Intraoperative Gamma Probe Detection of Neuroendocrine Tumors

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Previous studies of the intraoperative use of a handheld gamma probe to localize metastases and primary tumors of colorectal cancer have shown improved assessment of tumor spread and changes in surgical management based on added information gained by radioimmunoguided surgery. We conducted a prospective study to determine whether intraoperative radiodetection is able to reveal microscopic and occult disease of neuroendocrine tumors [medullary thyroid carcinomas (MTCs), gastroenteropancreatic (GEP) tumors]. **Methods:** After the injection of 180 MBq [^{111}In-diethylenetriaminepentaacetic acid (DTPA)-D-Phe^1]pentetreotide and/or 500 MBq ^{99m}Tc-dimercaptosuccinic acid (DMSA) (both for double-nuclide scintigraphy), preoperative somatostatin receptor imaging (12 patients with GEP tumors) and double-nuclide scintigraphy (10 patients with relapsing MTCs were performed. The results were combined with the information obtained from conventional imaging modalities (CT and sonography). Intraoperative radiodetection was performed 24 hr after administration of [^{111}In-DTPA-D-Phe^1]pentetreotide or 4 hr after the injection of ^{99m}Tc-DMSA using a handheld gamma probe. **Results:** Intraoperative gamma counting localized 70 somatostatin receptor-positive lesions of GEP tumors, whereas preoperative receptor imaging visualized 74%, surgical palpation visualized 44% and radiological imaging modalities localized only 43%. In 10 patients with recurrent MTCs, the surgeon was successful in localizing and removing 30 tumor lesions using the gamma probe. Twenty-seven of 30 lesions demonstrated tumor involvement, whereas 3 lesions were false-positive (lymphadenitis). Double-nuclide scintigraphy revealed 67% (Octreoscan, 7 of 20; ^{99m}Tc-DMSA, 13 of 20), surgical palpation revealed 60% and conventional imaging methods (CT, sonography) revealed only 50% of all lesions detected intraoperatively by the handheld gamma probe. The smallest lesion identified by the handheld probe (not palpated by the surgeon) was a lymph node metastasis (5-mm diameter). **Conclusion:** The preliminary data show that intraoperative handheld gamma probe detection of microscopic and occult endocrine tumors is feasible and more sensitive than external scintigraphy and conventional imaging.

Key Words: neuroendocrine tumors; intraoperative radiodetection; gastroenteropancreatic tumors; medullary thyroid carcinomas; double-nuclide scintigraphy

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High-affinity somatostatin receptors have been identified on neuroendocrine tumors of the gastrointestinal tract [gastroenteropancreatic (GEP) tumors] and medullary thyroid carcinomas (MTCs) (*1–3*). These neuroendocrine tumors tend to grow slowly and are notoriously difficult to localize, at least in the early stages. Metastases are in most cases already present at the time of diagnosis (*4,5*). [Indium-111-diethylenetriaminepentaacetic acid (DTPA)-D-Phe^1]pentetreotide scintigraphy has been shown to localize neuroendocrine tumors not detected by conventional imaging modalities (*6*). Furthermore, various tumor-avid radiopharmaceuticals such as ^{201}Tl-labeled chloride, ^{131}I- or ^{123}I-labeled metaiodobenzylguanidine, radiolabeled anti-carcinoembryonic antigen (CEA) antibodies and pentavalent ^{99m}Tc(V)-dimercaptosuccinic acid (DMSA) have been used for scintigraphic detection of MTC metastases (*7,8*).

Surgery is the only curative therapeutic option for neuroendocrine tumors. The effectiveness of surgical treatment is invariably dependent on the complete surgical excision of all tumor tissue; therefore, localization of primary as well as metastatic tumors (pre- and intraoperatively) is of utmost importance (*9–11*). Microscopic and occult disease not readily seen by the surgeon may remain in situ, leading to a shortened survival period (*12*). Previous studies of the intraoperative use of a handheld gamma probe to localize metastases and primary tumors of colorectal cancer have shown improved assessment of tumor spread and changes in surgical management based on added information gained by radioimmunoguided surgery (RIGS) (*13,14*).

The aim of this study was the intraoperative localization of primary and/or metastatic GEP tumors as well as the localization of recurrent MTC using a handheld gamma probe (Tec Probe 2000; Stratec Electronics, Birkenfeld, Germany) after the administration of [^{111}In-DTPA-D-Phe^1]pentetreotide (GEP tumors/MTC) and/or ^{99m}Tc(V)-DMSA (MTC) and to compare the results obtained by gamma probe counting with external scintigraphy, conventional imaging modalities and surgical palpation.

SUBJECTS AND METHODS

Patients

The study group consisted of 12 patients with primary or recurrent GEP tumors (7 women, 5 men; age range 24–74 yr; mean age 55.4 yr) and 10 patients with relapsing MTC (5 women, 5 men; age range 21–69 yr; mean age 51.75 yr) all scheduled for surgery. Ten patients suffered from carcinoids, 1 patient had a metastasizing gastrinoma and another suffered from insulinoma. All patients with GEP tumors showed elevated mean hormone levels (carcinoids: 5-hydroxyindoleacetic acid, 145.6 μmol/24 hr, normal range 10–50 μmol/24 hr; gastrinoma: gastrin, 5500 pg/ml, normal range <100 pg/ml; insulinoma: insulin, 56.5 μEq/ml, normal range 9.1–21.7 μEq/ml). Ten of 12 patients with GEP tumors were untreated before examination; 2 patients had undergone previous operation (one small bowel carcinoid resection, one resection of para-aortic lymph node metastases without identification of the primary carcinoid tumor) and presented with recurrent disease. In all patients with GEP tumors, preoperative chest roentgenograms and abdominopelvic ultrasound were obtained, as well as abdominopelvic CT within 4 wk preceding somatostatin receptor scintigraphy.

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All patients with relapsing (sporadic) MTC had undergone total thyroidectomy more than 3 yr previously, and 8 of 10 patients had repeated cervical lymph node dissection. A 67-yr-old woman with multiple endocrine neoplasia Type II demonstrated, additionally, a follicular thyroid carcinoma and a pheochromocytoma. In all 10 MTC patients, calcitonin levels were increased (mean = 6007 ng/ml; range 206–36,000 ng/ml) and CEA levels were considerably elevated in 6 patients (mean = 48.32 ng/ml; normal range 5.7–150 ng/ml).

Preoperative chest roentgenograms and ultrasound of the cervical region were obtained, and in all cases, thoracic CT was performed within 4 wk preceding double-nuclide scintigraphy.

Informed consent was obtained from all patients before the studies.

Radiopharmaceutical Kits

[Indium-111-DTPA-D-Phe^1]Pentetreotide. The somatostatin analog pentetreotide (Octreoscan) was obtained from Mallinckrodt (Petten, The Netherlands) in lyophilized form (10–20 μg) as a single-vial kit. Radiolabeling of [DTPA-D-Phe^1]pentetreotide by adding 111 to 222 MBq ^{111}In chloride was performed according to the manufacturer's instructions. The labeling procedure was complete within 30 min (labeling efficiency >95%, as measured by thin-layer chromatography).

Technetium-99m-V-DMSA. All patients with relapsing MTC were examined using an original DMSA kit (vial 1) from CIS Diagnostica (Dreieich, Germany) to which solutions of $NaHCO_3$ (vial 2) and penta-DMSA (vial 3), obtained from our pharmacy, were added. The instructions for use were as follows.

For the preparation of a bicarbonate solution for vial 2, 1.4% $NaHCO_3$ was dissolved in 10 ml distilled water for injection, and this aliquot was dispensed aseptically. For the preparation of a bicarbonate solution for vial 3, DMSA (2.5 mg) and $NaHCO_3$ (4 mg) were dissolved in 1 ml distilled water and also dispensed aseptically for injection. One milliliter of vial 3 was added to the freeze-dried DMSA kit (vial 1), and afterward, 1.3 ml of vial 2 and 2 ml ^{99m}Tc (1 GBq/2 ml) were added simultaneously to the DMSA solution and shaken sufficiently.

Operative Gamma Detection Probe

The Tec Probe 2000 consists of a cesium-iodide crystal (diameter 9.5 mm; length 15 mm), a photomultiplier (diameter 10 mm) and a collimator with an aperture of 8 mm and a length of 10 mm. Three channels are available for different radionuclides (e.g., ^{111}In, ^{99m}Tc). The probe is connected to an electronic unit providing both visual (liquid crystal display) and audible indication of the counting rate (range 0–25,000 counts per second (cps)) as the tumor is approached by the surgeon. Sterile latex covers, identical to those used for intraoperative ultrasound, were used to ensure sterility during surgery.

Imaging Procedure

Gastroenteropancreatic Tumors. The radiolabeled pentetreotide was administered intravenously (mean = 180 MBq; range 110–220 MBq). No adverse reactions were observed.

Multiple planar overlapping anterior and posterior images of the whole body were obtained 4 and 24 hr after injection (800–1000 kcts/image, 256 × 256 matrix; Sopha Medical Gamma Camera D 7.0) using both ^{111}In peaks (173 and 247 keV, window 20%). SPECT of the abdomen was performed 4–5 hr postinjection using a medium-energy, parallel-hole collimator (360° rotation, 30-min rotation time, frame reconstruction using the Wiener filter, slice thickness = 6 mm).

Medullary Thyroid Carcinomas (Double-Nuclide Scintigraphy). First, 180 MBq (mean) Octreoscan were injected over 2 min. After this, 500 MBq ^{99m}Tc(V)-DMSA were injected over approximately 30 sec. No adverse reaction was seen. Four hours after the injection, static (whole-body) and SPECT (thorax, abdomen) images were obtained as described above. For the double-nuclide technique, the analyzer was set at both ^{111}In peaks (173 and 247 keV; 20% window) and manually to the ^{99m}Tc peak (140 keV; window width 15%).

Crossover Assessment. In the framework of this study, crossover was quantified in phantom studies. Crossover for each radionuclide (^{111}In and ^{99m}Tc) was calculated (e.g., for ^{99m}Tc by the ratio of the counts in the ^{111}In energy window/counts in the ^{99m}Tc energy window with ^{99m}Tc in the phantom). The mean crossover was <5%.

In Vivo Gamma Probe Measurements and In Vitro Tissue Counting. Patients with GEP tumors were taken to surgery approximately 24 hr after the administration of 180 MBq (mean) [^{111}In-DTPA-D-Phe^1]pentetreotide. To reduce unspecific intestinal uptake of Octreoscan due to hepatobiliary secretion, all patients were treated with laxatives.

In cases of recurrent MTC, the tracer showing the highest uptake in double-nuclide imaging was injected (same dose) again preoperatively for intraoperative radiodetection. The operation was performed approximately 4 hr after the injection of ^{99m}Tc(V)-DMSA. For all patients, the surgeon reviewed the findings of radiological studies and scintigraphic imaging preoperatively. Standard laparotomy (GEP tumors), thoracotomy and/or neck dissection (MTC) were performed, in which all relevant structures (abdominal organs, peritoneal surfaces, mediastinum and major lymph node groups) were visualized and palpated. Intraoperatively, adjacent normal tissue, tumor tissue and anatomical areas at risk of micrometastatic involvement by tumor were counted for comparison. After resection of known tumor lesions (all foci and sites of increased activity obtained from preoperative imaging modalities), the tumor bed and resection margins were scanned. A tumor-to-nontumor count ratio of 2:1 or more was considered positive based on previous experience in detection of GEP tumors and MTC recurrences (*15,16*).

To determine tumor-to-nontumor ratios, tumor tissue, normal tissue and suspected metastases were measured in a gamma well counter. In addition, the tissues were prepared for histologic examination by the surgical pathologist, who was not informed about the results of the intraoperative measurements.

RESULTS

Gastroenteropancreatic Tumors (External Imaging Modalities)

Somatostatin receptor scintigraphy (planar and SPECT) successfully detected all 11 primary tumors (Fig. 1), whereas CT scan and sonography failed to detect the primary lesions in 5 cases.

Receptor scintigraphy localized 26 lymph node metastases in 8 patients (smallest lesion was 1 cm in diameter), whereas the conventional imaging modalities (CT scan and sonography) visualized only 14 para-aortic lymph node metastases (smallest lesion was 1.8 cm in diameter).

Fifteen liver metastases were detected in 6 patients by pentetreotide SPECT. In contrast, CT and sonography detected only 10 liver metastases in 4 patients, whereas intra-arterial digital subtraction angiography confirmed 3 of 4 lesions (localized by SPECT) in the patient with the metastasizing gastrinoma (Table 1). The smallest liver metastasis detected by receptor scintigraphy was 8 mm in diameter.

Intraoperative Tumor Localization

The results of intraoperative counting rates (cps) obtained from tumor tissue, normal organs, vessels and tumor surrounding tissue are listed in Table 2.

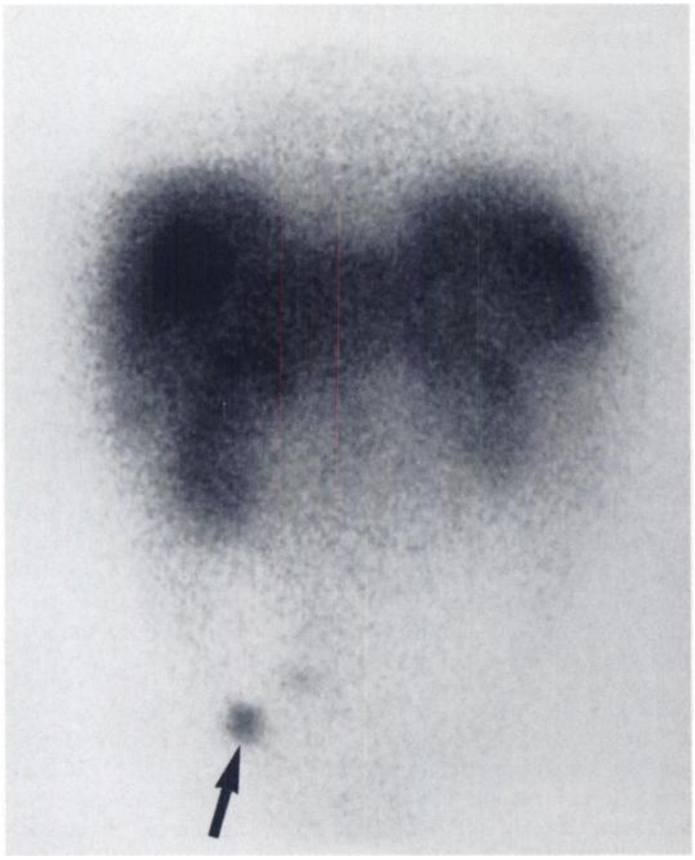

FIGURE 1. Anterior planar [^{111}In-DTPA-D-Phe^1]pentetreotide scintigram of a patient with a metastasizing carcinoid (liver metastases). Arrow indicates the primary tumor.

Tumor-to-nontumor ratios of at least 2:1 and, in most cases, more than 4:1 were observed; all tissues with fewer than 20 cps were considered tumor negative. Surgical palpation identified only 31 of 52 lesions preoperatively visualized by somatostatin receptor scintigraphy. Intraoperative counting using the handheld gamma probe identified 70 lesions, which were surgically removed and confirmed as tumor-involved sites by histology; i.e., no false-positive foci were identified intraoperatively. The smallest tumor lesion identified by the handheld probe (not palpated by the surgeon) was a 6-mm-diameter lymph node metastasis (located in the pelvis). All tumors detected by surgical palpation were 10 mm or more in diameter. Compared with those identified by CT scan and sonography, 40 additional lesions were detected with the handheld gamma probe (Table 1 and Fig. 2).

TABLE 1
Gastroenteropancreatic Tumors: Number of True-Positive Lesions Detected by Conventional Modalities, Somatostatin Receptor Scintigraphy, Standard Surgical Exploration and Intraoperative Gamma Probe Localization

	Primary tumor	Liver metastases	Abdomen (LN)	Pelvis (LN)	Σ
Palpation	9/11	6/18	16/35	0/6	31
CD	6/11	10/18	14/35	0/6	30
SRS	11/11	15/18	24/35	2/6	52
Probe	11/11	18/18	35/35	6/6	70

LN = lymph node metastases; CD = conventional diagnostics (CT, sonography); SRS = somatostatin receptor scintigraphy.

TABLE 2
Gastroenteropancreatic Tumors: Intraoperative Measurement of Tissue Radioactivity 24 Hours after Administration of [Indium-111-DPTA-D-Phe^1]Pentetreotide

Tissue	Range (cps)	Mean (cps)
Lymph node metastases	450–1400	1100
Primary tumor (Ileum)	400–2200	1526
Normal ileum	50–1100	459
Normal liver	600–1100	843
Liver metastases	1400–2200	1857
Lung	100–300	169
Heart/vessels	300–400	351
Kidneys	1000–4000	2753
Spleen	1500–1950	1675

Follow-Up

Eight patients are in complete remission after 2 yr of follow-up. One patient with liver metastases of a gastrinoma has normal gastrin levels 1 yr after primary tumor resection (identified only by receptor imaging) and postoperative somatostatin therapy (1500 μg of Sandostatin/day; Sandor AG, Nürnberg, Germany). Two patients with metastasizing carcinoids are in partial remission 1 yr after surgical treatment, whereas another patient shows progressive disease with multiple liver and lung metastases, diarrhea and weight loss.

Results of In Vitro Tissue Counting

Measurements of intraoperatively detected and surgically removed primary tumors and lymph node metastases and those of normal tissues were performed in a gamma well counter, and tumor-to-nontumor ratios were calculated from the counts per gram of tumor tissue to those of normal tissue. Tumor-to-blood ratios were also calculated. The lowest (2.4:1) and the highest (395:1) ratios resulted from a primary carcinoid tumor. Lymph node metastases revealed ratios between 4.8 and 51:1, whereas liver metastases ranged from 5.5 to 280:1.

Medullary Thyroid Carcinoma

External Imaging Modalities. Scintigraphy in double-nuclide technique (planar or SPECT) revealed 20 of 30 sites of focal

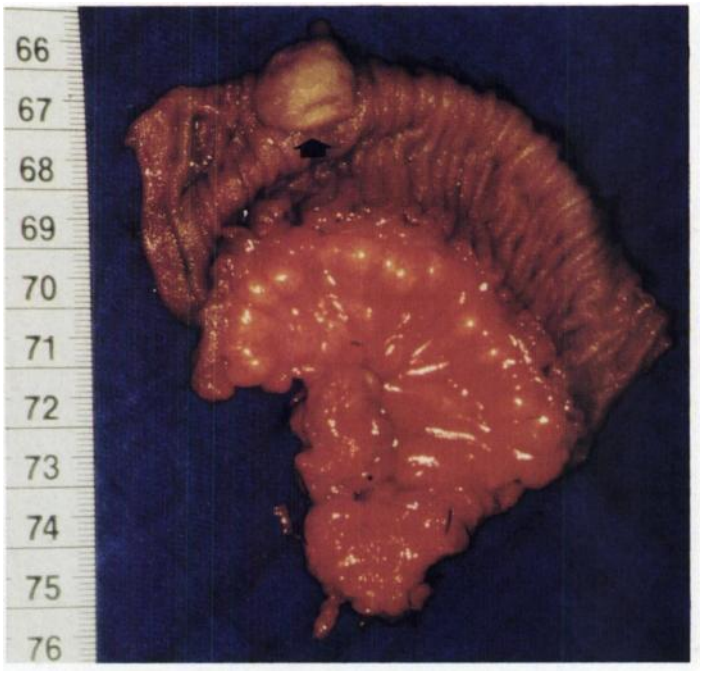

FIGURE 2. Carcinoid of the small bowel (primary tumor; see Fig. 1) identified by intraoperative radiodetection using the Tec Probe 2000 (not palpated by the surgeon).

TABLE 3
Medullary Thyroid Carcinoma: Number of True-Positive Lesions Detected by Conventional Modalities, Double-Nuclide Scintigraphy, Standard Surgical Exploration and Intraoperative Gamma Probe Localization

	Neck	Mediastinum	Σ
Palpation	12/19	6/11	18/30
CD	6/19	9/11	15/30
DNS	11/19	9/11	20/30
Probe	17/19	10/11	27/30

CD = conventional diagnostics (CT, sonography); DNS = double-nuclide scintigraphy.

TABLE 4
Medullary Thyroid Carcinoma: Intraoperative Measurement of Tissue Radioactivity 4 and 24 Hours After Administration of Technetium-99m-V-Dimercaptosuccinic Acid/[Indium-111-DTPA-D-Phe^1]Pentetreotide

Tissue	Range (cps)	Mean (cps)
Lymph node metastases	650–1600/300–1100	1100/950
Heart/vessels	100–250/200–300	171/226
Lung	50–150/100–250	85/152

accumulation imaging in 10 patients with recurrent MTC. CT scan and sonography visualized only 6 of 19 lymph node metastases in the cervical region and 9 of 11 lesions in the mediastinum (Table 3). Seven lesions were localized with [^{111}In-DTPA-D-Phe^1]pentetreotide (Fig. 3A), whereas 13 of 20 lesions were detected only with ^{99m}Tc(V)-DMSA (Fig. 3B, C). In the patient with multiple endocrine neoplasia Type II syndrome, somatostatin receptor scintigraphy localized a histologically proven pheochromocytoma of the right adrenal gland.

In Vitro/In Vivo Tumor Localization and Follow-Up. Intraoperative gamma probe counting using Tec Probe 2000 is limited to one energy window, and, therefore, only one radionuclide can be measured at a time. Thus, double-nuclide scintigraphy is able to select the optimal radiopharmaceutical localizing the highest number of lesions suspicious for MTC (showing the highest tumor uptake). Intraoperative measurements of counting rates, obtained from lymph node metastases and normal organs, are listed in Table 4. In comparison to the tumor-to-nontumor ratios obtained from GEP tumors, in most cases ratios higher than 4:1 were observed for intraoperative probe counting. All tissues with fewer than 20 cps were considered tumor negative. In vitro measurements of lymph node metastases revealed ratios between 30:1 and 126:1 (^{99m}Tc(V)-DMSA) and between 10:1 and 45:1 using [^{111}In-DTPA-D-Phe^1]pentetreotide.

Surgical palpation identified 18 of 30 lesions preoperatively visualized by double-nuclide imaging. Intraoperative radiodetection using the Tec Probe 2000 localized 30 lesions. Histologically, 27 of 30 (90%) suspected lesions were true positive for lymph node metastases, whereas 3 of 30 (10%) suspicious hot spots (^{99m}Tc(V)-DMSA positive, n = 2; [^{111}In-DTPA-D-Phe^1]-pentetreotide positive, n = 1) showed lymphadenitis (after radiotherapy). The size of the false-positive lesions was 6 mm in diameter. The smallest true-positive cervical lesion identified by the handheld probe (not palpated by the surgeon) was a lymph node metastasis (5 mm in diameter), whereas the smallest mediastinal lymph node metastasis was 8 mm in diameter. In 6 patients, there was a complete (calcitonin after pentagastrin stimulation and CEA levels negative at 1 yr follow-up), and in 3 other cases, there was nearly complete resection of metastases of MTC (partial remission). In 1 case, there were multiple small pulmonary metastases found intraoperatively, and no resection was performed.

DISCUSSION

Tumors of the GEP system and MTCs are rare and slowly growing neuroendocrine tumors. GEP tumors frequently metastasize to regional lymph nodes and the liver. The clinical signs and symptoms in the advanced stage are due to the tumor progress. A complete work-up, including transabdominal ultrasound, CT and angiography, frequently yields no positive evidence of localized tumors in these patients (*17–20*). In agreement with previous reports, our study of preoperative somatostatin receptor imaging demonstrated superior sensitivity to localize small GEP tumor sites (inclusive SPECT imaging) in patients for whom surgery is indicated but in whom no tumor localization can be found by radiological modalities (*6,21–23*). A particular advantage of somatostatin receptor scintigraphy in contrast to conventional diagnostic procedures is the fact that it images the body as a whole. Insulinomas are not palpable at the time of surgery in up to 20% of patients, whereas gastrinomas are not found during surgery in up to 40% of patients. To improve intraoperative tumor localization, Norton et al. (*24*) reported that in five patients with islet cell tumors surgical management was changed by intraoperative ultrasound. Small endocrine tumors (0.2–0.6 cm) in the duodenum have a greater

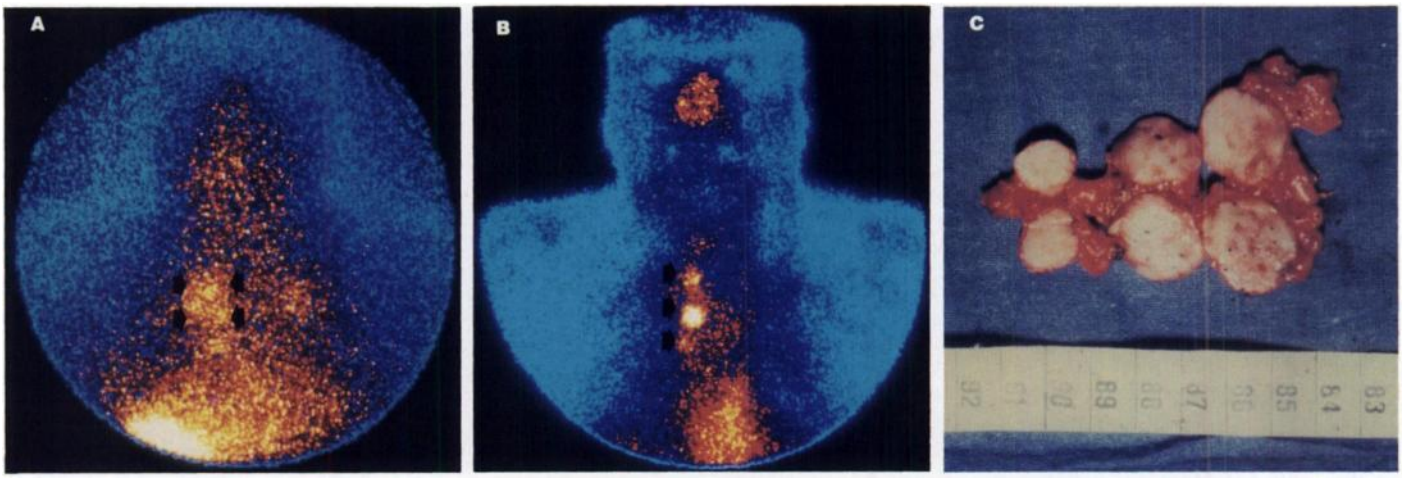

FIGURE 3. Anterior planar [^{111}In-DTPA-D-Phe^1]pentetreotide (A) and ^{99m}Tc(V)-DMSA (B) double-nuclide scintigraphy (4-hr postinjection) of a patient with MTC metastases identified by intraoperative radiodetection using the Tec Probe 2000 (C) and not palpated by the surgeon. Arrows indicates the sites of tumor).

likelihood of not being imaged by intraoperative ultrasound because of the mixed (gas–liquid–solid) background of the bowel (*25*). Furthermore, discrimination between reactive enlargement of lymph nodes and tumor-infiltrated nodes on morphologic criteria may be problematic.

Radioimmunoguided surgery systems (e.g., Neoprobe 1000; Neoprobe Corp., Columbus, OH) in which a tumor-to-background ratio of 1.5:1 or more is considered significant have been used extensively for the intraoperative localization of radiolabeled antibodies and led to the identification of tumor sites otherwise not detected by visual inspection or palpation (*11*).

The successful detection of primary tumors and metastases using a handheld gamma probe is dependent on both the biodistribution of the radiopharmaceutical and the physical properties of the labeling radionuclide. However, using radionuclides with low energy (e.g., ^{125}I), preoperative external scintigraphy is not possible (*26*). The use of high-energy radionuclides such as ^{131}I also places a requirement on increased shielding around the detector element, making the gamma probe heavy and bulky, thereby reducing its acceptability to the surgeon (*11*). In contrast, isotopes such as ^{99m}Tc or ^{111}In are preferable because they are readily available and have excellent physical properties for external and intraoperative imaging.

Schirmer et al. (*15*) were successful in intraoperative radiodetection of occult neuroendocrine tumors using [^{125}I-Tyr^3]octreotide. Intraoperative peptide-receptor detection with [^{111}In-DTPA-D-Phe^1]pentetreotide has potential advantages compared to [^{123}I-Tyr^3]/[^{125}I-Tyr^3]octreotide. The predominant hepatobiliary excretion of [^{123}I-Tyr^3]- or [^{125}I-Tyr^3]octreotide leads to a considerable amount of intestinal activity, reducing the reliability of somatostatin receptor scintigraphy in GEP tumors (*6*). The intestinal clearance of Octreoscan for intraoperative gamma probe counting can easily be overcome by the administration of laxatives. Images at 24 hr postinjection provide a better image quality due to an improved tumor-to-background ratio and, in our experience, this is the optimal time for intraoperative tumor detection. In our study, intraoperative measurements with the gamma probe revealed tumor-to-nontumor ratios in most cases more than 4:1, because substances with a low molecular weight (e.g., [^{111}In-DTPA-D-Phe^1] pentetreotide) are rapidly cleared, predominantly by the kidneys (*27*). In vitro measurements (gamma counter) of the resected tumor tissues confirmed our high tumor-to-nontumor ratios obtained from intraoperative probe counting. Lower tumor-to-nontumor ratios (1.5:1) obtained from intraoperative measurements using antibodies are caused by the fact that the mass of the antibody administered has an effect on the disappearance from the blood, where they disappear with a half-life of 26–38 hr (*28–30*). As our results show, an additional 36% of somatostatin receptor-positive lymph node metastases could be detected by intraoperative probe counting compared with those detected by preoperative receptor imaging. In the follow-up, eight patients are still in complete remission (at 2 yr), and three patients (at 1 yr) with bulky tumors benefit in terms of symptomatic improvement after tumor mass reduction.

Somatostatin receptor scintigraphy is also considered to localize recurrent disease and metastases of MTC in about 65% of patients; endogenous production of somatostatin by some of the human MTCs might hamper the in vivo detection of somatostatin receptors (*31*).

Ohta et al. (*32*) postulated that pentavalent DMSA resembles the phosphate ion and that this is the mechanism by which ^{99m}Tc(V)-DMSA accumulates in tumors, particularly in MTC in which calcification is a well-recognized phenomenon (*33*). Using ^{99m}Tc(V)-DMSA for metabolic imaging, Reiners (*34*) reported an overall sensitivity of 62% in 62 patients with MTC. To increase the sensitivity of detection of more metastases of MTC, we conducted a new approach using the two radiopharmaceuticals in a double-nuclide scintigraphy. Our results demonstrate that double-nuclide scintigraphy was able to localize more (17%) true-positive lesions of MTC than conventional imaging modalities. Neither ^{99m}Tc(V)-DMSA nor [^{111}In-DTPA-D-Phe^1]pentetreotide is completely specific for MTC, as 3 of 30 lesions (10%) were observed in inflammatory tissue in the cervical compartment after radiation therapy. Somatostatin receptor scintigraphy only demonstrates some tumor sites and cannot localize small tumor lesions (<1 cm) (*35*). Using the handheld gamma probe, we were able to localize more and smaller (≤5 mm) metastases of MTC than conventional imaging modalities, surgical palpation and somatostatin receptor scintigraphy. This new operative approach may improve the survival of these patients, because the prognosis of thyroid cancer depends on tumor size, invasion of vessels by the tumor, grade of differentiation, tumor stage, metastases and radicality of the operation (*36*).

Other working groups demonstrated in 45 patients with recurrent disease of colorectal cancer that RIGS detected more tissue involved in disease process [184 RIGS-positive sites (4.1 sites/patient)] than traditional exploration [116 sites (2.6 sites/patient)] (*37*).

These results show that RIGS assessment is a highly sensitive method for detecting occult tumor deposits and may guide therapeutic intervention in patients with colorectal carcinoma (*38*).

CONCLUSION

In summary, this preliminary study shows the feasibility of intraoperative detection of endocrine tumors using [^{111}In-DTPA-D-Phe^1]pentetreotide or ^{99m}Tc(V)-DMSA when conventional methods fail. Double-nuclide scintigraphy is able to select the optimal radiopharmaceutical to localize the highest number of lesions suspicious for MTC (showing the highest tumor uptake). With small molecules such as [^{111}In-DTPA-D-Phe^1]pentetreotide or ^{99m}Tc(V)-DMSA, higher tumor-to-nontumor ratios can be obtained than with antibodies. Compared with other radiopharmaceuticals labeled with, e.g., ^{125}I or ^{131}I, ^{111}In- and ^{99m}Tc-labeled substances have excellent imaging properties and less abdominal interference. The detection of microscopic and occult disease with intraoperative probe counting may guide therapeutic intervention in patients with neuroendocrine tumors.

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Fluorine-18-Fluorodeoxyglucose and Carbon-11-Methionine Evaluation of Lymphadenopathy in Sarcoidosis

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Uptake of ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-methionine (Met) in mediastinum and hilar lymph nodes was studied using PET in 31 patients with sarcoidosis. The aim of our study was to examine whether these different tracers play a differential role in clinical assessment of pulmonary involvement. **Methods:** Fluorine-18-fluorodeoxyglucose and ^{11}C-Met PET were administered on different days. The differential absorption ratio of these tracers was calculated for the region of interest with the highest level of activity. Clinical reassessment of sarcoidosis was made at least 1 yr after the first PET examination. In seven patients whose lymph nodes still remained visible by other imagings at the time of reevaluation, the same PET study was performed again. **Results:** Both FDG and Met were accumulated in the lymph nodes in all but one patient. The FDG and Met uptake ratios in all patients were not correlated, but they could be divided into the FDG-dominant group (FDG/Met uptake ratio $\geq$ 2) and the Met-dominant group (FDG/Met uptake ratio $<$ 2). Within each group, the FDG and Met uptake values were correlated. The rate of improvement assessed by clinical status and chest radiographs was considerably higher in the FDG- (78%) than in the Met-dominant group (33%). In the seven patients of the repeated PET examination, their FDG/Met uptake ratios were generally unchanged after 1 yr. **Conclusion:** The results suggest that the FDG/Met uptake ratio using PET may reflect the differential granulomatous status in sarcoidosis and be a useful tool for pretreatment evaluation.

Key Words: PET; fluorine-18-fluorodeoxyglucose; carbon-11-methionine; sarcoidosis; mediastinum-bilateral lymphadenopathy

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PET provides greater spatial resolution and quantitative analysis than other imaging techniques and may provide biophysiological and biochemical information superimposed on the anatomical topography. Fluorine-18-fluorodeoxyglucose (FDG) and L-methyl-^{11}C-methionine (Met) are widely applied tumor-seeking agents used together with PET, and they appear useful for assessing the biological behavior of malignant tumors (*1–5*). The mechanism of accumulating FDG into malignant tissue is due to its enhanced glucose metabolism. A high rate of glycolysis is a biochemical feature of malignant tissue. FDG is transported, phosphorylated and metabolically trapped intracellularly because it cannot be metabolized further and cannot

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