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Special collaboration

Radioguided surgery in neuroendocrine tumors. A review of the literature☆

P. García-Talavera[a,*], R. Ruano[b], M.E. Rioja[c], J.M. Cordero[d], P. Razola[e], S. Vidal-Sicart[f]

[a] Servicio de Medicina Nuclear, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
[b] Servicio de Medicina Nuclear, Hospital Clínico Universitario de Salamanca, Salamanca, Spain
[c] Servicio de Medicina Nuclear, Hospital Universitario Ramón y Cajal, Madrid, Spain
[d] Servicio de Medicina Nuclear, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
[e] Servicio de Medicina Nuclear, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[f] Servicio de Medicina Nuclear, Hospital Clínic de Barcelona, Barcelona, Spain

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ABSTRACT

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 radiopharmaceutical, dose of radiotracer, timing between injection and surgery. In this paper, we review these issues, describing the experience of different authors in diverse tumors.

Cirugía radioguiada de tumores neuroendocrinos. Revisión de la literatura

Palabras clave:
Tumores neuroendocrinos
Cirugía radioguiada
Sonda gammadetectora
Análogos de la somatostatina

RESUMEN

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.

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[1,2] and is successfully carried out in a wide variety of tumors (melanoma, breast and other gynecological tumors, head and neck tumors...). 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).[3]

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.[4] began to use a radiolabeled SSA (^{123}I-Tyr^3-octreotide) for scintigraphy in carcinoid tumors and other NET.

Other tracers were later developed with the same objective, ^{111}In-DTPA-Phe-octreotide (^{111}In-pentetreotide) being the most frequently used. Scintigraphy with radiolabeled SSA has a high sensitivity for localizing NET and may provide functional

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* Corresponding author.
E-mail address: palomagtalavera@gmail.com (P. García-Talavera).

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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).[5] In addition to radiolabeled SSA, other tracers are used in daily clinical practice, such as ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) or PET tracers such as ^{18}F-FDG. The latter is especially indicated in tumors with a high Ki67 proliferation index >15%.[6]

With regard to the approach to NET, this depends on the histopathology, the localization and the extension of the disease. In localized tumoral 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 radiolabeled with ^{90}Y and ^{177}Lu 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.[7] 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.[8] Consequently, the gamma probe could be more efficient in lesions from 0.5 to 1 cm in size.[7,9]

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.[10] 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.[5,9,11–15]

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[11] 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:

^{125}I-Tyr^3-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, ^{125}I 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.

Martínez et al.[16] reported good results with ^{125}I-Tyr^3-octreotide in neuroblastoma (sensitivity 100% and specificity 71%). Likewise, Schirmer et al.[17] obtained good detection rates in the intraabdominal localization of GEP NET.

^{111}In-DTPA-Phe^1-octreotide

^{125}I-Tyr^3-octreotide was replaced by ^{111}In-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.[18]

^{111}In-pentetreotide is currently widely used in scintigraphy for the study of NET and some authors have used it in radioguided surgery.

^{99m}Tc labeled somatostatin analogs

Tyr^3-octreotide labeled with ^{99m}Tc (^{99m}Tc-Tricine-HYNIC-TOC) is a SSA which was developed by Béhé and Maecke,[19] 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[20] demonstrated greater uptake, more rapid renal excretion and less activity in blood, liver and small bowel. Gabriel et al.[21] demonstrated that 2 whole body scintigraphy acquisitions with ^{99m}Tc-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 ^{99m}Tc is more adequate than that of ^{111}In for detection with gamma probes, and its short half-life allows the use of greater activity as well as less renal uptake.[22]

Hubalewska-Dydejczyk et al.[23] used another technetium SSA, ^{99m}Tc-EDDA/HYNIC-octreotate, with greater affinity than octreotide for sstr2 and with a biodistribution similar to ^{111}In-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.

^{123}I-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.[24] MIBG can be labeled with ^{131}I, ^{125}I or ^{123}I, 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.

^{68}Ga-somatostatin analogs

In a large group of patients with different NET, Baum et al.[25] used a SSA labeled with ^{68}Ga, DOTA-1-Nal^3-octreotide (DOTA-NOC) and reported an elevated diagnostic precision in the detection of metastatic lesions with PET/CT. Gulec and Baum[5] found that peptides labeled with ^{68}Ga 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 ^{68}Ga-DOTA-Tyr3-octreotide (DOTA-TOC) in the localization of tumors with positive SS receptors is as follows: