Feasibility of Radio-Guided Surgery with [68]Gallium-DOTATATE in Patients with Gastro-Entero-Pancreatic Neuroendocrine Tumors

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Abstract

Background.—Surgery is the only definitive therapy for gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), and achieving complete tumor resection is an important prognostic factor. Radiopharmaceuticals such as ^{68}Ga-DOTA peptides have been developed that offer superior accuracy for localization of GEPNETs. The study aim was to determine the feasibility of radio-guided surgery (RGS) using ^{68}Ga-DOTATATE in patients with primary and recurrent GEPNETs.

Methods.—Fourteen patients with GEPNETs were enrolled onto a prospective study to determine the feasibility of RGS with ^{68}Ga-DOTATATE. Findings from preoperative imaging, intraoperative exploration, RGS, and pathology were analyzed.

Results.—The median decay corrected target count rate was 172.6 (range 28.15–2341) for tumors, with a tumor-to-background ratio (TBR) of 4.46 (range 1.6–43.56). The median lesion size was 1.55 (range 0.5–15) cm. There was no significant correlation between preoperative imaging maximum standardized uptake value (SUV_{max}) of the lesions and TBR (Spearman $r = -0.01$, $p = 0.9$), TBR and tumor size (Spearman $r = 0.29$, $p = 0.14$), and SUV_{max} and tumor size (Spearman $r = 0.22$, $p = 0.28$). The probe showed correct identification for gastric and small intestine neuroendocrine tumor (NET), including lymph node metastasis in 17 (81.0 %) of 21 cases, with a median TBR of 3.5 (1.6–40.2). For pancreatic NETs and lymph node metastasis, 16 (66.7 %) of 24 were correctly identified by RGS.

Conclusions.—Our study shows that RGS with ^{68}Ga-DOTATATE is feasible and correctly confirms bowel NETs and metastatic mesenteric lymph nodes. Further studies are needed to determine the benefit of RGS with ^{68}Ga-DOTATATE.

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The incidence of gastro-entero-pancreatic neuroendocrine tumors (GEPNETs) has increased to about 7.8 cases per 100,000 persons each year, and the prevalence is approximately 35 cases per 100,000 persons.[1,2] Surgical resection is the only curative treatment option for patients with early-stage disease, and complete tumor removal is an important prognostic factor in patients with GEPNETs. A recent consensus statement emphasized that resection should be the first-line treatment option for patients with advanced GEPNETs if at least 90 % of the disease burden is resectable.[3] Also, the presence of metastatic disease and tumor grade are important prognostic factors.[4,5] Thus, an accurate assessment of the extent of disease before surgical therapy and confirming complete resection of disease is important. Further, in patients with recurrent/persistent locoregional GEPNETs, a reoperation can be challenging because of scar tissue, inflammation, altered anatomy, or low volume of disease. In some patients with functioning primary localized GEPNETs (e.g., gastrinoma, insulinoma), small primary or locoregional disease can be difficult to identify at the time of operation. For this reason, several radiopharmaceuticals have been used for radio-guided surgery (RGS) to optimize disease localization during an operation and/or to confirm removal of tumor in patients with GEPNETs.[6–9]

A unique feature of GEPNETs is the expression of somatostatin receptors (SSTR), which can be targeted with radiolabeled peptides for imaging and treatment.[10–12] Positron emission tomography/computed tomography (PET/CT) utilizing somatostatin analogs labeled with positron-emitting ^{68}gallium (^{68}Ga-DOTA peptides) has been shown to be more accurate than other agents for detecting GEPNETs and is an important tool in the clinical management of patients with GEPNETs.[13–15] Radiolabeled analogs such as ^{111}In-pentetreotide, ^{123}I-metaiodobenzylguanidine, and ^{99}technetium–sulfur have been used in the past for RGS in patients with GEPNETs.[6,16–18] To date, there have been two case reports and one surgical series in nine patients with GEPNETs in which RGS with ^{68}Ga-DOTA peptides were used as preoperative scanning dose but not injected at the time of the operation.[19–21] ^{68}Ga-DOTA peptides are investigational in the United States, and to our knowledge, there has been no prospective study using ^{68}Ga-DOTATATE for RGS in patients with primary and/or recurrent GEPNETs after selection based on preoperative ^{68}Ga-DOTATATE PET/CT imaging results.

The aim of this prospective study was to assess the feasibility of RGS and its utility in detecting GEPNETs using an intraoperative dose of ^{68}Ga-DOTATATE and a handheld detector.

MATERIALS AND METHODS

Patients were enrolled onto a prospective study investigating ^{68}Ga-DOTATATE PET/CT. The decision to perform RGS was made on the basis of positive preoperative ^{68}Ga-DOTATATE PET/CT results. This prospective study was performed under an investigational new drug approval from the United States Food and Drug Administration and approved by the National Cancer Institute review board and the National Institutes of Health Radiation Safety Committee (). Written informed consent was obtained from all study participants.

For preoperative ^{68}Ga-DOTATATE PET/CT imaging, 5 mCi of ^{68}Ga-DOTATATE was administered through a peripheral vein. After approximately 60 min, images from the upper

thighs to midskull were obtained (Biograph mCT; Siemens Medical Solutions USA). A low-dose, noncontrast CT was used for attenuation correction and anatomic localization. Maximum standardized uptake values (SUV_{max}) were measured on the basis of patient total body weight. Imaging was performed within a median of 84 (range 1–214) days before the operation.

At the time of the operation, a median dose of 5.0 (range 4.09–5.33) mCi of ^{68}Ga-DOTATATE was injected intravenously. At an average of 78.2 ± 51.13 (range 10–193) minutes after injection, a Neoprobe handheld gamma detector (model 2300; Neoprobe Corporation, Dublin, OH, USA) was used for the radio-guided explorations. Background count rates (counts per second) were obtained from the liver and mesenteric or omental fat. The gamma probe was used to explore the abdomen in a systematic fashion, and in vivo count rates of each tumor were obtained. The target count was determined on the basis of the highest count rate and normalized to the background count rate [tumor-to-background ratio (TBR)]. When the absolute target count rates are stated, they were decay corrected and normalized to the injected dose of ^{68}Ga-DOTATATE using the following formula: $C_0 = [C_t \times$ Exp $(0.693/\text{half-life} \times \text{interval time})]/\text{injected dose}$. Ex vivo counts were performed once the tumor was resected. Before resection, the palpation and visibility of each lesion by the surgeon was recorded. A summary of the steps for the gamma probe protocol is shown in Table 1.

The radiation dose to the surgeons was measured by a radiation protection dosimeter (Luxel +, optically stimulated luminescence dosimeter; Landauer, Glenwood, IL) worn on the chest.

For immunohistochemistry, primary antibody for SSTR2 [(UMB1) ab134152; Abcam, Cambridge, MA] and SSTR5 [(UMB4) ab109495; Abcam] were used at 1:60 dilution. GEPNETs were scored using the World Health Organization (WHO) classification system.[22] In our study, SSTR2 immunohistochemical staining was assessed on the basis of both the extent of staining and cellular localization using a scoring scale as follows: 0 = no staining, 1 = cytoplasmic only, focal or diffuse, 2 = membranous in <50 % tumor cells (irrespective of cytoplasmic staining), and 3 = membranous in >50 % tumor cells (irrespective of cytoplasmic staining). SSTR5 cases in which staining was present in >10 % tumor cells were scored as positive, as previously described.[23]

GraphPad Prism 5 software (GraphPad Software, La Jolla, CA) was used for statistical analyses. Data for continuous variables are presented as mean ± standard deviation (SD) or median (range). Spearman correlation was used to measure and test the association between two continuous variables.

RESULTS

A total of 14 patients underwent RGS for GEPNETs using ^{68}Ga-DOTATATE. The clinical characteristics and operations performed are summarized in Table 2. Nine patients had pancreatic primary tumors, 3 had primary ileal tumors, and 2 had primary gastric/duodenal tumors, and 9 of 14 patients had undergone previous abdominal surgeries.

There were 44 lesions identified on pathology. Thirty-five (79.6 %) of 44 lesions were concordant among pathology, probe, and imaging results, and 9 (20.4 %) of 44 lesions were discordant, with preoperative imaging and RGS being positive but pathology being negative (eight lymph nodes and one pancreas tail lesion). The median SUV_{max} of the target lesions on ^{68}Ga-DOTATATE PET/CT was 46.8 (range 5.4–307). The median corrected target count rate was 172.6 (range 28.15–2341) counts per second, with a TBR of 4.46 (range 1.6–43.56) for resected lesions. The overall median lesion (tumors and lymph nodes) size was 1.55 (range 0.5–15) cm. There was no significant correlation between SUV_{max} and TBR (Spearman $r = -0.01$, $p = 0.9$), TBR and tumor size (Spearman $r = 0.29$, $p = 0.14$), and SUV_{max} and tumor size (Spearman $r = 0.22$, $p = 0.28$).

When we performed analysis by the organs involved, RGS had the highest correct identification by pathology for gastric and small bowel neuroendocrine tumors (NETs), including mesenteric lymph nodes (17 of 21, 81.0 %). For these 21 lesions (7 primary lesions and 14 lymph nodes), the median TBR was 3.5 (range 1.6–40.2). An example of a patient in whom ^{68}Ga-DOTATATE PET/CT showed a known mesenteric mass and found multiple unknown bowel lesions is presented in Fig. 1 (Table 2, patient 10). RGS revealed a primary small bowel NET with multiple sites with a TBR ranging from 1.6 to 3.5 and a mesenteric mass with a TBR of 6.3. A mesenteric lymph node from a primary pancreatic NET that had a high TBR [3.4 for a 0.8 cm lesion (WHO grade 1 on pathology)] and that was found with the probe is shown in Fig. 2 (Table 2, patient 5). This patient had undergone previous surgery for a pancreatic NET and was found to have metastatic lymph nodes seen on preoperative ^{68}Ga-DOTATATE PET/CT.

We found that lesions in the pancreas and peripancreatic lymph nodes were difficult to detect with the probe as a result of high relative background counts. In such cases, palpation and intraoperative ultrasound were most useful. The gamma probe correctly identified 16 (66.7 %) of 24 lesions. However, there was one case of a sporadic insulinoma (Table 2, patient 9) in which the probe was helpful in confirming the location of a single lesion with a TBR of 43.6 (WHO grade 1 insulinoma). We did not find that the probe was helpful for detecting liver lesions: in 3 patients with liver metastases found on ^{68}Ga-DOTATATE PET/CT, the background count for the liver was high, with an average of 499.7 ± 89.0, and target lesions therefore could not be distinguished. Resection was guided by ultrasound.

When we analyzed the surgeon's ability to identify lesions intraoperatively by palpation or visualization of the lesions and compared it to findings of the probe and pathology results, we found that 3 (8.6 %) of 35 concordant lesions had not been seen or palpated by the surgeon and could have been missed (present on imaging, but not seen or palpated by the surgeons before probe scanning); they represented three small bowel lesions (smallest size, 0.7 cm). For the nine discordant lesions with negative pathology, four of them had not been seen or palpated, and five were either palpated or both palpated and visualized.

We did not find a significant difference in the target count rate by WHO tumor grade (mean target count rate 504.9 ± 534 for WHO grade 1 versus 205 ± 147 for WHO grade 2 lesions; Mann–Whitney $p = 0.5$). SSTR2 staining was performed in 12 of the resected samples, with a higher TBR in the group with more membranous SSTR2 staining (SSTR2 score 3: median

TBR 6.5 [3.4–14.9] vs. SSTR2 score 2: 3.7 [3.5–6.3]), but it was not statistically significant (Mann–Whitney $p = 0.23$) (Fig. 2d–g).[23]

The average interval between the times of injection to measurements with the probe was 78.2 ± 51.13 (range 10–193) min. Even though ^{68}Ga tracers have a short half-life of 68 min, we found no significant correlation between the length of time between tracer injection to the time point of gamma probe scanning and the level of target count rate (Spearman $r = 0.19$, $p = 0.18$, Fig. 3) or between the time elapsed from tracer dose injection and background count and TBR value.

The radiation exposure to the surgeons was measured quarterly with dosimeters applied to the chest, and included two attending and three clinical fellow surgeons. For the 14 cases, the average exposure for the deep dose (internal organs) was 13.2 ± 9.1 (range 4–27) mrem per surgeon (annual limit for occupational workers is 5000 mrem per year).

After the lesions with positive TBR were resected, we performed ex vivo counts. The overall median ex vivo count rate was 133 (14–1300). However, there were 11 positive lesions on pathology that had a negative ex vivo count.

DISCUSSION

We show that RGS is feasible using ^{68}Ga-DOTATATE. Our results showed that TBR is independent of size and preoperative SUV_{max} on ^{68}Ga-DOTATATE PET/CT. Further, we showed that small bowel NET and metastatic mesenteric lymph nodes are detected with the probe in more than 81 % of lesions, and that the probe was helpful in confirming multiple locations of NET and found additional lesions. In cases of pancreatic NETs and liver metastases, RGS with ^{68}Ga-DOTATATE was not as helpful as a result of relatively high background counts.

Surgical resection is the only curative treatment option for patients with well-differentiated GEPNETs. Complete or near-complete tumor resection in patients with advanced and metastatic GEPNET provides survival benefit, improves quality of life, and can reduce recurrence.[4,24,25] Therefore, it is important to accurately determine the extent of disease before operations and to confirm that all sites of disease have been removed. A significant number of patients may have undetected residual low-volume disease, especially in patients who have undergone previous operations and who develop recurrent/persistent GEPNET disease. In such cases, RGS can facilitate the identification and removal of all or most sites of disease and allow confirmation of tumor removal by obtaining ex vivo counts.

Several studies using analogs such as ^{111}In-pentetreotide, ^{123}I-metaiodobenzylguanidine, or ^{99}technetium–sulfur have been performed.[6,16–18,26] They showed improved detection using RGS.[16] Because of the higher sensitivity and superiority of ^{68}Ga-DOTA peptides than PET/CT to detect GEPNET, the application of this radiopharmaceutical in RGS could be helpful to surgeons in detecting small, non-visible lesions or when trying to identify and remove tumors in patients who have undergone previous operations.[13,14] To date, there have been 2 case reports with pancreatic NETs and one series of nine patients using ^{68}Ga-DOTA peptides for RGS.[19–21] Kaemmerer et al. reported a pilot study with nine patients (seven

ileal NET, one pancreatic lesion, and one patient with an unknown primary lesion) using either ^{68}Ga-DOTATOC or DOTATATE. They reported the detection of small lesions (0.5 cm) and additional lesions with the probe.[21] However, in that study, only one patient had a pancreatic NET, and furthermore, the time interval between injection and probe use were not analyzed.

To our knowledge, our study is the largest prospective study using RGS using ^{68}Ga-DOTATATE in patients with GEPNETs. We found that the probe successfully detected lesions as small as 0.5 cm. It is known that the uptake of ^{68}Ga-DOTA analogs in normal tissue is highly variable and the high physiologic retention of radiopharmaceutical in the liver, kidney, spleen, and pancreas can compromise the detection capability of RGS, as has been reported by Wang et al. using the somatostatin analog ^{111}In-pentetreotide.[6,27] Similar to that observation, we also found a lower detection rate for primary pancreatic lesions and peripancreatic lymph nodes, as well as liver metastases.

An important variable with RGS for any tumor is the timing of tracer injection relative to surgical access of the target lesion or lesions. This is especially important in the setting of reoperations (as in 65 % of our cohort), as lysis of adhesions can take a long time before arriving to the target tumor region. ^{68}Ga-DOTA peptides have a half-life of about 68 min; thus, there is a risk of scanning tissues intraoperatively either too early or too late. The average time interval in our study was 78.2 min, ranging from 10 min to 3 h maximum from the time of tracer injection to obtaining TBR values. We did not find an optimal time point for peak counts, but most importantly, the TBR was not significantly different by the time interval from injection to target count determination. Several factors also may influence the TBR or target count rate values during RGS using ^{68}Ga-DOTATATE and include primary and metastatic tumor site, tumor grade, geometry of scanning (angle of probe and distance to target), and time-dependent washout of ^{68}Ga-DOTATATE, which can be different for each organ and patient. The latter might also explain the negative ex vivo count rate encountered in histologically confirmed positive tumors with positive in vivo TBR counts. Furthermore, long-term follow-up is needed to definitively determine the true value of the probe and the completeness of the resection, as lesions could have been missed and account for the discordant findings.

In conclusion, our study revealed that RGS with ^{68}Ga-DOTATATE in patients with GEPNETs is safe and feasible. The identification of small bowel NETs and metastatic mesenteric lymph nodes were best. However, performing further studies in a larger cohort and randomizing patients to operations with and without RGS could better determine whether it benefits patients with GEPNETs.

ACKNOWLEDGMENT

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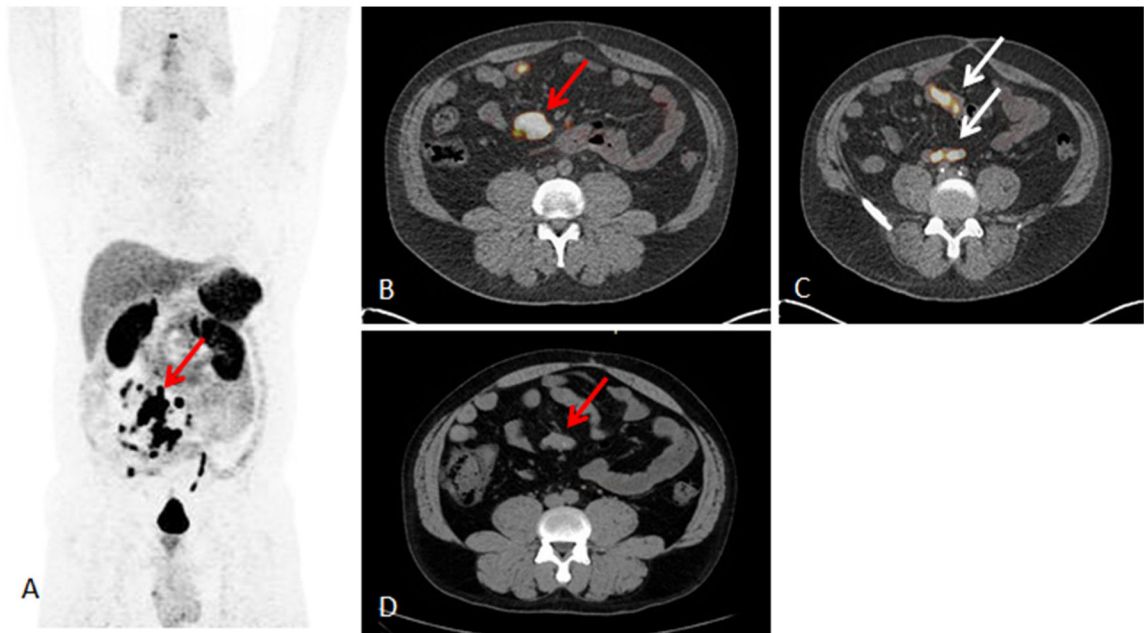
FIG. 1.

A 43-year-old man in whom ^{68}Ga-DOTATATE PET/CT showed known mesenteric mass but also multiple bowel lesions (Table 2, patient 10). Surgery revealed primary small bowel NET with multiple sites of intestinal lesions, and mesenteric mass showed TBR of 6.3. **A** ^{68}Ga-DOTATATE PET maximum intensity projection image showing mesenteric mass (*red arrow*), additional small bowel lesions, and multiple mesenteric lymph nodes. **B** ^{68}Ga-DOTATATE PET/CT image showing mesenteric mass with SUV_{max} of 117.4 (*red arrow*). **C** ^{68}Ga-DOTATATE PET/CT image showing small bowel uptake (*white arrows*). **D** Noncontrast CT showing corresponding mesenteric mass (*red arrow*), but small bowel lesions were not seen on CT or magnetic resonance imaging
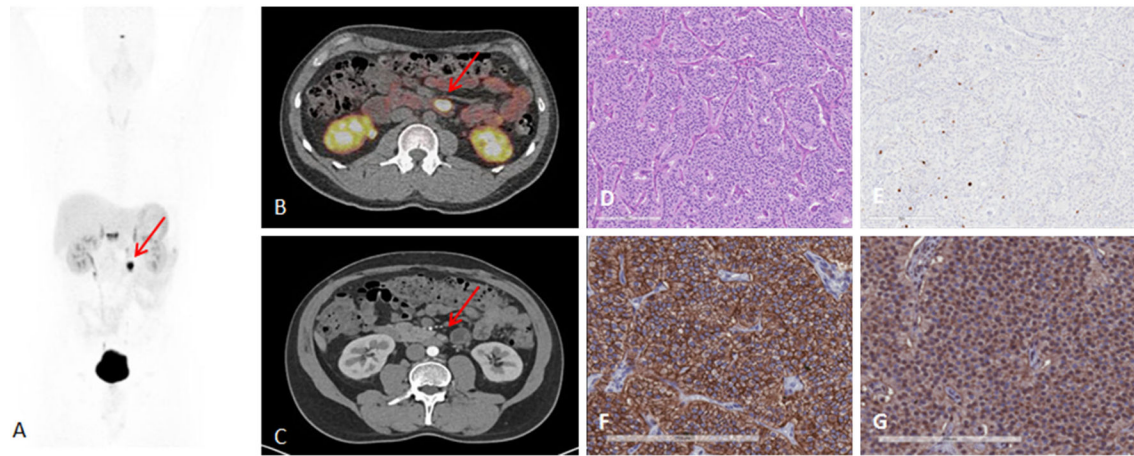
FIG. 2.
A 41-year-old man with metastatic lymph nodes on ^{68}Ga-DOTATATE PET/CT. He had undergone previous surgery for pancreatic NET (Table 2, patient 5). Mesenteric lymph node from primary pancreatic NET was found with probe with TBR of 3.4 for this 0.8 cm lesion (WHO grade 1). **A** ^{68}Ga-DOTATATE PET maximum intensity projection image showing mesenteric/duodenal lesion in segment 3 (*red arrow*) and multiple retroperitoneal lymph nodes. **B** ^{68}Ga-DOTATATE PET/CT image showing mesenteric mass with SUV_{max} of 72.8 (*red arrow*). **C** Arterial phase CT showing corresponding mesenteric mass (*red arrow*). **D** Representative hematoxylin and eosin staining of tumor showing NET in lymph node, WHO grade 1. **E** Representative immunohistochemistry for MIB-1 staining showing <2 % of cells positive. **F** Immunohistochemistry for SSTR2 showing representative image for score 3 (membranous pattern of SSTR2 staining in >50 % of tumor cells) (original magnification, ×20). **G** Immunohistochemistry for SSTR5 showing representative image of tumor with >10 % of tumor cells positive (original magnification, ×20)
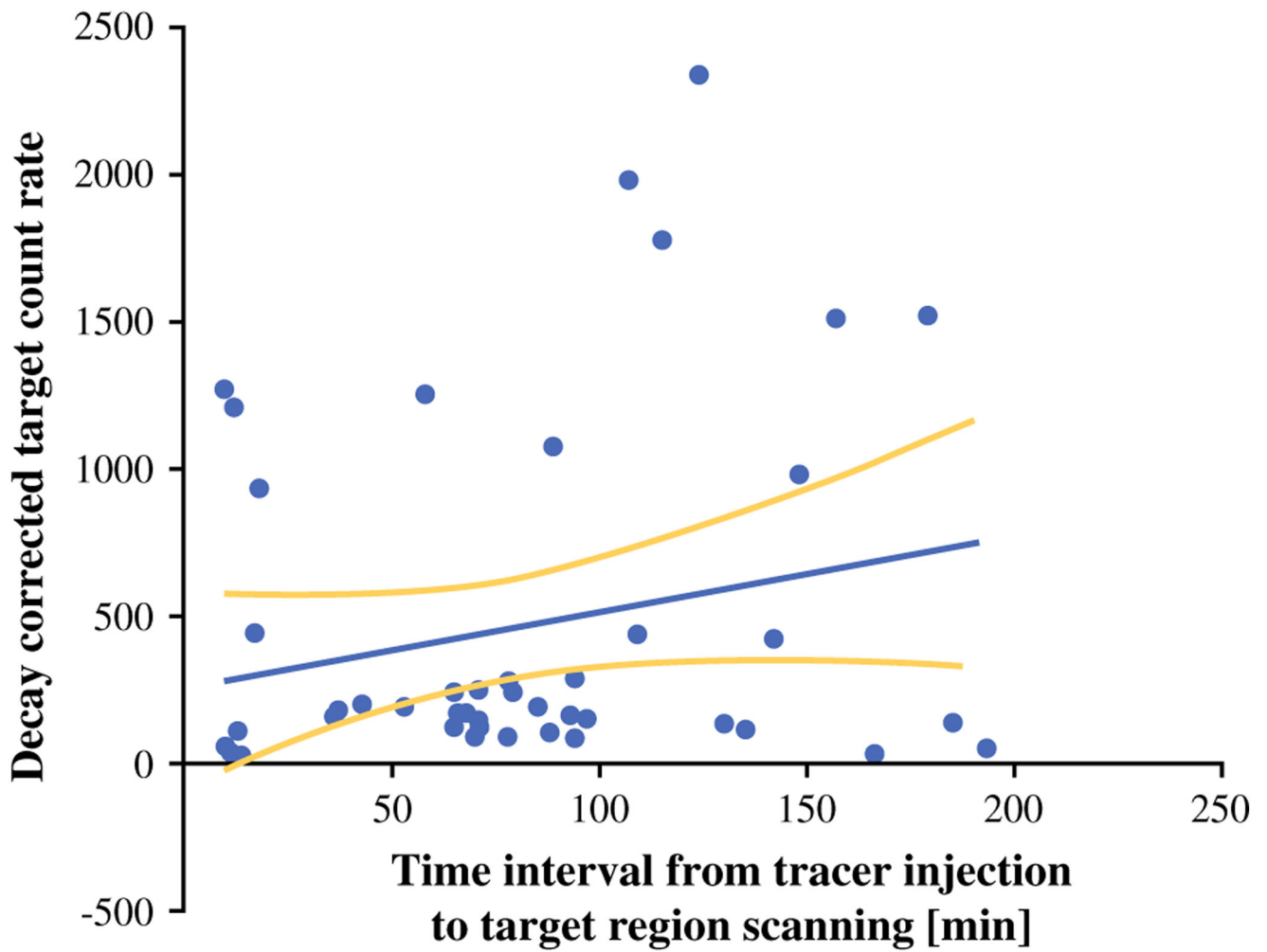
FIG. 3.
Time interval between injection of ^{68}Ga-DOTATATE and decay-corrected, normalized target lesion count rate detected with gamma probe ($n = 47$, Spearman $r = 0.19$, $p = 0.18$)

TABLE 1

68Ga-DOTATATE intraoperative administration protocol

Step		Description
Intraoperative timing of tracer injection to surgical exploration		68Ga-DOTATATE was injected intravenously at start of surgery in operating room
Gamma probe		Gamma probe (high-energy gamma probe with detection capability at 511 keV)
Detection setup	1	At PET tracer detection range: 511 keV with specific radionuclide selection
	2	Sterile probe preparation
	3	Verify system connection and settings
	4	Set to dynamic pitch mode
Intraoperative use		Probe verification with survey at counts-per-second mode to select dynamic pitch range and volume
	1	Probe scanning to measure background, on liver and at distance from target (visceral fat, nontumor tissue); select background count
	2	Scanning of target tissue area at a rate of 1–2 cm/s to detect maximum counts per sound
	3	Target-to-background measurement (TBR >1.5 at target lesion region)
	4	Ex vivo count once tissue resected
		Repeat 1–4 in patients with multiple lesions observed on preoperative imaging with 68Ga-DOTATATE

TABLE 2

Clinical characteristics, histology, and procedures in study cohort

Patient no.	Age/sex	Tumor type, histology, and stage	Type of operation
1	50 male	MEN1, metastatic gastrinoma, WHO 1, pT2 N1 (13/24)	Duodenotomy and resection of primary tumor, LN resection
2	51 female	MEN1, PNET WHO 2, pT2 N0 (0/3)	Pancreatic EN, LN dissection
3	49 male	VHL, PNET with LN: Giant cell reaction/traumatic neuroma	Retroperitoneal and pericaval LN dissection
4	40 male	MEN1, PNET WHO 1, pT2 N0 (0/10)	Pancreatic EN, LN dissection
5	41 male	MEN1, PNET metastatic to LN, WHO 1	Periportal and retropancreatic LN dissection
6	38 female	MEN1, PNET WHO 1, gastrinomas, N1 (10/11); uterus: NEC, pT3 N1 (4/7)	Pancreatic EN, duodenotomy, peripancreatic and periaortic LN dissection, and salphingo-oophorectomy
7	31 female	VHL, PNET WHO 2 pT2 N0 (0/4)	Extended distal pancreatectomy
8	65 male	MEN1, gastric and duodenal NET, WHO 2, N1 (9/29), liver: NET	Aortocaval, retropancreatic and porta hepatis LN dissection, resection of duodenal gastrinoma, gastric wedge resection, and biopsy liver segment III lesion
9	47 female	Sporadic insulinoma, PNET, WHO 1	Pancreatic EN
10	43 male	Metastatic ileal NET, multiple, WHO 1, N1 (3/5)	Small bowel resection and mesenteric LN resection
11	47 female	VHL, PNET	Exploration and resection of periduodenal lesion
12	39 male	VHL, PNET WHO 2, N0 (0/1)	Total pancreatectomy
13	58 female	Unknown primary lesion, ileal NET, WHO 1, pT2 N0 (0/13) M1 (liver)	Small bowel and mesenteric LN dissection, nonanatomic resection of lesions in segment II and IV of liver
14	70 female	Positive margins at anastomosis from prior ileal NET (WHO 1, N1 [4/18]). No tumor on histology	Resection of ileocolic anastomosis

Tumor, node, metastasis classification stage according to American Joint Committee on Cancer[28,29] and World Health Organization (WHO) histologic classification for PNET (1 low-grade NET, 2 intermediate NET, 3 high-grade NEC)[22]

MEN1 multiple endocrine neoplasia type 1, *EN* enucleation, *LN* lymph node, *PNET* pancreatic neuroendocrine tumor, *VHL* von Hippel–Lindau, *T* tumor size, *N* lymph node