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Most intended management changes after ^{68}Ga-DOTATATE PET/CT are implemented

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ABSTRACT

Background: In this prospective referring physician based survey, we investigated the definite clinical impact of ^{68}Ga-DOTATATE positron emission tomography / computed tomography (PET/CT) on managing patients with neuroendocrine tumors (NET). *Methods:* We prospectively studied 130 patients with ^{68}Ga-DOTATATE PET/CT referred for initial or subsequent management decisions (NCT02174679). Referring physicians completed one questionnaire prior to the scan (Q1) to indicate the treatment plan without PET/CT information; one immediately after review of the imaging report to denote intended management changes (Q2); and one 6 months later (Q3) to verify whether intended changes were in fact implemented. To further validate the Q3 responses a systematic electronic chart review was conducted. *Results*: All 3 questionnaires were completed by referring physicians for 96/130 patients (74%). ^{68}Ga-DOTATATE PET/CT resulted in intended treatment management changes (Q2) in 48/96 patients (50%). These changes were finally implemented (Q3) in 36/48 patients (75%). Q3 responses have been confirmed in all patients with available electronic chart (36/96; 38%). *Conclusion*: This prospective study confirms a significant impact of ^{68}Ga-DOTATATE PET/CT on intended management of patients with NET (50% of changes) and notably demonstrates a high implementation rate (75%) of these intended management changes.

INTRODUCTION

Somatostatin receptor PET/CT imaging using ^{68}Ga-DOTATATE is reproducible (*1*) and affects patient management (*2*). Recent retrospective analyses suggest that intended management changes are in fact implemented (*2*). We have recently reported intended management changes in 60% of patients with NET after ^{68}Ga-DOTATATE PET/CT imaging (*3*). In this subsequent prospective study, we investigated the definite clinical impact of ^{68}Ga-DOTATATE PET/CT on NET patient management by comparing intended with actually implemented treatment strategies.

MATERIALS AND METHODS

Registration and Authorization

After an initial investigational new drug (IND) application for 100 patients (NCT01873248)(*3*), we obtained an expanded Access IND from the FDA that allowed us to study an additional 300 patients (IND #122332; NCT02174679). We enrolled 130 patients with suspected or histologically proven NET who were referred to the University of California, Los Angeles (UCLA) for a ^{68}Ga-DOTATATE PET/CT scan. The UCLA Institutional Review Board (IRB) approved the protocol, informed consent forms, participant information forms and the prospective referring physician questionnaires (IRB#12-001920). All patients provided informed consent.

Patient Preparation and Image Acquisition

A standard ^{68}Ga-DOTATATE PET/CT protocol was used (*3*). The median injected dose of ^{68}Ga-DOTATATE was 5 mCi (range 2.3-5.7 mCi). The median tracer uptake time was 61 min (range 46-97 min). Images were acquired using the Biograph 64 or Biograph

mCT (Siemens) after intravenous (110-120 mL Omnipaque 350) and oral contrast application.

Survey

Referring physicians completed one first questionnaire prior to the scan to indicate the treatment plan without ^{68}Ga-DOTATATE PET/CT information (Q1), a second questionnaire immediately after receipt of the written clinical report and the images (on a DVD) to denote intended management changes (Q2), and a final third questionnaire mailed 6 months later to verify whether intended management was in fact implemented (Q3). To further verify and confirm the validity of Q3 responses, an electronic chart review was conducted when available.

RESULTS

Referring Physicians and Questionnaires

Fifty-six different physicians referred 130 patients. Ninety-six complete sets of three questionnaires were returned (response rate 74%) (Fig. 1). Q1 was completed within a median of 11 days before the scan (range 0-59 days). Q2 and Q3 were completed within a median of 28 (range 1-281 days) and 207 days (range 89-725 days) after the scan. In 14 patients, due to delayed responses by referring physicians, Q2 and Q3 were completed at the same time. In the 82 remaining patients, the median time interval between Q2 and Q3 completion was 183 days (range 131-713 days).

Patient Population

The demographics of the 96 patients are presented in Table 1.

Impact on Intended Patient Management:

The intended treatment strategies before (Q1) and after (Q2) ^{68}Ga-DOTATATE PET/CT, and the final implemented management (Q3) are summarized in Table 2. ^{68}Ga-DOTATATE PET/CT resulted in intended management changes in 48/96 patients (50%) (Fig. 1).

Implementation of Intended Management

Intended management changes after ^{68}Ga-DOTATATE PET/CT (as indicated in Q2) were in fact implemented in 36/48 patients (75%) as specified in Q3 (Fig. 1).

Twelve of the 21 patients (57%) initially considered for surgery were eventually switched to conservative treatment. Conversely, 8/75 patients (11%) in whom surgery was not considered initially had surgery (example in Fig. 2). Nine of 17 patients (53%) who were initially scheduled for chemotherapy were eventually switched to alternative strategies. Nine of 69 patients (13%) in whom some treatment was considered were finally switched to watch and wait.

Implementation rates were similar in the small group of patients in whom Q2 and Q3 were completed at the same time (10/14; 71%) and in the 82 patients with a Q2 to Q3 completion interval of 131-713 days (65/82; 79%).

The intended management (as indicated in Q2) was not implemented in 21 of the 96 patients (22%; see Table 3). Reasons for non-implementation were: final tumor board / medical decision (10/21; 48%), second opinion in another institution (2/21; 10%), patient decision (1/21; 5%), financial issue (1/21; 5%), lost to follow-up (3/21; 14%) or unknown (4/21; 19%).

In 36/96 patients (38%) an electronic chart review of patients managed at our institution was possible (all other patients were referred from outside institutions). All implemented management changes as stated in Q3 were confirmed (median time interval of 14 months (range 2-29 months) after PET.

DISCUSSION

This prospective survey enabled a systematic assessment of how referring physicians act on ^{68}Ga-DOTATATE PET/CT study information. Management changes were intended in 50% of the patients and these changes were implemented in 75% of these cases.

Impact on management of any diagnostic test suggests value for patients and is a prerequisite for widespread acceptance. The broad coverage of ^{18}F-FDG PET/CT by CMS was the result of the National Oncology PET Registry (NOPR) which showed a significant impact of ^{18}F-FDG PET/CT on the management of tens of thousands of cancer patients (40% of management change) (*4*). However, one concern about NOPR was that intended treatment changes may not have been implemented (*5,6*). In the current study ^{68}Ga-DOTATATE PET/CT resulted in intended treatment management changes in 48/96 patients (50%) which is comparable to results from prior retrospective studies (*2,3,7–11*). However, no prospective study has elucidated prospectively the rate of implemented management changes. We demonstrated a high implementation rate of these intended management changes (36/48; 75%).

Potential reasons for lack of implementation may be due to conflicting results and conclusions made by tumor boards vs. treating physicians resulting in different

recommendations. Q2 timing did not uniformly allow clinicians to take all other factors into account that can affect final decision making. Moreover, few patients elected not to follow the intended treatment plan for personal or financial reasons or decided to obtain a second opinion at another institution (Table 4).

Major limitation of this study is a possible responder bias (*12–14*). However a high number of different referring physicians (>50) returned the questionnaires at a high response rate of 74% indicating limited bias. If all non-responding physicians would have indicated that intended management was not implemented the overall implementation rate would still have been 58%. In addition, we confirmed questionnaire responses via systematic electronic chart review in 36/96 patients (38%).

CONCLUSION

This prospective referring physician based survey confirms the significant impact of ^{68}Ga-DOTATATE PET/CT on intended management of patients with NET (50% of changes) and notably demonstrates a high implementation rate (75%) of these intended management changes.

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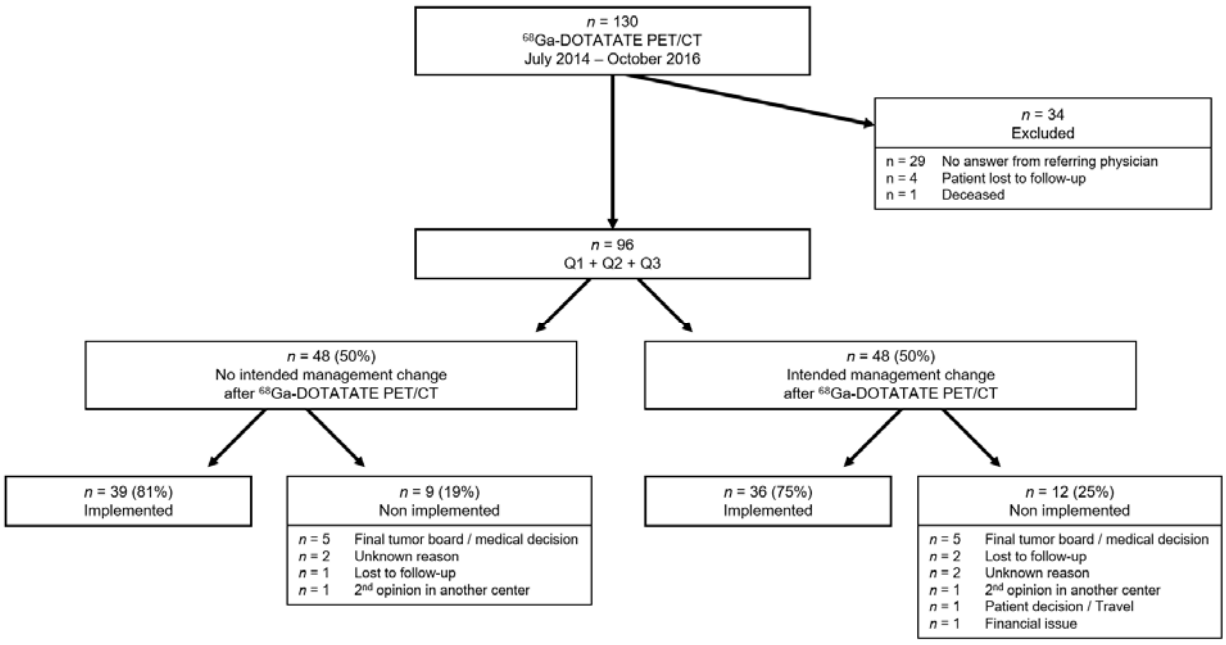

Figure 1: Patient flowchart for inclusion and management change.

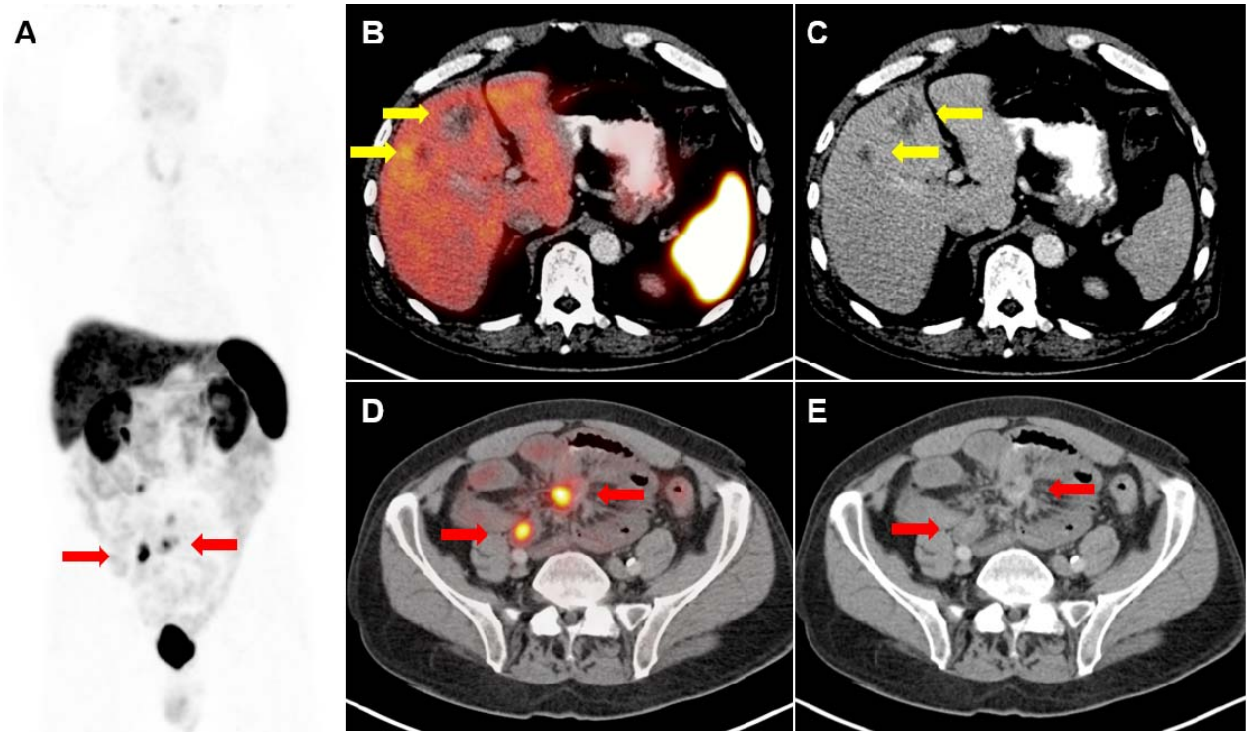

Figure 2: Example of a 62-year-old male referred for initial staging of metastatic small bowel low grade NET. CT and MRI showed mesenteric mass, enlarged abdominal lymph nodes and equivocal liver lesions (hemangiomas vs metastases). He has had prior slightly increased 24h urine 5-HIAA supporting the suspicion of hepatic metastases. The referring physician indicated in Q1 he was considered for octreotide. ^{68}Ga-DOTATATE PET/CT ruled out hepatic metastasis (yellow arrows), confirmed mesenteric primary site and lymph node involvement (red arrows), as seen on ^{68}Ga-DOTATATE PET MIP (A), fused ^{68}Ga-DOTATATE PET/CT axial views (B,D) and corresponding CT axial views (C,E). In Q2, the referring physician indicated an intended management change toward surgery which was confirmed later in Q3. The patient finally underwent resection of small bowel NET with wide margins. Follow-up MRI and urinary carcinoid biomarker showed no disease recurrence.

TABLES AND TABLE LEGENDS

Table 1: Patient characteristics.

Abbreviations: PRRT= Peptide Receptor Radionuclide Therapy; SSTR= somatostatin receptor; SPECT= single photon emission computed tomography

		Primary Staging *n* = 23 (24%)	Restaging *n* = 73 (76%)
Primary Tumor Location			
	Chest	1	9
	Pancreas	5	16
	Small Bowel	6	31
	Colon	0	2
	Other	2	5
	Unknown	9	10
Tumor Grade			
	Low	7	35
	Intermediate	4	17
	High	0	6
	Unknown	12	15
Tumor Stage			
	I	0	7
	II	0	2
	III	1	10
	IV	2	40
	Unknown	20	14
Prior Treatment			
	Surgery	4	50
	Chemotherapy	0	15
	Octreotide	1	42
	PRRT	0	6
	Other	0	20
Prior SSTR Imaging			
	SPECT	5	15
	PET	2	8
	Both	1	1

Table 2: Summary of the different treatment options as indicated on Q1, Q2 and Q3. Note that the total number of items is higher than 100% as multiple treatment options were possible for Q1, Q2 and Q3.

Abbreviations: DOTATATE= ^{68}Ga-DOTATATE PET/CT; XRT= External Beam Radiotherapy; PRRT= Peptide Receptor Radionuclide Therapy; w/w= Watch and Wait.

	Considered before DOTATATE (Q1)	Intended after DOTATATE (Q2)	Finally Implemented (Q3)
Surgery	21 (22%)	18 (19%)	17 (18%)
Chemotherapy	17 (18%)	12 (13%)	13 (14%)
XRT	7 (7%)	4 (4%)	3 (3%)
Octreotide	43 (45%)	32 (33%)	34 (35%)
PRRT	10 (10%)	12 (13%)	9 (9%)
w/w	27 (28%)	33 (34%)	31 (32%)
Other	12 (13%)	6 (6%)	3 (3%)

Table 3: Detailed treatment management of the 21 patients with no implemented intended management

DOTATATE: ^{68}Ga-DOTATATE PET/CT; CTx: Chemotherapy; XRT: External Beam Radiotherapy; PRRT: Peptide Receptor Radionuclide Therapy; w/w: Watch and Wait

Considered before DOTATATE (Q1)	Intended after DOTATATE (Q2)	Final implemented management	Reason of non-implementation
Surgery	→ CTx/Other	→ CTx	Tumor Board/Final Medical Decision
Surgery	→ w/w	→ Surgery	Tumor Board/Final Medical Decision
w/w	→ Surgery	→ Octreotide/Other	Tumor Board/Final Medical Decision
CTx/PRRT	→ CTx	→ XRT/Other	Tumor Board/Final Medical Decision
CTx/PRRT	→ PRRT	→ CTx/PRRT	Tumor Board/Final Medical Decision
CTx/PRRT/Octreotide/Other	→ CTx/PRRT/Octreotide/Other	→ Surgery/CTx/Octreotide	Tumor Board/Final Medical Decision
XRT	→ XRT	→ Surgery/CTx	Tumor Board/Final Medical Decision
PRRT	→ PRRT	→ Octreotide	Tumor Board/Final Medical Decision
PRRT/Octreotide	→ PRRT/Octreotide	→ CTX/Octreotide	Tumor Board/Final Medical Decision
Surgery	→ Surgery	→ Surgery/Other	Tumor Board/Final Medical Decision
Surgery/Octreotide	→ Surgery	→ Octreotide/w/w	2nd opinion in another institution
Octreotide	→ Octreotide	→ PRRT	2nd opinion in another institution
Surgery/XRT/w/w	→ XRT	→ w/w	Patient decision/Travel
CTx	→ PRRT	→ CTX/Octreotide	Financial issue
Surgery	→ w/w	Unknown	Lost to Follow-up
CTx/XRT/Octreotide	→ CTx/Other	Unknown	Lost to Follow-up
Other	→ Other	Unknown	Lost to Follow-up
Other	→ Octreotide/Other	Unknown	Unknown
Octreotide/w/w	→ Surgery/Octreotide/w/w	Unknown	Unknown
Surgery	→ Surgery	Unknown	Unknown
w/w	→ w/w	Unknown	Unknown