Radioguided surgery in neuroendocrine tumors. A review of the literature

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A B S T R A C T

Radioguided surgery can be a useful technique in the localization of neuroendocrine tumors. It detects more and smaller lesions compared to pre-surgical imaging and intraoperative digital palpation by the surgeon. It detects residual lesions and also indicates the shortest access route to the lesion. Nevertheless, its use has not become widespread because of technical difficulties. There is a limited number of published series, a lack of standardized protocol because of the great variability regarding type of radio-pharmaceutical, dose of radiotracer, timing between injection and surgery. In this paper, we review these issues, describing the experience of different authors in diverse tumors.

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Cirugía radioguiada de tumores neuroendocrinos. Revisión de la literatura

R E S U M E N

La cirugía radioguiada puede ser útil en la localización de tumores neuroendocrinos, detectando más lesiones y de menor tamaño que las pruebas de imagen prequirúrgicas y la palpación por el cirujano, detectando lesiones residuales e indicando una ruta más corta para acceder a la lesión. No obstante, su uso no se ha generalizado, ya que plantea dificultades técnicas, las series publicadas son limitadas, y no existe una uniformidad de criterios, debido a la gran variabilidad en cuanto al tipo de radiofármaco, dosis a emplear e intervalo entre la inyección del trazador y la cirugía. De estos aspectos nos ocupamos en esta revisión, describiendo la experiencia de distintos grupos, en los diversos tumores.

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Introduction

Radioguided surgery is based on the intraoperative localization of a tissue presenting activity by a radiotracer injected prior to the intervention. This radiotracer generally emits gamma radiation which is detected by a hand-held gamma probe. During surgery the lesion to be resected is the one presenting the greatest count compared to the surrounding tissues. Radioguided surgery is mainly used to detect the sentinel lymph node and is successfully carried out in a wide variety of tumors (melanoma, breast and other gynecological tumors, head and neck tumors, etc.). Indeed, its indications are still expanding. This procedure is used in surgery for hyperparathyroidism and in the localization of other tumors including neuroendocrine tumors (NET). It must be remembered that a learning curve is required for this technique, with the experience of the team being directly correlated with surgical success.

NET are a heterogeneous group of neoplasms which originate in the neuroendocrine cells and may derive from the neural crest (ganglioneuroma, neuroblastoma, paraganglioma), the endocrine glands (adenoma of the hypophysis, pheochromocytoma), islet cells (thyroid medullary carcinoma – TMC – the pancreas, Merckel-cutaneous cells) and the diffuse endocrine system (gastrointestinal, bronchopulmonary, thymic and urogenital).

Most NET overexpress somatostatin (SS) receptors, mainly types 2 and 5 (sstr2 and sstr5). Given the short half-life of SS (2 min) different somatostatin analogs (SSA) have been developed for the treatment of these tumors, including octreotide acetate (Sandostatin®), among others. This SSA has a half-life of approximately 1 h and is also more potent than native SS. On the other hand, at the end of the 1980s, Krenning et al. began to use a radiolabeled SSA (123I-Tyr3-octreotide) for scintigraphy in carcinoid tumors and other NET.

Other tracers were later developed with the same objective, 111In-DTPA-Phe-octreotide (111In-pentetreotide) being the most frequently used. Scintigraphy with radiolabeled SSA has a high sensitivity for localizing NET and may provide functional...
assessment of the disease. Moreover, it can add specificity and increase the confidence in the diagnosis of a visible lesion in other conventional imaging studies (CT, MR, ultrasonography). In addition to radiolabeled SSA, other tracers are used in daily clinical practice, such as 123I-metaiodobenzylguanidine (123I-MIBG) or PET tracers such as 18F-FDG. The latter is especially indicated in tumors with a high Ki67 proliferation index >15%. 

With regard to the approach to NET, this depends on the histopathology, the localization and the extension of the disease. In localized tumor disease surgical treatment is usually elective and in situations with advanced tumors or disseminated disease systemic treatments are used. The SSA, interferon, angiogenesis inhibitors, tyrosin–kinase inhibitors or protein kinase mTOR inhibitors are included among the systemic treatments. Treatment with SSA radio-labeled with 90Y and 177Lu is another alternative which is reserved for cases with metastatic disease in which prior treatments have failed.

Radioguided surgery may be incorporated in the surgical treatment of NET to facilitate detection and resection. Some authors have reported that the gamma probe can identify more lesions than manual examination by the surgeon. Adams et al. detected up to 57% of additional gastroenteropancreatic tumors (GEP) with this procedure compared to digital examination. The gamma probe can also identify smaller lesions than the preoperative images with SSA receptors. In this sense scintigraphy is particularly efficient in tumors larger than 1 cm, with a detection rate of 92%, falling to 38% in tumors which are smaller in size. Consequently, the gamma probe could be more efficient in lesions from 0.5 to 1 cm in size.

For planning radioguided surgery a whole body scintigraphy must be performed and, if possible, a SPECT or SPECT-CT study of the area of interest with the aim of assessing the uptake of the lesions to be surgically removed. SPECT-CT reportedly helps to plan the surgical approach and contributes to the success of radioguided surgery. In addition, several hours before the intervention a scintigraphic image is recommended after another injection of the tracer to verify adequate uptake by the lesion to be removed. Although intraoperative radioguided localization seems to be a useful technique to detect small tumors, establishing the shortest surgical route to approach a lesion or detect a residual tumor mass has not been generalized in radioguided surgery of NET.

This is due, in part, to the lack of standardization of the type of radiotracer and the dose and interval to be used between tracer injection and surgery. We will discuss these aspects in the present review, describing the experience of various groups in different tumors.

Radiotracers

The radiotracers most commonly used in radioguided surgery of NET are:

125I-Tyr3-octreotide

This radiotracer has been used for intraoperative detection of NET but it has the disadvantage of presenting elevated biliary excretion, making manual occlusion of the biliary duct necessary to avoid false positive results due to radiotracer accumulation. In theory, 125I is the most appropriate radionuclide for intraoperative procedures of superficial tumors due to its low energy and, thus, lesser influence of the radiation from deeper tissues. Martinez et al. reported good results with 125I-Tyr3-octreotide in neuroblastoma (sensitivity 100% and specificity 71%). Likewise, Schirmer et al. obtained good detection rates in the intraabdominal localization of GEP NET.

111In-DTPA-Phe1-octreotide

125I-Tyr3-octreotide was replaced by 111In-pentetreotide because of the several advantages which this radiotracer provides such as easy preparation, availability, appropriate half-life and less interference from physiological activity in the upper abdomen due to its predominantly urinary excretion. 111In-pentetreotide is currently widely used in scintigraphy for the study of NET and some authors have used it in radioguided surgery.

99mTc labeled somatostatin analogs

Tyr3-octreotide labeled with 99mTc (99mTc-Tricine-HYNIC-TOC) is a SSA which was developed by Béhé and Maecke, who demonstrated that this radiotracer has adequate clinical characteristics (elevated and specific affinity for receptors, good biodistribution, renal excretion, low radiation exposure), availability and cost-effectiveness. This tracer also provides high image quality and earlier diagnosis (images at 10 min to 4 h).

With the introduction of a coligand, EDDA, Decristoforo and Mather demonstrated greater uptake, more rapid renal excretion and less activity in blood, liver and small bowel. Gabriel et al. demonstrated that 2 whole body scintigraphy acquisitions with 99mTc-EDDA/HYNIC-TOC on the same day plus a SPECT have an overall sensitivity 80%, specificity 94.4% and precision 82.9% in patients with GEP tumors. With regard to radioguided surgery, the energy of 99mTc is more adequate than that of 111In for detection with gamma probes, and its short half-life allows the use of greater activity as well as less renal uptake.

Hubalewska-Dydejczyk et al. used another technetium SSA, 99mTc-EDDA/HYNIC-octreotate, with greater affinity than octreotide for ssTr2 and with a biodistribution similar to 111In-pentetreotide. This SSA has a higher lesion/healthy tissue ratio in the study of carcinoid tumors, detects more metastatic lesion and is effective in the staging, follow-up and determination of the state of the SS receptors of well-differentiated NET and in the localization of lesions not detected with other imaging techniques.

123I-Metaiodobenzylguanidine

Other types of NET, such as pheochromocytoma and neuroblastoma, are preferentially studied with MIBG. This tracer is structurally similar to that of norepinephrine and is the object of an active mechanism of amine uptake through the cellular membranes of the sympathetic-adrenergic tissues, being stored in granules of intracellular catecholamines. MIBG can be labeled with 131I, 125I or 123I, although the physical characteristics of the latter (gamma energy of 159 KeV and physical period of 132 h) make it preferable. Prior to its injection, it should be taken into account that some drugs may interfere with its uptake and should be previously withdrawn.

68Ga-somatostatin analogs

In a large group of patients with different NET, Baum et al. used a SSA labeled with 68Ga, DOTA-1-Nal3-octreotide (DOTANOC) and reported an elevated diagnostic precision in the detection of metastatic lesions with PET/CT. Gulec and Baum found that peptides labeled with 68Ga accumulated rapidly in tumors (80% in 30 min) and showed rapid renal clearance. With considerably low tissue concentrations they provide high contrast images and may, at the same time, be advantageously used in radioguided surgery. The protocol recommended by these authors for the use of 68Ga-DOTA-Tyr3-octreotide (DOTA-TOC) in the localization of tumors with positive SS receptors is as follows:
- Standard image. PET/CT 60–180 min after the iv injection of 185–555 MBq.
- Time for surgery. On another day, 1–3 h postinjection of 74 MBq.
- Preparation. Hydration of the patient.
- Detector probe. High energy, capacity to detect 511 KeV.
- Intraoperative use:
  - Measurement of sites of uptake/physiological accumulation.
  - Confirmation: tumor/background ratio (T/B) >1.5.

Factors affecting detection

The greatest limitation of intraoperative detection with the radiotracers mentioned is the elevated physiologic activity of the liver, spleen and kidneys thereby making its extremely important to avoid directing the gamma probe toward these organs. During the intervention wide, maleable retractors can be placed below the liver and spleen to diminish the background activity. Some authors use laxatives prior to surgery to reduce intestinal activity. To avoid the possible blockage of the receptors, Hodolic et al. withdrew the therapy with SSA 3 days before the intervention and 30 min prior to this they blocked thyroid and gastric uptake of free pertechnetate with perchlorate or lugol (since they used a technetium tracer). They also ensured good patient hydration and immediately before the intervention furosemide was administered to minimize urinary activity.

Different factors may affect lesion detectability when radiolabeled SSA are used. False negative results are obtained in:

- Tumors with low cellularity and low receptor density.
- Tumors with elevated SS production (pheochromocytoma, somatostatinoma, TMC).
- Tumors with receptor subtypes which do not recognize ligands such as octreotide.
- Tumors in areas with elevated background. For example, the localization of the tumor inside or close to organs such as the liver, spleen or kidneys, in the case of 111In-pentetreotide.
- Tumors localized inside the hematooencephalic barrier (due to its poor permeability for this ligand).

There are also false positive results, such as:

- Tumors localized inside a damaged hematooencephalic barrier (unspecific ligand entrapment).
- Other types of tumors, not derived from endocrine cells which express receptors for SS (mainly sstr2): tumors of the central nervous system, lymphoma, breast cancer, hepatocellular cancer, sarcoma and gastric carcinoma.
- Identification of receptor-positive non-tumoral tissue (activated lymphocytes, vessels and granulomas).

Hodolic et al. considered that the factors which affect detectability are: the grade of lesion uptake, the proximity of this to organs with elevated physiological tracer uptake and the experience of the surgeon in the management of the gamma probe. In contrast, the type of surgical reintervention or tumor size did not influence detectability. In this sense, Öhrvall et al. indicated that the accumulation of the radiotracer in the tumor depends on the size of the tumor, although they found no significant correlation between tumor size and radioactivity count since, according to these authors, uptake also depends on other factors such as the type and the density of the receptors, the specificity of the radiotracer and the proportion of non-tumoral tissue inside the lesion. Benjegard et al. studied different types of tumors and reported that the count ratio varied markedly with the type and localization of the tissue.

Tumor detection by this method theoretically depends on the minimum T/B ratio. One factor fundamentally influencing the obtainment of an adequate ratio is the interval between tracer injection and the surgery. The shorter the interval, the greater is the count in the lesion. In parallel, the concentration in normal tissues seems to diminish more quickly than in tumoral tissue and therefore a greater interval between the injection and the surgery improves the ratios. Nonetheless, the limitation imposed by the half-life of the isotope used should always be taken into account.

Radioguided surgery in neuroendocrine tumors

Pulmonary neuroendocrine tumors

Pulmonary NET comprise a wide spectrum of tumors with different aggressiveness: typical carcinoids (low grade), atypical carcinoids (intermediate grade), large cell neuroendocrine carcinoma and small cell carcinoma (both of high grade). Pulmonary carcinoid tumors are infrequent and constitute approximately 1–2% of pulmonary neoplasms, and their localization is usually perihilar.

111In-pentetreotide has shown to be of significant clinical value in the study of pulmonary carcinoids and their metastasis, which are occasionally not detected by conventional imaging techniques. Different authors therefore use this radiotracer for the diagnosis and follow up of these tumors. However, the uptake of this radiotracer is not specific in non-NET probably due to the presence of activated lymphocytes in the proximity of the tumor surface as well as in inflammatory processes. It is of note that 111In-pentetreotide plays an important role in the differential diagnosis of the hypersecretion of ACTH, distinguishing between pituitary adenomas and bronchial carcinoid tumors which secrete ACTH and, in the latter case, localizing the tumor responsible for ectopic secretion.

Several authors have performed radioguided surgery after the administration of 111In-pentetreotide. The procedure not only allows precise localization of the tumor but determines its total resection, and, in the case of residual lesion, completes the resection. It is therefore an easy and safe method for the management of bronchial carcinoid tumors which secrete ACTH and is useful in tumors detectable by scintigraphy, providing better results than conventional surgery regarding the level of resectability. For Porziella et al., this technique is able to precisely localize subcentimetric metastatic adenopathies detected in the presurgical scintigraphy as well as detect lymph node metastases not visualized in the previous scintigraphy due to their smaller size.

Different protocols describe the dose to inject, varying from 92.5 to 222 MBq and the interval between injection and surgery, from 24 h to 5 days (Table 1).

Gastroenteropancreatic neuroendocrine tumors

GEP NET are localized in the gastric mucosa, bowel, rectum or pancreas. The WHO classifies (2010) these tumors as neuroendocrine neoplasms G1 (low grade), G2 (intermediate grade) and G3 (high grade). The latter corresponds to poorly differentiated tumors while the first two include well-differentiated tumors which are more frequent.

Scintigraphy with radiolabeled SSA is a good option for the study of these tumors. Lambert et al. demonstrated both in vitro and scintigraphy that most pancreatic and carcinoid tumors have an elevated expression of SS receptors, sstr2 being the most frequently expressed in primary midgut tumors and their metastases. Although some tumor types present less receptor density, such as...
insulinoma, according to Bertherat et al., sstr2 and sstr5 are also present in 70% of these latter tumors, thereby allowing their scintigraphic detection. In contrast, Krenning et al. were only able to visualize 61% of these tumors.

The utility of scintigraphy followed by radioguided surgery has been demonstrated in both the detection of occult and small tumors (Fig. 1) and in relapse surgery in which the presence of scar tissue usually hinders correct visualization of the surgical field or the performance of cytoreductive surgery in the case of metastatic disease.

**Table 1**

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Dose (MBq)</th>
<th>Time from injection to surgery</th>
<th>Ratios of uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez et al.</td>
<td>1</td>
<td>222</td>
<td>5 days</td>
</tr>
<tr>
<td>Porziella et al.</td>
<td>2</td>
<td>92.5</td>
<td>24 h</td>
</tr>
<tr>
<td>Mansi et al.</td>
<td>1</td>
<td>111</td>
<td>4 days</td>
</tr>
</tbody>
</table>

*T: tumor; B: background; LN: metastatic lymph node.*

**111In-pentetreotide**

In small patient samples some authors have achieved a 90% success rate in the detection of GEP NET using scintigraphy with 111In-pentetreotide followed by radioguided surgery. On comparing the latter with scintigraphy and intraoperative palpation, other authors have demonstrated greater sensitivity in the detection of primary tumors and their metastasis resulting in more effective surgery. According to Adams et al., radioguided surgery seems to be the most sensitive technique to detect occult and subcentimetric NET. In a group of 12 patients they reported that with 111In-pentetreotide the gamma probe detected 70 lesions, 52 of which had been preoperatively visualized and 31 were palpable in surgery. The smallest lesion detected by palpation was of 10 mm while that detected by the probe was of 6 mm. Öhrvall et al. considered that screening of non-palpable lesions with the probe is relatively efficient in the pancreas but requires a great deal of time in wider zones of the abdomen. According to these authors, the verification of lesions suggestive of NET by palpation or ultrasonography is the main indication of the gamma probe, being more effective than SPECT for the detection of small tumors. Ruling out the localization of liver metastasis, which is not adequate with this procedure, 34–60 lesions were identified with SPECT, although lesions <9 mm in size were not detected. In contrast, the gamma probe identified 91% of the lesions with a detection threshold of 5 mm. Banzo et al. reported that the gamma probe was able to detect lymph node metastasis, especially that only identified by scintigraphy with SSA and with uncertain localization.

Cytoreduction is one of the most effective treatments of NET. Additionally, for successful surgery it is important to differentiate between metastatic lymph nodes, mesenteric desmoplastic reactions and extranodal tumor infiltration. In these cases, the gamma probe may be useful. According to Wang et al., the use of the gamma probe could shorten the operative time, diminish unnecessary dissection and surgical trauma and optimize cytoreduction. On reintervention after the use of 111In, the gamma probe was useful in 97% of the 30 cases with carcinoid tumor of the midgut and was essential in 3 patients. The authors indicated that the probe is particularly useful when the lesion has an unusual localization such as...
as in the neck or mediastinum and allows determining if the tumor has been devitalized or remains viable in patients with chemotherapy or radioembolization of liver metastasis. With regard to the \( T/B \) ratio, Wang et al. described a wide range in the detection of lymph node metastasis or peritoneal implants due to the different density of receptors among different patients and different sites of metastasis in the same patient as well as the different doses and time intervals between the injection and surgery. A greater ratio is achieved at 5 days with a dose of 222 MBq, although the elevated physiological activity remaining in the liver and spleen makes it preferable to wait until the 7th day (Table 2).

99mTc-labeled somatostatin analogs

Fettich et al.\(^\text{22}\) reported successful intraoperative localization of 4 tumors – 2 gastrinoma, one carcinoid and one insulinoma – after the injection of 99mTc-EDDA/HYNIC-TOC and concluded that radioguided surgery makes the intervention easier and short and increases the success of surgical treatment of GEP NET.

Hodolic et al.\(^\text{11}\) studied 16 patients diagnosed with NET (clinical, biochemical and imaging) to determine the factors influencing radioguided surgery using this radiotracer. In their experience, scintigraphy and the gamma probe detected lesions not visible in preoperative localization with conventional imaging studies (CT, MR, endoscopic ultrasonography). The surgery was satisfactory in 11 patients, but lesions localized in the pancreatic region by the imaging techniques were not found in the remaining 5 (Table 3).

99mTc-EDDA/HYNIC-octreotate has also been used in radioguided surgery of occult GEP NET. Hubalewska-Dydejezyk et al.\(^\text{48}\) studied 9 patients with clinical symptoms and biochemical tests suggestive of GEP NET localized by scintigraphy with this tracer and other negative preoperative imaging studies. Radioguided surgery localized primary tumors and lymph node metastases, albeit not visible on scintigraphy or during surgery, as well as neoplastic infiltrations in the tumor bed, thereby influencing decision making concerning the extension of the surgery and indicating more radical treatment. Adams et al.\(^\text{7}\) described the smallest metastasis of 6 mm in size using 111In-pentetreotide.

68Ga-somatostatin analogs

Kaefferer et al.\(^\text{49}\) studied 9 patients with primary or recurrent GEP tumors. Whole body PET/CT was performed 2–4 weeks prior to surgery, and 1.5–2 h before the intervention an additional PET/CT of the region of interest was carried out after the injection of 180 MBq of 68Ga DOTA-NOC (DOTA-1-Na\(^\text{13}\)-octreotide) or DOTA-TATE (DOTA-D-Phe\(^\text{1}\)-Tyr\(^\text{3}\)-Thr\(^\text{8}\)-octreotide). A gamma probe with a CsI (T1) detector and tungsten collimator were used for intraoperative localization, detecting more lesions than beforehand in 4 patients and leading to a change in the surgical procedure. These analogs are therefore an interesting option for real time detection of primitive tumors and small metastases (Table 4).

123I-MIBG

In a review of 20 studies on the role of MIBG in radioguided surgery of NET van Hulsteijn et al.\(^\text{50}\) concluded that this tracer has less sensitivity than the radiolabeled SSA to detect metastatic lesions of carcinoid tumors. In a previously referenced work by Wang et al.\(^\text{47}\) in 6 patients with NET (5 of the small bowel and one pancreatic) presenting low scintigraphic uptake of 111In-pentetreotide, 123I-MIBG was used in the radioguided surgery and was only found to be useful in one of the patients. The authors

Table 2

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Type of tumor</th>
<th>Dose (MBq)</th>
<th>Injection/surgery interval</th>
<th>T/B ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohvral et al.(^\text{5})</td>
<td>21</td>
<td>8 pancreatic NET, 13 metastatic carcinoid tumors (midgut)</td>
<td>108–194</td>
<td>24–48 h</td>
</tr>
<tr>
<td>Benjegard et al.(^\text{12})</td>
<td>7</td>
<td>6 carcinoid tumors (midgut)</td>
<td>200–260</td>
<td>1–7 days</td>
</tr>
<tr>
<td>Wang et al.(^\text{48})</td>
<td>34</td>
<td>4 lower cervical and upper mediastinal lymph node dissection, 30 middle bowel (5 reinterventions)</td>
<td>37–276</td>
<td>1–8 days</td>
</tr>
<tr>
<td>Adams et al.(^\text{7})</td>
<td>12</td>
<td>10 carcinoid, 1 metastatic gastrinoma, 1 insulinoma</td>
<td>180</td>
<td>24 h</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Type of tumor</th>
<th>Dose (MBq)</th>
<th>Injection/surgery interval</th>
<th>T/B ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hubalewska-Dydejezyk et al.(^\text{48})</td>
<td>9</td>
<td>4 carcinoid (1 FP by Crohn disease), 4 insulinoma, 1 glucagonoma</td>
<td>700</td>
<td>24 h</td>
</tr>
<tr>
<td>Hodolic et al.(^\text{11})</td>
<td>16</td>
<td>5 carcinoid, 2 insulinoma, 2 gastrinoma, 3 carcinoma-NOS</td>
<td>550–650</td>
<td>3–6 h</td>
</tr>
</tbody>
</table>

Source: Hodolic et al.\(^\text{11}\), Hubalewska-Dydejezyk et al.\(^\text{48}\)

T: tumor; B: background; FP: false positive; NOS: not otherwise specified.
assumed this to be due to the short interval between injection and the surgery.

Nevertheless, some authors have successfully used this radio-tracer, although generally in isolated cases. For example, van Luijk et al. localized ovarian metastasis of a carcinoid tumor with $^{123}$I-MIBG. Likewise, Yüksel et al. used this tracer to detect lesions with discrepancies between the radioisotopic images and those obtained by conventional techniques, localizing 2 lymph node metastases of a jejunal carcinoid tumor with diameters of 1 and 1.8 cm. The authors stated that the use of $^{123}$I-MIBG may be advantageous in preoperative localization and radioguided surgery of metastatic NET lesions if these are near a zone of elevated uptake of $^{111}$In-pentetreotide, such as the kidneys or spleen.

**Medullary thyroid carcinoma**

Medullary thyroid carcinoma is a NET which originates in the parafollicular C cells of the thyroid glands and secretes calcitonin and polypeptides such as the carciinoembryonic antigen, VIP and SS. This carcinoma is often progressive and invasive and has an elevated potential of metastasis. The prognosis depends on its extension at diagnosis, the grade of differentiation and the possibility of complete resection, with lymph node metastasis being the most important prognostic factor. The initial treatment involves total thyroidectomy, with dissection of the central compartment or modified dissection of the neck.

Despite aggressive surgery, approximately 50% of the patients with TMC develop recurrence which is often difficult to localize even with imaging studies with high anatomical resolution. Compared to these studies, scintigraphy with $^{111}$In-pentetreotide has demonstrated a greater sensitivity in occult recurrences. Surgery of local recurrences may be difficult even in the hands of an expert surgeon. The gamma probe is very useful in cervical examinations based on doubtful anatomical images and positive scintigraphy with $^{111}$In-pentetreotide. Likewise, the gamma probe may facilitate the localization of a poorly defined lesion in an operative field with fibrosis. However, Guleç and Baum stated that detection is only useful when the preoperative scintigraphy with $^{111}$In-pentetreotide demonstrates a lesion with a T/B ratio >1.5.

Different groups have used radioguided surgery with $^{111}$In-pentetreotide in TMC. In 5 patients, Benjegård et al. successfully detected 70% of the tumors (7/10 lesions). Waddington et al. detected cervical recurrence in one case with previous surgical failure. Adams et al. studied 25 patients with suspicion or risk of recurrent TMC and reported that surgical palpation identified lymph node metastasis with a sensitivity of 65% while the gamma probe achieved a sensitivity of 97%. These authors detected more lesions and with a smaller size with the gamma probe than with intraoperative palpation and presurgical dual-tracer imaging ($^{111}$In-pentetreotide and $^{99m}$Tc-V-DMSA). Although the sensitivity of scintigraphy in the localization of cervical metastases was of only 66%, it did indicate the selection of a tracer with greater uptake with a view of the intraoperative localization, with the smallest cervical and mediastinal metastases detected with the probe being 5 mm and 8 mm, respectively.

Although van Hulsteijn et al. reported that $^{123}$I-MIBG has less sensitivity than radiolabeled SSA for detecting recurrences of TMC, Sihimotake et al. used this tracer in a 7-year-old patient with type 2B MEN to localize a lesion in an area with fibrosis due to previous surgery (Table 5).

**Paraganglioma**

Tumors of the carotid body are non-chromaffin paragangliomas. They are infrequent and contain SS receptors. The main signs and symptoms include a pulsatile slow-growing mass in the carotid bifurcation and peripheral cervical neuropathy and may remain clinically silent for a long period of time.

Ultrasoundography, angio-CT and angio-MR are the main techniques used in the study of these tumors, but scintigraphy with $^{111}$In-pentetreotide is able to identify the primary tumor, possible metastases and/or rule out postoperative recurrences, which may develop early in 6% of the cases.

Martinelli et al. studied 12 patients with a carotid body tumor who underwent intervention 24 h after the injection of 150 MBq of $^{111}$In-pentetreotide. These authors support the use of ultrasoundography together with scintigraphy for presurgically localizing cervical paragangliomas and determining their nature, size and involvement of adjacent structures in addition to detecting distant metastasis with a whole body scan. During radioguided surgery, the gamma probe did not show uptake in a tumor which was a neura-fold, in contrast, it did identify all the paragangliomas (15 tumors). The use of the probe in a tumor in vivo (T/B ratio >2, mean value 3) allowed the detection of small residual tumors as well as even the smallest lesions, leading to their extirpation.

**Pheochromocytoma and neuroblastoma**

Ten of the studies reviewed by van Hulsteijn et al. included pheochromocytomas (25 patients) and ganglioneuromas or neuroblastomas in 6 (91 patients). In 72% out of the 130 procedures,
radioguided surgery contributed to decision making during resection. First, it helped localize the lesion, particularly when this was small, not visible or palpable or was found in an area with post-surgical fibrosis. It was also useful for detecting lesions which are difficult to localize because of discrepancy among the imaging techniques used. In one probe the event detected 2 localizations of a pheochromocytoma not visualized by scintigraphy.

In 3 patients with recurrent pheochromocytoma, Adams et al. used 123I-MIBG. All the subdiaphragmatic paravertebral lesions (≥2 cm) visualized in the images with MIBG were localized by surgical palpation and the probe. However, the authors indicated that hepatic and biliary uptake can occult sites of MIBG uptake, especially in the subdiaphragmatic or paravertebral region with a T/B ratio <1.5. According to Ricard et al. intraoperative localization of the pheochromocytoma with MIBG can be used in ectopic localizations even in small lesions. van Hulsteijn et al. considered that radioguided surgery helps to localize small, non-palpable tumors which are difficult to visualize in conventional imaging studies or those localized in an area with fibrotic tissue.

On the other hand, some authors included in the review described cases in which the probe was not necessary because the lesion was large and unevenly removed, with negative results due to technical problems in 4 cases. In addition, in 58 cases of neuroblastoma (66 procedures) Martelli et al. reported the uptake to be insufficient in 5, in another 4 the size of the probe did not allow adequate examination, and in 7 patients with adrenal tumor, detection with the probe was not necessary. These authors indicated that the procedure was useful in 65% of the interventions.

Data related to radioguided surgery with MIBG in NET do not, as yet, recommend its routine use. However, in selected cases it does seem to improve the quality of resection. Although SSA are preferable in other NET, in pheochromocytoma and neuroblastoma MIBG may provide a sensitivity and specificity of 90% (Table 6).

### Conflict of interest

The authors declare no conflict of interest.

### References


### Table 6

Radioguided surgery in neuroblastoma, pheochromocytoma and ganglioneuroma.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Type of tumor</th>
<th>Tracer</th>
<th>Dose (MBq)</th>
<th>Injection/surgery interval</th>
<th>T/B ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martelli et al. 57</td>
<td>Neuroblastoma</td>
<td>123I-MIBG (36)</td>
<td>1854</td>
<td>24–48 hours</td>
<td>≥2</td>
</tr>
<tr>
<td>Adams et al. 26</td>
<td>Pheochromocytoma</td>
<td>123I-MIBG (30)</td>
<td>180</td>
<td>3–5 days</td>
<td>≥1.5</td>
</tr>
<tr>
<td>Ricard et al. 56</td>
<td>Recurrent or multiple pheochromocytoma</td>
<td>123I-MIBG</td>
<td>0.74–37</td>
<td>48 h</td>
<td>2.1</td>
</tr>
<tr>
<td>van Hulsteijn et al. 15</td>
<td>Ganglioneuroma</td>
<td>123I-MIBG</td>
<td>370</td>
<td>24 h</td>
<td>&gt;2</td>
</tr>
</tbody>
</table>

T: tumor; B: background.

### Conclusion

Radioguided surgery is a feasible technique for the localization of NET. It detects more lesions and with a smaller size than presurgical imaging studies and surgical palpation and detects residual lesions which could lead to recurrence. 111In-Pentetreotide is the tracer most commonly used in most of tumors, except for pheochromocytomas or neuroblastomas in which MIBG is the best option. The protocols used vary greatly, mainly in radioguided surgery with 111In-Pentetreotide of carcinoid and pancreatic tumors. Although most authors accept that T/B ratios improve over time, surgery may be performed at 24–48 h after the injection of the radiotracer, depending on the isotope used and the dose administered, with the T/B ratios usually being of ≥2. SSA labeled with 99mTc-HYNIC are currently an alternative to 111In-Pentetreotide, overall because of the greater detectability of 99mTc with the gamma probe in surgery carried out from 3 to 24 h after the injection of the tracer and with doses between 500 and 700 MBq. Radioguided surgery could, therefore, be considered as an adequate option in cases of NET requiring extirpation.