them has already been shown to provide higher diagnostic accuracy.

In summary, ⁶⁸Ga-DOTATATE PET/CT affects the intended management of 60% of patients with SSTR expressing neuroendocrine tumors. Future studies will need to determine prospectively whether these management changes are implemented and if treatment changes have an impact on patient outcome.

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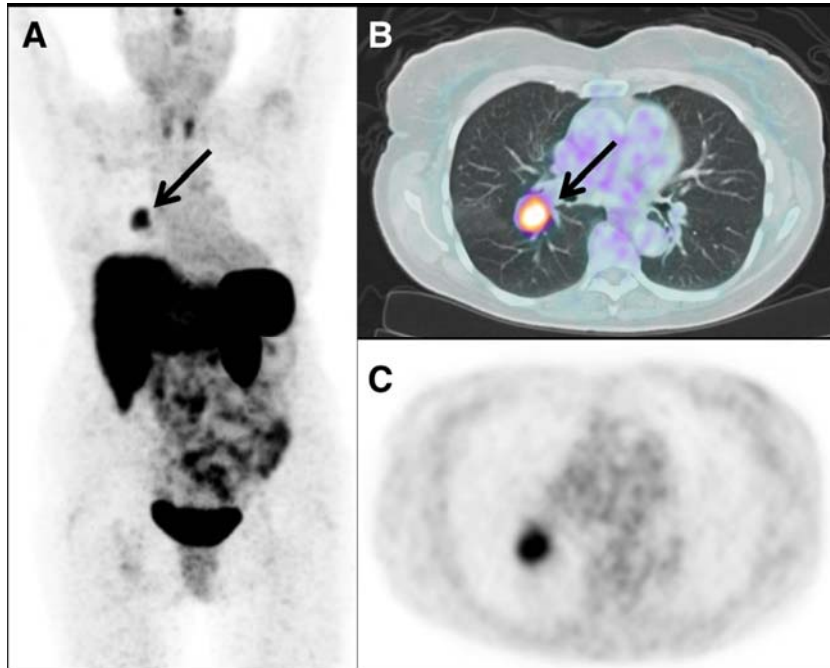


Figure 1: 75 year-old female patient with stage IIIB pulmonary carcinoid (arrow; A-C; maximum intensity projection (A) and axial images (B, C)). The level of suspicion for metastasis decreased from moderate to low after the DOTATATE study. As the previously biopsied tumor was positive for SSTR expression by imaging the intended management was switched from surgery to surgery plus sandostatin.

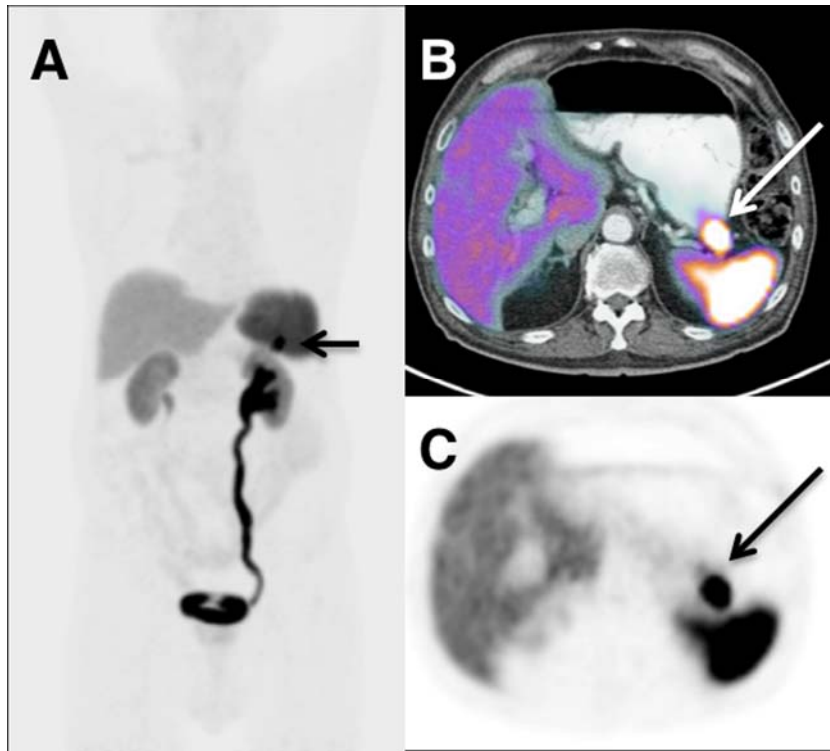


Figure 2: 78 year-old male patient whose pancreatic head NET had been resected. Other imaging tests including a recent CT revealed no evidence for metastatic disease. An unexpected pancreatic tail lesion was identified by DOTATATE (arrow; A-C; maximum intensity projection (A) and axial images (B, C)). Based on this finding, the level of suspicion for metastatic disease increased from low to high. The intended treatment was switched from watch and wait to somatostatin therapy and surgery.

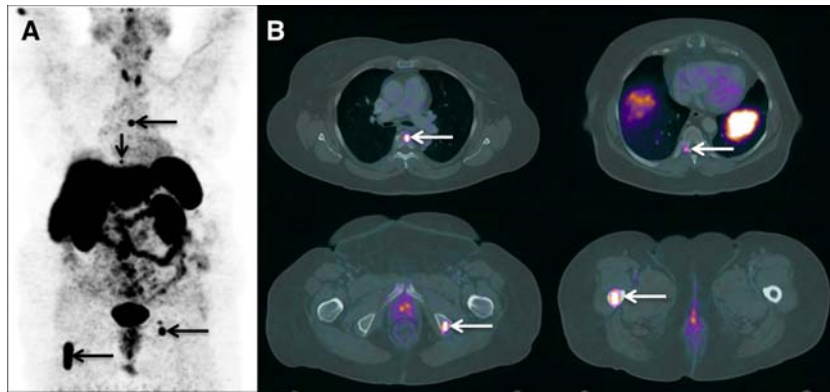


Figure 3: 70 year-old female with a history of midgut carcinoid with known soft tissue and bone metastases based on outside ^{111}In -Octreotide study. Outside MRI reported a 6.5 cm lesion within the right proximal femur diaphysis with a benign appearance and without gadolinium enhancement. Corresponding DOTATATE maximum intensity projection (A) revealed multiple mesenteric and pelvic, as well as multiple unexpected osseous metastases (arrows) shown in more detail in the axial images (B). Level of suspicion for metastases remained unchanged (high), but intended treatment was switched from surgery and somatostatin to surgery, somatostatin and selective radiotherapy of the bone metastases.

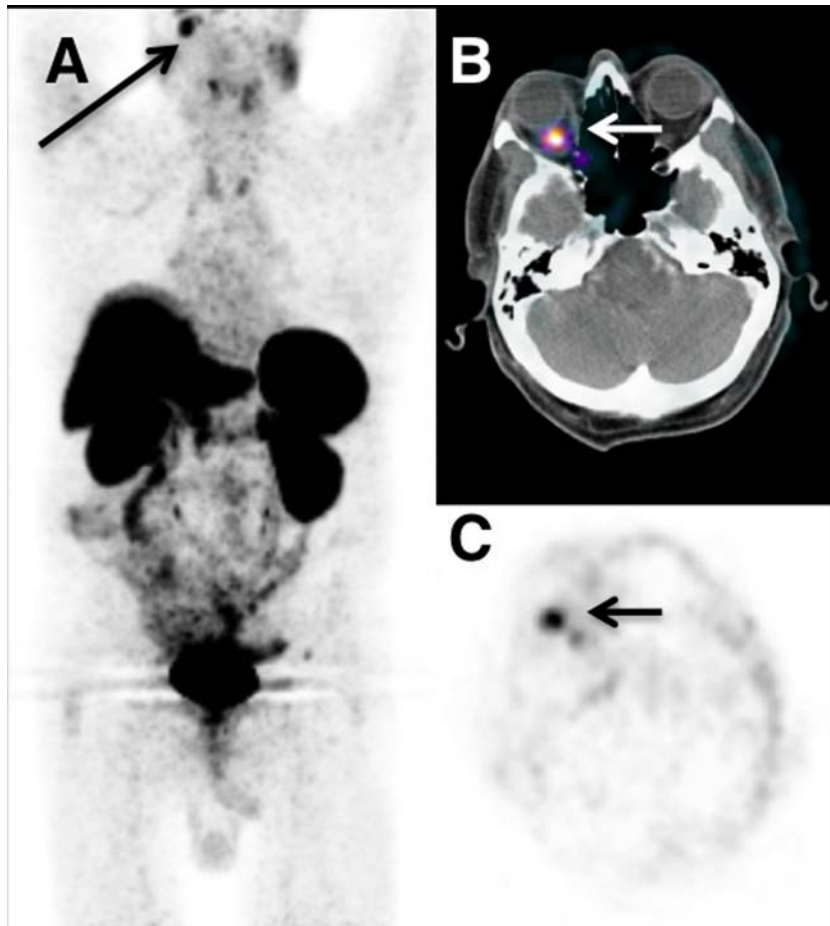


Figure 4: 74 year old male with a history of NET and recurrence in the right orbit. DOTATATE revealed orbital metastases (maximum intensity projection (A) and axial images (B, C) show metastases in the right retroorbital region (arrows)) which were histopathologically confirmed by biopsy. No other metastases were identified. Intended treatment was therefore switched from chemotherapy, somatostatin and surgery to somatostatin and surgery.

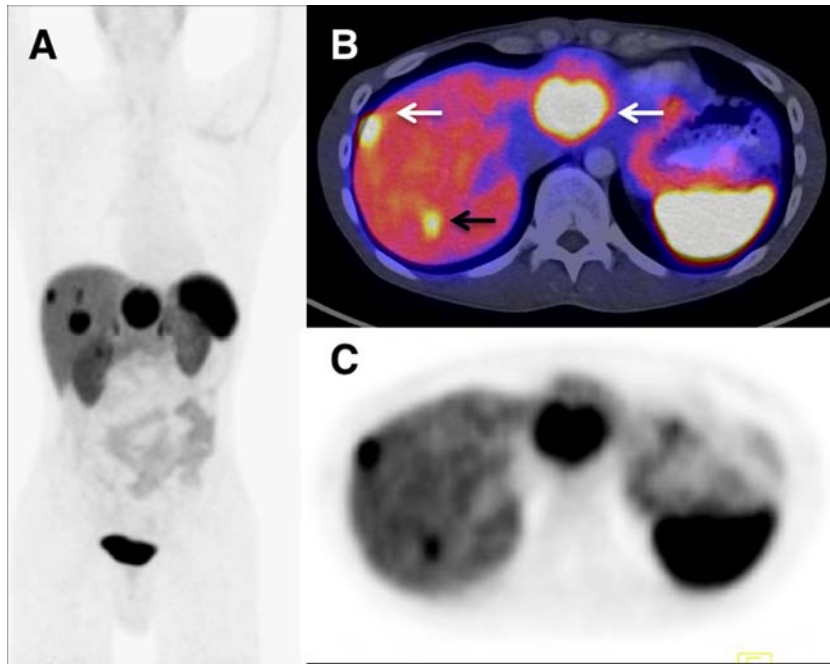


Figure 5: 36 year-old male with pancreatic neuroendocrine tumor and known liver metastases was referred for subsequent treatment strategy assessment. Multiple liver metastases are seen on the maximum intensity projection image (A). Axial views (B, C) show the known (white arrows, B) and an unexpected additional liver metastasis (black arrow, B). Despite an additional metastasis discovered by DOTATATE, both the suspicion level for metastatic disease (high) and the intended management (surgical removal of liver metastases) remained unchanged.

Table 1: Patient characteristics.

		Primary Staging (n=12)	Restaging (n=76)
Primary Tumor Location		12 (100.0%)	76 (100.0%)
	Chest	3 (25.0%)	10 (13.2%)
	Pancreas	4 (33.3%)	18 (23.7%)
	Small Bowel	1 (8.3%)	30 (39.5%)
	Colon	1 (8.3%)	4 (5.3%)
	Other	0 (0.0%)	5 (6.6%)
	Unknown	3 (25.0%)	9 (11.8%)
Tumor Grade			
	Low	6 (50.0%)	34 (44.7%)
	Intermediate	2 (16.7%)	26 (34.2%)
	High	0 (0.0%)	7 (9.2%)
	Unknown	4 (33.3%)	9 (11.8%)
Tumor Stage			
	I	0 (0.0%)	8 (10.5%)
	II	1 (8.3%)	2 (2.6%)
	III	1 (8.3%)	12 (15.8%)
	IV	3 (25.0%)	48 (63.2%)
	Unknown	7 (58.3%)	6 (7.9%)

Table 2: Changes of M1 suspicion

Increased Suspicion for M1 disease	9	Decreased Suspicion for M1 disease	12
Low to intermediate	2	Intermediate to Low	10
Low to high	6	High to Low	2
Intermediate to high	1	High to Intermediate	0

Table 3: Extract of Intended Treatment Changes after ⁶⁸Ga-DOTATATE PET/CT:

Treatment Change	N	%
CTx + Somatostatin ---> Somatostatin	6	6.8%
CTx + Somatostatin ---> Somatostatin + Surgery	1	1.1%
CTx + Somatostatin ---> Watch and Wait	1	1.1%
CTx + Somatostatin + Other ---> Somatostatin	2	2.3%
CTx + Somatostatin + PRRT ---> Somatostatin	1	1.1%
CTx + Somatostatin + PRRT ---> Somatostatin + Surgery	1	1.1%
CTx + Somatostatin + PRRT + Other ---> Surgery	1	1.1%
CTx + Somatostatin + PRRT + Other ---> Somatostatin + Surgery	2	2.3%
CTx + Somatostatin + Surgery ---> Somatostatin	1	1.1%
CTx + Somatostatin + Surgery ---> Somatostatin + Surgery	1	1.1%
CTx + Somatost. + Surg. + PRRT ---> Somatost. + Surg. + Other	1	1.1%
CTx + Somatostatin + Surgery + PRRT + Other ---> Somatostatin	1	1.1%
RTx + CTx + Surgery ---> PRRT	1	1.1%
Total	20	22.7%
Somatostatin ---> CTx + Somatostatin	1	1.1%
Watch and Wait ---> CTx + Somatostatin + Surgery	1	1.1%
Watch and Wait ---> CTx + Somatostatin + Surgery + Other	1	1.1%
Total	3	3.4%
Watch and Wait ---> Somatostatin + Surgery	2	2.3%
Watch and Wait ---> CTx + Somatostatin + Surgery	1	1.1%
Watch and Wait ---> CTx + Somatostatin + Surgery + Other	1	1.1%
Watch and Wait + Somatostatin ---> Somatostatin	1	1.1%
Watch and Wait + Somatostatin ---> Somatostatin + Surgery	1	1.1%
Total	6	6.8%
Surgery ---> Watch and Wait	1	1.1%
Somatostatin ---> Watch and Wait	2	2.3%
Somatostatin + Surgery + Other ---> Watch and Wait	1	1.1%
CTx + Somatostatin ---> Watch and Wait	1	1.1%
Total	5	5.7%
Watch and Wait ---> Somatostatin + Surgery	2	2.3%
Watch and Wait ---> CTx + Somatostatin + Surgery	1	1.1%
Watch and Wait ---> CTx + Somatostatin + Surgery + Other	1	1.1%
Watch and Wait + Somatostatin ---> Somatostatin	1	1.1%
Watch and Wait + Somatostatin ---> Somatostatin + Surgery	1	1.1%

Total	6	6.8%
Surgery ---> Somatostatin + Surgery	2	2.3%
Surgery ---> Watch and Wait	1	1.1%
Total	3	3.4%
CTx + Somatostatin + PRRT + Other ---> Surgery	1	1.1%
Total	1	1.1%

Abbreviation: CTx: chemotherapy; RTx: radiotherapy; Somatost.: Somatostatin