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CHAPTER 12

Is there a Role for Radioguided Surgery with Iodine-labeled Metaiodobenzylguanidine in Resection of Neuroendocrine Tumors?

Leonie T. van Hulsteijn$^1$, Eleonora P.M. Corssmit$^1$, Bernies van der Hiel$^2$, Johannes W.A. Smit$^1$, Marcel P. Stokkel$^3$

$^1$Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, the Netherlands
$^2$Department of Nuclear Medicine, Leiden University Medical Center, Leiden, the Netherlands
$^3$Department of Nuclear Medicine, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

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Abstract

Background: The aim of this study was to systematically review literature, exploring the role of radioguided surgery with iodine-labeled metaiodobenzylguanidine (MIBG) in resection of neuroendocrine tumors.

Methods: PubMed, EMBASE, Web of Science, COCHRANE, CINAHL, Academic Search Premier, ScienceDirect and Wiley and references of key articles were searched to identify potentially relevant studies.

Results: Twenty studies were included. A total of 130 procedures in 120 patients were performed. Ninety percent of included studies concerned case reports or –series. It is described that radioguided surgery with iodine-labeled MIBG can improve the quality of macroscopic resection of neuroendocrine tumors in selected cases, i.e. in cases where the tumor is small, nonpalpable, difficult to visualize on conventional imaging studies, or located in an area with adhesional scar tissue from previous surgery. However, in a substantial number of cases the gamma probe failed due to technical problems.

Conclusions: Since there is limited evidence that radioguided surgery contributes substantially in resection of neuroendocrine tumors, we cannot advocate its use in general. However, we can conclude that it can seemingly improve the quality of resection in selected cases. When radioguided surgery is performed in neuroendocrine tumors, we advocate the use of I-125 to label MIBG.
Introduction

Neuroendocrine tumors (NETs) are rare, slow growing tumors, characterized by the expression of different peptides and biogenic amines.\(^1\) Although most NETs are asymptomatic in early stages, hypersecretion of these peptides, amines or their metabolic byproducts can cause various clinical symptoms, e.g. flushing and secretory diarrhea due to hypersecretion of serotonin.\(^2\)-\(^3\) Surgical removal is the treatment of choice to lengthen survival and bring relief from hyperfunctional status.\(^4\) However, NETs may be difficult to localize, especially in the early stages.

Recently, radioguided surgery (RGS) with iodine-labeled metaiodobenzylguanidine was successfully utilized in our centre for resection of two 5 mm left para-aortic ganglioneuromas, which, because of their small size, would probably have been difficult to localize otherwise.\(^5\) Metaiodobenzylguanidine (MIBG) is a guanethidine analogue, which resembles norepinephrine. Therefore, it is taken up by and stored in sympatho-adrenergic tissue of NETs(6). MIBG can be labeled with iodine isotopes (I-123, I-125 or I-131) at the benzoic ring of this tracer. Radioactive MIBG is commonly used in imaging studies to identify NETs. However, it can also be used in radioguided surgery (RGS) of these tumors, in which a hand-held gamma probe is used to detect in situ tumor binding of radioactive MIBG.

To date, no systematic review has been published giving an overview of the contribution of RGS in resection of NETs. Therefore, the aim of the present systematic review was to assess the role of RGS with iodine-labeled MIBG in resection of neuroendocrine tumors.

Materials and Methods

Eligibility criteria

Original manuscripts describing surgical procedures for (metastatic) NETs in which RGS with iodine-labeled MIBG was used, were eligible for inclusion. Comments and editorials were excluded.

Eligible studies were restricted to languages familiar to the author (English, French, German and Dutch). Furthermore, in case of multiple studies describing the same cohort of patients, only the study which comprised the highest number of subjects was included for this review.

Search strategy

In July 2011, PubMed, EMBASE, Web of Science, COCHRANE, CINAHL, Academic Search Premier, ScienceDirect and Wiley were searched to identify potentially relevant studies (see Table 1). References of key articles were assessed for additional relevant articles.
Table 1: Search strategy

| (radioguided surgery OR radiosurgery OR radiosurg* OR "Radiosurgery"[mesh] OR RGS OR 
| "gamma probe" OR "gamma probes" OR (gamma[tw] AND (probe[tw] OR probes[tw]))) OR 
| radioguided OR radioguidance OR "radio-guided" OR radioguid* OR "intraoperative detection" 
| OR "intraoperative localization" OR "intraoperative localisation" OR "intra-operative detection" 
| OR "intra-operative localization" OR "intra-operative localisation" OR "intraoperative probe" OR 
| "intraoperative probes" OR "radioisotope guided" OR "radionuclide guided" OR "radio-isotope 
| guided" OR "radio- nuclide guided") AND (MIBG OR MIBG* OR radiolabeled MIBG OR 
| radiolabelled MIBG OR radiolabeled metaiodobenzylguanidine OR radiolabelled 
| metaiodobenzylguanidine OR "I 123 MIBG" OR "I 123 metaiodobenzylguanidine" OR "iodine 
| 123 MIBG" OR "iodine 123 metaiodobenzylguanidine" OR "iodine 125 
| metaiodobenzylguanidine" OR "iodine 125 MIBG" OR "metaiodobenzylguanidine" OR "MIBG 
| scintigraphy" OR "metaiodobenzylguanidine scintigraphy" OR "3-Iodobenzylguanidine"[Mesh]) |

Data extraction

All studies obtained from the search strategy were entered into reference manager software 
(Reference Manager version 12) and were screened on title and abstract. Potentially relevant 
studies were retrieved for detailed assessment.

For all included studies, the following data were extracted: first author and year of 
publication, type of NET, number of patients studied, contribution of the gamma probe to the 
surgical procedure, isotope used, site where the NET was localized and size of the NET.

Results

Search strategy and study selection

The initial search resulted in 133 unique records; 21 were selected for detailed assessment 
(Fig. 1). After detailed assessment, four articles were excluded for the following reasons: no 
original data (n=1) and cohort of patients already reported in other included studies (n=3). 
Three new articles were found in references of key articles, so a total of 20 studies were 
included in the present review.7-26 Of these 20 studies, 14 were written in English, 2 in 
German and 4 in French.
**Study characteristics**

Individual study characteristics are displayed in Table 2. Included studies were published from 1984 to 2011. Eighteen studies (90%) concerned case reports or – case series. A total of 130 procedures in 120 patients were performed.

Regarding type of NET in which RGS with iodine-labeled MIBG was performed, most studies\(^7-9,12-15,19-21,26\) concerned (metastases of) pheochromocytomas.\(^7-9,12-15,19-21,26\) Furthermore, 6 studies concerned ganglioneuromas/(ganglio)neuroblastomas,\(^10,14,16-18,25\) three metastases of carcinoid tumors\(^11,22,24\) and one a medullary thyroid carcinoma.\(^23\)

Concerning type of isotope, I-123 was used in 13 studies,\(^8,9,14-16,19-26\) I-125 in \(^4,11-13,17\) and I-131 in one.\(^7\) One study compared I-125 to I-123 in RGS for neuroblastoma.\(^18\) In one study, it was not reported which iodine radionuclide was used.\(^10\)
**Role of RGS with iodine-labeled MIBG in resection of NETs**

RGS contributed to the surgical decision making in resection of NETs in 93 of 130 procedures (72%). RGS was of use to the surgeon in several ways (see Table 2). First, it contributed in localizing the lesion, especially when the lesion was small and therefore not visible or palpable, or when it was embedded in an area with scarring due to previous surgery. It was also helpful in detecting lesions which were difficult to localize beforehand because of discrepancy between images made by conventional imaging techniques, i.e. computed tomography (CT) or magnetic resonance imaging (MRI), and radionuclide imaging techniques, e.g. MIBG or somatostatin receptor scintigraphy. Furthermore, using the gamma probe contributed in detecting lesions which were preoperatively not visualized at all: Proye *et al.*\(^{12}\) described a case in which the gamma probe identified 2 malignant pheochromocytoma deposits behind the inferior vena cava, which were preoperatively not visualized by I-131 MIBG scanning.

RGS also proved helpful in defining the extent of tumors and tumor limits. Subsequently, the resected area can be reduced: Spapen *et al.*\(^{9}\) used the gamma probe to detect a metastasis of a pheochromocytoma as small as 15 mm in the right hilum of the lung, allowing surgery to be limited to a right lower lobectomy. In addition, after excision of the tumor, the gamma probe could be used to check the tumor bed for completeness of resection, by the demonstration of counts that were down to normal-tissue levels. In 7 procedures, it was not reported whether the use of RGS had influenced surgical decision making.

Despite the positive results, some disadvantages in using RGS with iodine-labeled MIBG were reported. In 1 out of 7 surgical procedures for neuroblastoma described by Gruner *et al.*\(^{10}\) the gamma probe failed due to technical problems. Technical problems were also an issue in one of 19 surgical interventions for neuroblastoma, described by Huglo *et al.*\(^{17}\) and in 2 of 66 surgical procedures, also for neuroblastoma, described by Martelli *et al.*\(^{18}\) Furthermore, in the latter study, the MIBG uptake was insufficient to provide a positive signal in five cases and in four cases, the shape and diameter of the straight probe prevented detailed exploration of intervertebral foramina or interspaces. At last, several studies report MIBG detection as not contributory in cases where the tumor was large and thus complete removal was easy.\(^{18-19}\)
<table>
<thead>
<tr>
<th>Author</th>
<th>Type NET</th>
<th>Patients</th>
<th>Contribution</th>
<th>Isotope</th>
<th>Site</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasshauer</td>
<td>Metastases of pheochromocytoma</td>
<td>2</td>
<td>Localize lesions in area with scarring due to previous surgery ($n=2$)</td>
<td>I-131</td>
<td>Above right renal vein, between aorta and vena cava ($n=1$), 1 lesion between right renal vein and vena cava, 1 lesion in area of left adrenalectomy ($n=1$)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Lehnert</td>
<td>Metastases of pheochromocytoma</td>
<td>1</td>
<td>Detect lesion with discrepancy between images made by conventional- and radionuclide imaging techniques</td>
<td>I-123</td>
<td>1 lesion lower left abdomen, 1 lesion close to aortic wall</td>
<td>n.r.</td>
</tr>
<tr>
<td>Spapen</td>
<td>Metastasis of pheochromocytoma</td>
<td>1</td>
<td>Localize lesion and reduce resected area</td>
<td>I-123</td>
<td>Between right main bronchus and a pulmonary vein</td>
<td>15 mm</td>
</tr>
<tr>
<td>Gruner</td>
<td>Neuroblastoma</td>
<td>6 (7 procedures)</td>
<td>Contributed in 6 procedures: detect unrecognized lesions ($n=3$), confirm completeness of excision ($n=3$)</td>
<td>n.r.</td>
<td>Abdominal ($n=3$), abdominal/mediastinal with intervertebral foramen localization ($n=3$), suprarenal ($n=1$)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Carnaille</td>
<td>Metastases of carcinoid tumor</td>
<td>1</td>
<td>Confirm localization of lesions</td>
<td>I-125</td>
<td>Hepatic</td>
<td>n.r.</td>
</tr>
<tr>
<td>Poye</td>
<td>Pheochromocytoma</td>
<td>8</td>
<td>Localize two lesions not visualized on preoperative MIBG scanning ($n=1$), n.r. ($n=7$)</td>
<td>I-125</td>
<td>2 lesions in right adrenal bed, behind inferior vena cava ($n=1$), n.r. ($n=7$)</td>
<td>1 mm</td>
</tr>
<tr>
<td>Ricard</td>
<td>Multiple or recurrent pheochromocytoma</td>
<td>6</td>
<td>Confirm completeness of excision ($n=3$), localize ectopic nonpalpable lesion ($n=1$), localize lesion in area with scarring due to previous surgery ($n=2$)</td>
<td>I-125</td>
<td>Right adrenal region ($n=3$), left adrenal region ($n=2$), posterior to vena cava, behind liver ($n=1$)</td>
<td>Smallest lesions ≤ 1 cm</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Diagnosis</td>
<td>Procedure Count</td>
<td>Additional Details</td>
<td></td>
<td></td>
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<tr>
<td>Aslam</td>
<td>1996</td>
<td>Mature ganglioneuroma/Neuroblastoma</td>
<td>2</td>
<td>Localize lesion in area with scarring due to previous surgery (n=1), define extent of primary tumor and localize liver lesions (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams</td>
<td>1997</td>
<td>Metastasis of pheochromocytoma</td>
<td>1</td>
<td>Localize lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heij</td>
<td>1997</td>
<td>Recurrent neuroblastoma/ganglioneuroma/ganglioneuroblastoma</td>
<td>5 (6 procedures)</td>
<td>Correctly identify active neuroblastoma tissue seen on preoperative MIBG scan and scan tumor bed for residual activity after excision (n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huglo</td>
<td>1997</td>
<td>Neuroblastoma</td>
<td>19</td>
<td>Contributed in 13 cases: detect unrecognized lesions (n=3), define tumor limits (n=2), confirm completeness of excision (n=8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martelli</td>
<td>1998</td>
<td>Neuroblastoma</td>
<td>58 (66 procedures)</td>
<td>Contributed in 43 procedures: localize small and nonvisible/nonpalpable tumors (n=8), define tumor limits and extension to locoregional lymph nodes (n=33), explore interspaces/intervertebral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Tissue Type</td>
<td>Lesion Characteristics</td>
<td>Imaging Technique</td>
<td>Size (n)</td>
<td></td>
<td></td>
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<tr>
<td>--------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adams (2001)</td>
<td>Metastases of phaeochromocytoma</td>
<td>Foramina after excision of tumor (n=2)</td>
<td>I-123</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brunaud (2002)</td>
<td>Metastasis of phaeochromocytoma</td>
<td>Confirm lesions found by surgical palpation</td>
<td>I-123</td>
<td>Paravertebral subdiaphragmatic region (n=3) ≥ 2 cm (n=3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buhl (2002)</td>
<td>Metastases of phaeochromocytoma</td>
<td>Detect lesions with discrepancy between images made by conventional- and radionuclide imaging techniques</td>
<td>I-123</td>
<td>Behind vena cava 1 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shimotake (2005)</td>
<td>Recurrent medullary thyroid carcinoma</td>
<td>Detect lesion in area with scarring from previous surgery</td>
<td>I-123</td>
<td>Neck region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yüksel (2005)</td>
<td>Metastases of carcinoid tumor</td>
<td>Detect lesions with discrepancy between images made by conventional- and radionuclide imaging techniques</td>
<td>I-123</td>
<td>One para- and two pre-aortic lymph nodes 1.8 cm (para-aortic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wachowiak (2010)</td>
<td>Metastases of neuroblastoma</td>
<td>Localize lesion</td>
<td>I-123</td>
<td>2 cm cranially to aortic bifurcation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirkman (2011)</td>
<td>Recurrent phaeochromocytoma</td>
<td>Confirm completeness of excision of tumor in area with scarring due to previous surgery</td>
<td>I-123</td>
<td>Above junction of left renal vein, with vena cava extending posteriorly 2x1.5x1 cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NET = neuroendocrine tumor; n.r. = not reported
Discussion

The present review aimed to assess the role of RGS with iodine-labeled MIBG in resection of neuroendocrine tumors. The results indicate that RGS with iodine-labeled MIBG may be feasible in the resection of NETs in selected cases. However, the main limitation of this review is that 90% of included manuscripts concerned case reports or case series. This methodological limitation prohibits simple generalization of the results from the perspective of a review, since the two larger studies will skew all conclusions. More cohort studies are warranted to further evaluate the role of RGS in NETs.

The included manuscripts used I-123, I-125 or I-131 as radionuclides. The study with the I-131 labeled tracer was published in 1984. I-131 was the first radionuclide of iodine used in RGS and the principle gamma photon emission energy principally utilized is that of the 364 kiloelectron volts (keV) gamma photon. However, the highly energetic nature of these gamma photons increases background counts, secondary to scatter, and subsequently reduces tumor detection efficiency of the gamma probe. Secondly, the beta particulate emissions of I-131 contribute significantly to the absorbed dose of radiation to the patient and thus limit the amount of activity that can be administered.

The principle gamma photon radiation emissions for I-123 are 159 or 529 keV and are therefore characterized as medium- to high-energy emissions, while I-125 has a very low-energy emission of 35 keV. This low gamma photo emission energy, in combination with the high soft tissue attenuation of I-125, makes this radionuclide advantageous in gamma probe detection of tumor in RGS. This is demonstrated by Martelli et al., who compared the use of I-125 to I-123 to label MIBG in RGS for neuroblastoma. In this study, the sensitivity (positive probe detection/total tumor samples found by the pathologist) was equal for I-123 and I-125 (91% and 92%). However, the specificity (negative probe detection/total tumor-free samples) of I-125 was significantly higher than that of I-123 (85% and 55%). Furthermore, false-positive results were more frequent with I-123 than with I-125. This can be explained by the short half-life of I-123, which requires surgery to be performed 24 to 48 hours after injection, when the level of the normal tissue background is still high. As a matter of fact, the depth of the field is increased by the medium- to high-energy emission of I-123, which enlarges the investigated area, with an uncertain origin of signal. Therefore, using I-125 to label MIBG appears to have several advantages over using I-123.

Based on our own successful experience with radioguided surgery (RGS) with iodine-labeled MIBG in resection of two small ganglioneuromas, in this review, we sought to assess the role of RGS using radiolabeled MIBG as a tracer. Radiolabeled MIBG was the first radiopharmaceutical used for imaging and therapy of NETs, however, its sensitivity and specificity vary between different types of NETs. For detection of neuroblastoma and pheochromocytoma, radiolabeled MIBG scintigraphy has a sensitivity and specificity of more
than 90%, but in detecting other NETs a sensitivity of only 17-71% has been reported. Consequently, it seems most feasible to perform RGS using radiolabeled MIBG as a tracer in resection of adrenomedullary tumors.

Other tracers have been used for the detection of NETs. Somatostatin analogs are taken up by NETs expressing somatostatin receptors on their surface, such as gastroenteropancreatic tumors. Therefore radiolabeled somatostatin analogs, e.g. In-111 pentetreotide, are also routinely used for detecting NETs, although uptake is sometimes also visible in tumors other than NETs, granulomas and autoimmune disease. In-111 pentetreotide scintigraphy has a higher sensitivity than I-123 MIBG scintigraphy for detecting metastatic lesions in patients with carcinoid tumors, pancreatic islet cell tumors and medullary thyroid carcinomas, but a lower sensitivity for detecting malignant pheochromocytomas/paragangliomas. For that reason, it might be feasible to perform RGS with radiolabeled somatostatin analogs instead of radiolabeled MIBG in resection of NETs, other than adrenomedullary tumors. A few cases have already been described in which RGS with radiolabeled octreotide was successfully used for resection of the following NETs: bronchial carcinoids, head-and-neck paragangliomas, midgut carcinoids and an endocrine pancreatic tumor.

In recent years, the introduction of imaging techniques combining both anatomic and functional information, i.e. positron emission tomography/computed tomography (PET/CT) and single photon emission tomography/computed tomography (SPECT/CT), has led to a vast improvement in the detection of occult cancer and preoperative tumor localization. For PET studies, there are several highly specific radiopharmaceuticals available that reflect different metabolic pathways of NETs, e.g. F-18 fluorodeoxyglucose (FDG) in glucose metabolism, F-18 fluorodopamine (FDA) and F-18 3,4-Dihydroxy-6-fluoro-DL-phenylalanine (DOPA) in the uptake of hormone precursors and Ga-68 DOTA-TATE in the expression of somatostatin receptors. These new PET radiopharmaceuticals might make MIBG redundant in the future: several studies have reported a superior sensitivity of F-18 FDG, F-18 FDA, F-18 DOPA and Ga-68 DOTA-TATE compared to MIBG for the detection of NETs, especially those with a high proliferation index.

Although some promising results have been reported concerning radioguided surgery using an intraoperative PET probe for differentiated thyroid cancer, metastatic colon cancer, melanoma and recurrent ovarian cancer, its role in RGS for NETs has yet to be explored.

Conclusions

We conclude that data on the use of RGS with iodine-labeled MIBG in resection of neuroendocrine tumors are scarce; therefore we cannot advocate its use in general. However, in selected cases, RGS with radiolabeled MIBG does seem able to improve quality of resection; i.e. in cases where the tumor is small, nonpalpable, difficult to visualize on
conventional imaging studies, or located in an area with adhesional scar tissue. RGS using radiolabeled MIBG as tracer seems most feasible in resection of adrenomedullary tumors. We advocate the use of I-125 to label MIBG.
Reference List


