European Journal of
Nuclear
Medicine

Short communication

Intraoperative detection of pheochromocytoma with iodine-125 labelled *meta*-iodobenzylguanidine: a feasibility study

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Received 28 January 1993

Abstract. We evaluated the feasibility of intraoperative detection of pheochromocytoma sites after injection of *meta*-iodobenzylguanidine labelled with iodine-125. Six patients with multiple or recurrent pheochromocytoma were injected for intraoperative detection. During surgery, all count rates were recorded using a CdTe detector diode. Tumour foci were found in all cases. Tumour count rates ranged from 50 to 1000 counts per second (mean $\approx$400). Blood activity, used as a reference level, ranged from 10 to 50 counts per second (mean $\approx$35). In all patients, the intraoperative probe was helpful to the surgeon and facilitated the discovery of the pathological foci even when they were small ($\leq$1 cm). Complete resection under probe control was correlated with postoperative normalization of urinary normetanephrine excretion. The use of a probe designed to detect low-energy gamma-ray radionuclides bound to a highly specific molecule provides an accurate detection tool which is well adapted for ectopic localizations and for small foci.

Key words: Intraoperative detection – Pheochromocytoma – *meta*-Iodobenzylguanidine – Iodine 125 – Semiconductor detector

Eur J Nucl Med (1993) 20:426–430

Introduction

Radio-iodinated *meta*-iodobenzylguanidine (mIBG) has been used for imaging pheochromocytoma and for therapy in patients with the malignant form of the disease [1]. Surgery is the most effective therapeutic procedure for pheochromocytoma and aims at removing all neoplastic tissue. Peroperative probes are useful for the localization of a number of tumours such as osteoid osteoma using a bone-specific tracer labelled with technetium-99m [2–4], tumours of various origins using radiolabelled antibodies [5–7], thyroid carcinoma using radioiodine [8] and neuroendocrine tumours including pheochromocytoma using mIBG [9–11]. The use of these probes appears to be particularly helpful in patients with ectopic or unusual localizations, and in cases of reoperation. This prompted us to combine the use of radiolabelled mIBG and surgery for the treatment of pheochromocytoma in patients with significant mIBG tumour uptake. In this report, we describe our experience in six consecutive patients.

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Materials and methods

Detection probe and radioelement selection

The detection device used in this study is the "Gammed 2" provided by CIS Bio-International (Gif-sur-Yvette, France). The probe consists of a cylinder measuring 2 cm in diameter and 10 cm in length (Fig. 1) and uses a CdTe diode ($5 \times 5 \times 1.2$ mm) as a detector. This diode detector has been miniaturized because of its high density ($\rho = 6.06$ g cm^{-1}) and high mean atomic number (Z = 50). The probe is connected to an electronic unit providing both visual (Liquid Cristal Display and ratemeter) and audible indication of the counting rate.

Three iodine isotopes can be used for mIBG labelling (Table 1) and the clinical use of each isotope must take into account its physical characteristics. Thus, iodine-123 is only used for diagnosis, whereas iodine-131 is used for both diagnosis and therapy. For intraoperative detection, accurate localization is mainly dependent on spatial resolution, on the sensitivity of the probe and on the type and energy of the detected particles. So, the best results should be obtained with a non-penetrating β emission or with low-energy X- or gamma rays, but due to state-of-the-art probe technology, the detection of β emission is difficult and only the detection of low-energy X- or gamma rays is possible. Moreover an uncollimated probe would be easier to handle for the surgeon. This led to

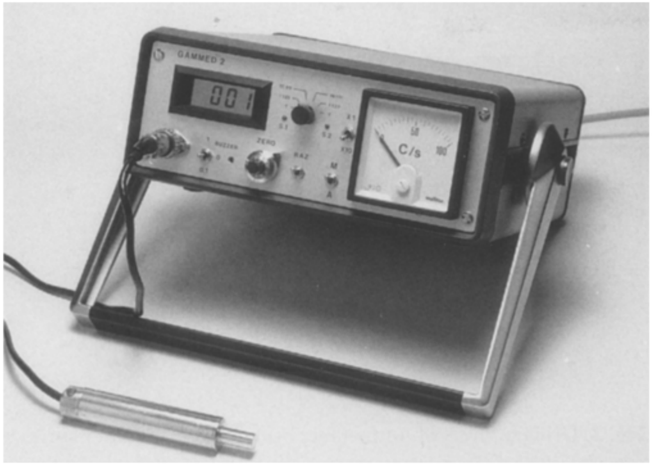

Fig. 1. CdTe probe with electronics counting unit, providing both visual and audible indication of the number of counts being detected

Table 1. Characteristics of main X- and gamma rays for ^{123}I, ^{125}I and ^{131}I

Isotope	Half-life	X- or gamma energy (keV)	% of emission
Iodine-123	13.2 h	159	83.3
Iodine-125	59.9 days	27.2	39.6
		27.4	73.8
		30.9	21.3
		31.7	4.3
		35.5	6.7
Iodine-131	8 days	364.5	81.6

the use of iodine-125, which presented an "effective dose equivalent" equal to 3.7 10^{-2} and 1.2 10^{-2} mSv MBq^{-1}, respectively, in the case of a 5-year-old child and an adult with suppressed thyroid uptake [12]. With ^{125}I, the probe showed, in air at 10 mm of a point source, an efficiency of ≈20 counts per second per kBq (cts s^{-1} kBq^{-1}) and a resolution index of 8 mm. The resolution index corresponds to the full width at half maximum of a point spread function measured by probe scanning in front of the point source.

Clinical procedure

A scintigraphic examination was performed preoperatively with mIBG labelled with ^{123}I for the localization of tumour foci. Single photon emission computed tomography (SPET) examinations (Starcam 500A, General Electric, Milwaukee, USA) were also carried out when necessary for precise spatial localization, and data were superimposed with those of computed tomography (CT) scans (Exel 2400, Elscint, Haifa, Israel). To ensure that the slices were obtained at the same level, skin marks or internal structures like bones were used [13] to determine the precise sites of uptake. Thereafter, 48 h before surgery, mIBG labelled with ^{125}I was injected for intraoperative detection after suppression of thyroid uptake by the administration of Lugol's solution. Initially, 37 MBq (1 mCi) of ^{125}I was injected (Table 2). As the probe is highly sensitive, a lower amount of radioactivity (3.7 MBq–0.1 mCi) could be injected in patients 2 and 3 and only 740 kBq (20 μCi) was injected in patient 1.

During surgery, tumour counting rates were noted before and after excision. The reference level of activity was measured in blood from large vessels because this varied less between patients than did activity in surrounding tissues.

Urinary excretion of metanephrines was measured before surgery and 90 days after surgery [14].

Patients

Case 1. A 42-year-old female patient with hypertensive crisis. Urinary excretion of normetanephrine was elevated. A mIBG scintigraphy showed high uptake in the right adrenal region corresponding to a mass of 5 cm in diameter on CT scan.

Case 2. A 14-year-old boy, who had been submitted to surgery for a right pheochromocytoma 2 years previously, complained of hypertensive crisis and had stopped growing. Urinary excretion of normetanephrine was elevated. A mIBG scan showed high uptake in the left adrenal region corresponding to a mass of 1.1 cm in diameter on CT scan.

Case 3. A 17-year-old man with von Hipple-Lindau disease who had undergone surgery for a left pheochromocytoma 3 years ear-

Table 2. Counting rates and ratios obtained with CdTe diode after injection of mIBG labelled with ^{125}I

Patient no.	Injected activity MBq (mCi)	Counting rates				Ratio (before/after)
		Days before surgery	Blood background (cts s^{-1})	Before excision (cts s^{-1})	After excision (cts s^{-1})	
1	≈0.74 (0.02)	3	10	≈40	10	≈4
2	3.7 (0.1)	2	40	150	10	15
3	3.7 (0.1)	3	10	50	5	10
4	37 (1)	2	50	Focus 1: 500	Focus 1: 50	10
				Focus 2: 500	Focus 2: 100	5
5	37 (1)	2	40	>1000	40	>25
6	18.5 (0.5)	2	50	500	50	10

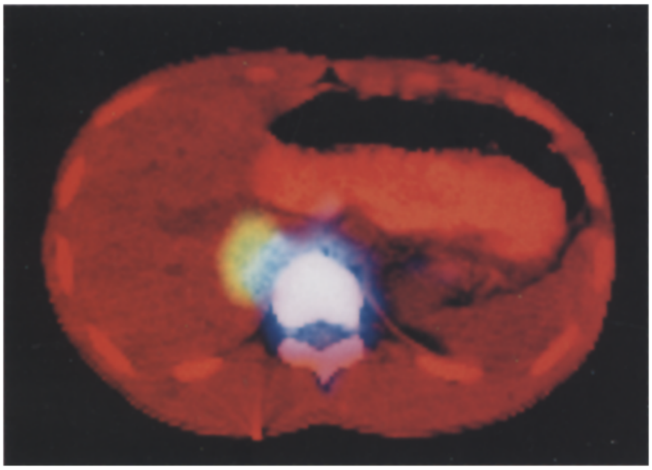

Fig. 2. Digital superimposition of CT scan (*red*) and SPET images (*green* for ^{123}I-mIBG and *blue* for bone tracer labelled with ^{99m}Tc). The lesion posterior to the vena cava is clearly demonstrated and appears in *yellow*, due to the superimposition of red and green images

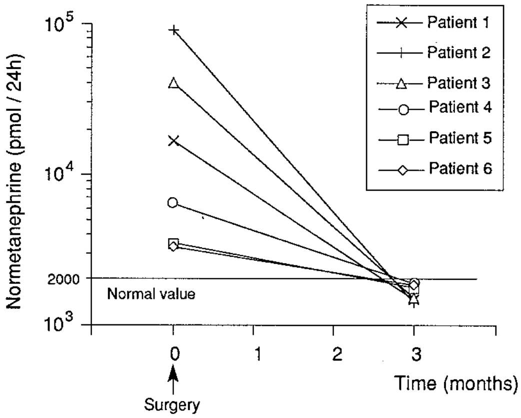

Fig. 3. Urinary levels of normetanephrine before and after surgery

lier. Urinary excretion of normetanephrine was elevated. A mIBG scan showed uptake in the right adrenal region corresponding to a mass of 3 cm in diameter on CT scan.

Case 4. An 18-year-old man who had already undergone surgery on two occasions for a right pheochromocytoma, 3 and 2 years before the study. Urinary excretion of normetanephrine was elevated. A mIBG scan showed two foci, one located in the left adrenal region, corresponding on CT scan to a lesion of 1.2 cm in diameter, and one in the right paravertebral region. The latter lesion was not visualized on CT scan and appeared to be located behind the vena cava ($\leq$1 cm in diameter), in front of the right diaphragm pillar, when CT and SPET images were superimposed (Fig. 2).

Case 5. A 22-year-old woman with MEN IIB who had undergone resection 9 years earlier for a left pheochromocytoma and 3 years earlier for a right pheochromocytoma with partial excision of the right adrenal gland. Urinary excretion of normetanephrine was elevated and mIBG scan showed upake in the right adrenal region corresponding to a mass of 1 cm in diameter on CT scan.

Case 6. A 19-year-old man who had undergone surgery for a left pheochromocytoma 10 years earlier and for a left relapse 2 years before the study. He had also undergone resection for a right pheocromocytoma 5 years before the study and a partial adrenalectomy was then performed. Urinary excretion of normetanephrine was elevated. A mIBG scan showed uptake in the left adrenal region, but CT scan interpretation was difficult due to the presence of surgical clips.

Results

Table 2 shows the counting rates, in counts per second (cts s^{-1}), obtained with the CdTe detector. Detection was always performed with a high count rate, avoiding statistical problems. In addition the ratios between the count rates before excision and after excision were always greater or equal to 4, even for patient 4, who received a low amount of radioactivity.

The practical interest of the peroperative probe is extremely dependent on the patient's history:

Patients 1, 2 and 3. These three patients presented with a typical pheochromocytoma. The adrenal mass was evident and the detection probe confirmed elevated activity in the adrenal area. Excision was easy and its completeness was checked peroperatively by the probe. Histological examination confirmed the diagnosis of pheochromocytoma. Postoperatively, biological (Fig. 3) and scintigraphic findings normalized in all patients.

Patients 4, 5 and 6. These three patients had undergone surgery on several occasions before the study. These repeated surgical procedures caused local sclerosis, and the presence of surgical clips impeded precise morphological examinations with CT scan or magnetic resonance imaging. In these three patients, the peroperative use of the probe greatly helped the surgeon. In patient 4, due to its ectopic localization, the right neoplastic focus was not palpable during surgery and only the probe permitted its finding. In cases 5 and 6, tumour foci were surrounded by fibrosis due to previous surgery, making the dissection difficult, and the probe was necessary for the surgeon to localize precisely the tumour foci and to check the completeness of the resection. Histological examination confirmed pheochromocytoma. In these three cases, biological and scintigraphic findings normalized after surgery (Fig. 3).

Discussion

Curative treatment of primary and metastatic pheochromocytoma is based on surgery. Most pheochromocytomas (>90%) show high mIBG uptake [15]. The patients included in this study showed abdominal sites of mIBG uptake on the preoperative scintigraphy, which prompted CT scan and SPET image superimposition. This technique proved to be useful during second-look procedures when small lesions were difficult to visualize on the CT scan in the absence of functional information.

In the three patients who had undergone previous surgery, the intraoperative probe was helpful to the surgeon and permitted the discovery of pathological foci even when they were small (≤ 1 cm) and impalpable. The probe was particularly useful in the patient in whom the lesion had an ectopic localization posterior to the vena cava, behind the liver, but it was also of value in two patients in whom neoplastic foci were surrounded by intense fibrosis.

Our findings are consistent with previous small series [10] in which 18.5 MBq (500 μCi) of ^{125}I-mIBG was administered 3 days before surgery. Five cases of radioguided surgery in pheochromocytoma have been reported, including one case with bone metastases. Two patients did not show significant mIBG uptake preoperatively but the tumour was found in one of them with the use of the probe during surgery. Also, in a patient with pulmonary metastases, the peroperative probe proved to be useful after injection of mIBG labelled with ^{123}I [9].

^{125}I allows good differentiation between normal and pathological tissue owing to its physical properties and high counting rates. Ratios between the counting rates before and after surgery were significant in all cases. However, the counting rate for a given patient is essentially a function of tumour uptake. The signal-to-noise ratio is affected by the metabolism of mIBG, which is physiologically concentrated by some normal tissues such as the liver. This was noticeable in patient 4, who had two foci, one located in the left adrenal area with low background activity and the other adjacent to the right liver which showed non-specific mIBG uptake. This explains why the counting rates were different after tumour excision.

Blood background activity is also closely related to the individual metabolism. It is therefore very important to inject radiolabelled mIBG at least 2 or 3 days before surgery in order to increase the contrast between tumour and blood or adjacent normal tissues such as a healthy liver.

An appropriate amount of activity is injected so that conditions for detection are good while exposure is kept as low as reasonably achievable [16]. Internal contamination is the main risk for surgical staff as external exposure is low due to the low-energy gamma radionuclide. Surgical staff can avoid contact with the radioactive source by taking precautions such as wearing gloves and mask. Consequently the annual limit of intake, namely 2×10^6 Bq (same value as for ^{125}I and ^{131}I), is not exceeded [17]. Moreover no probe contamination was observed during surgery when the probe was removed from the surgical field.

To conclude: Positive tumour tracers such as mIBG have demonstrated their interest as major modalities for pre- and postoperative imaging of patients. When functional criteria are added, intraoperative probes help the surgeon to identify neoplastic tissue and verify that resection is complete, at least scintigraphically. The hypothesis that all tumour foci concentrate the tracer seemed acceptable in this study. Our study has demonstrated the feasibility of using mIBG labelled with ^{125}I and a miniaturized CdTe probe for reoperation procedures in pheochromocytoma. We are now extending the use of this method to the surgical treatment of neuroblastoma.

Acknowledgements. The authors thank Dr. Bernard Aubert, Department of Medical Physics, Institut Gustave-Roussy, Villejuif, France, for constructive discussions and comments, and Dr. Raymond Regal, Centre de Recherche Nucléaire, Laboratoire Phase, Strasbourg, France, for suggestions and excellent technical assistance. We are also grateful to Lorna Saint-Ange for her assistance in revising the manuscript.

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