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Review

Radioguided surgery with radiolabeled somatostatin analogs: not only in GEP-NETs

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Abstract

Radioguided surgery (RGS) is a surgical technique that, using intra-operative probes, enables the surgeon to identify tissues preoperatively "marked" by a radiopharmaceutical. Somatostatin receptors (SSTRs) are present in the majority of neuroendocrine cells and may be over-expressed not only by tumor cells, but also by endothelial cells of peritumoral vessels, inflammatory cells and cells of the immune system, such as activated lymphocytes, monocytes and epithelioid cells. This extra neoplastic uptake is the rationale for the use of radiolabeled somatostatin analogs (SSAs) either in some tumors not expressing SSTRs or in various non-oncological diseases. The crucial point of RGS technique lays in the establishment of a favorable tumor-to-background ratio (TBR). A wide range of probe systems are available with different detectors and many radiopharmaceuticals have been experimented and utilized, mainly using γ-detection probes; in order to widen RGS application field, newer approaches with β^- or β^+ emitting radioisotopes have also been proposed. Together with the consolidated clinical use, a promising and effective employment of RGS may be found in neuroendocrine tumors (NETs) using ^{111}In-pentetreotide (OCT). RGS with OCT has been demonstrated useful in the management of patients with gastroenteropancreatic (GEP) tumors, lung, brain and breast cancer. Preoperative scintigraphy or PET with DOTA-peptides combined with RGS increases the rate of successful surgery. Preliminary studies with β^- probes using ^{90}Y-SSA suggest the possible interest of this approach in patients undergoing peptide receptor radiotherapy.

KEY words: somatostatin analogs, ^{111}In-pentetreotide, radioguided surgery, intraoperative probes, neuroendocrine tumors, breast cancer, lung cancer, brain cancer

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Background

In the last decades, diagnostic imaging witnessed a tremendous development in both hardware and software that allowed the establishment of procedures such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). In any field of application, surgeons have been helped in pre-operative tumor identification and extension definition, which is crucial to define the best surgical approach in terms of radicality. However, intra-operatively, surgeons still have to rely on their anatomical knowledge and on traditional methods, mainly inspection and palpation (with a possible support by ultrasounds), to define the limits of tissues that need to be removed or sampled with a biopsy. In this sense, radioguided surgery (RGS) represents a more suitable approach and an important tool, which could help surgeons during operations, simplifying the process of cancerous tissue identification and allowing the detection of lesions, which could not be seen or palpated. The first report of RGS dates back to 1960 with William Myers, who intravenously injected radiolabeled compounds in a pre-operative stage, as a lead to locate intra-operatively the tumor, by using a hand-held γ-detecting probe [1]. The fundamental concept of this technique is the three-point counting principle. The first count is done *in vivo*, to localize the tissue that needs to be removed; the second step consists of an *ex vivo* count in order to confirm that the pathological tissue was excised, and finally the interested area is probed again to check for potential leftovers of radioactivity. Usually, the detecting system provides data in the form of both visual and acoustic signals of counting rate (counts per second), which increase as the surgeon moves the probe nearer to the "hottest" radiation source, i.e. the affected tissue to be removed [2]. The crucial point of RGS applications lays in the establishment of a favorable lesion-to-background ratio, which can occur, in presence of

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a low background activity, either via a selective radiopharmaceutical binding, such as in presence of somatostatin receptors (SSTRs) in neuroendocrine tumors (NETs), or via a non-specific/localized uptake at level of the target that has to be surgically removed.

SSTRs are present in the vast majority of normal neuroendocrine cells and may be over-expressed not only by tumor cells, but also by endothelial cells of peritumoral vessels, by inflammatory cells and by cells of the immune system, such as activated lymphocytes, monocytes and epithelioid cells. This extra neoplastic uptake is the rationale for the use of somatostatin analogs (SSAs) either in some tumors not expressing SSTRs or in various non-oncological diseases [3–5].

RGS success is testified by its growing diffusion, not only in biggest and most specialized hospitals, but also in smaller ones. Most valuable applications concern sentinel lymph node (SLN) radio-guided biopsy in patients with breast cancer or cutaneous malignancies [6] and ^{99m}Tc colloid albumin for pre-operative and intra-operative localization (ROLL) of non-palpable breast lesions [7–11].

Other clinical applications have been investigated and RGS has been applied with variable results to many neoplasm, as parathyroid adenoma and osteoid osteoma [12, 13].

Detection probe systems

Due to the progressive diffusion of RGS, various systems of hand-held intra-operative probes have been developed to allow proper radiation detection. With respect to the specific type of detected radiation, they can be divided in γ probes, the only ones widely diffuse in the surgical practice β^- probes, and PET probes, detecting radiations originating from positron emitters [14–18].

As concerning gamma-detector technologies, there are two main categories commercially available and already used within the operating room: scintillation-based and semiconductor ionization-based detectors. These two systems share the type of detector source, which is represented by crystalline materials, even if the basic principle behind the detection system and the specific crystalline materials are completely different. In the first case, i.e. in scintillation detectors, the emitted radiation excites atoms within the scintillation crystal, producing visible light in proportion to the energy absorbed. A photomultiplier tube enhances the resultant visible light, then converted into an electrical pulse collected by the detection unit. Semiconductor ionization detectors instead, take advantage of crystalline materials such as cadmium telluride (CdTe), cadmium zinc telluride (CdZnTe), and mercuric iodide (HgI2). In this case, the operating principle is based on the ionization of the semiconductor crystal, which is made possible by the transfer of free electrons emitted from the radionuclide that create an electrical pulse collected and amplified by the detection unit [19, 20]. Scintillation-type and semiconductor ionization-type detection systems have their own pros and cons, which tend to complement each other for possible application in any scenario. Scintillation-type detection systems have higher sensitivity (especially for medium to high energy gamma photons) thanks to a much bulkier probe head profile design, but have poorer energy resolution and scatter rejection. On the other hand, semiconductor ionization-type detection systems have higher energy resolution and scatter rejection, but have a lower sensitivity (especially for medium energy to high energy gamma photons), because of a much more compact probe head profile design. When considering the performance of any type of γ-detection probe system, there are different parameters that need to be evaluated: overall sensitivity (efficiency), spatial resolution (lateral sensitivity distribution), spatial selectivity (radial sensitivity distribution), energy resolution (spectral discrimination), and contrast. Overall sensitivity can be defined as the efficiency of the detection probe system and is determined by the detected count rate (photons detected) per unit of activity (photons emitted) registered at the tip of the probe profile. Spatial resolution, instead, represents the lateral sensitivity distribution and can be defined as the ability of the γ-detection probe to pinpoint accurately the position of a target source of activity, along with the capability to distinguish and separate two radioactive sources located relatively close to each other. Radial sensitivity distribution is represented by spatial selectivity, which is described by the width of the resultant measurement cone out of which radiation is being detected at a defined distance. In case of a wider measurement cone, background signal may exceed target source signal thus leading to interference with detection of target signal. On the contrary, with a narrower measurement cone, background counts will be reduced and detection of the target source signal will be more likely, even in the presence of an increased background noise. Energy resolution is directly related to the concept of spectral discrimination, the capacity of the gamma-detection system to distinguish between emitted radiations of differing energies. This is crucial in two particular situations: firstly, in case of two simultaneously administered radionuclides that have different energies; secondly, when higher-energy nuclides are administered to distinguish between primary and scattered photons. Finally, contrast, which is directly related to all of the aforementioned performance variables of the γ-detection probe system and reflects the ability of the gamma-detection probe to distinguish between activity within the target tissue and background activity within the surrounding non-target tissue [21–24].

To complete the information, it must also be remembered the commercial availability of hand held gamma cameras, not yet spread, because it has not yet demonstrated a favorable cost/effectiveness [24, 25].

Radioguided surgery radionuclides and radiopharmaceuticals

Radioguided surgery takes advantage of many radiopharmaceuticals that have been experimented and utilized, mainly utilizing γ-detection probes. The very first implementations were based on the utilization of radionuclides of Iodine as radiopharmaceutical agents (firstly ^{125}I and ^{131}I, afterwards ^{123}I). With the diffusion of ^{99m}Tc, nowadays the great majority of procedures, ranging from radioguided sentinel lymph-node biopsy to the surgical management of many other pathological conditions, are performed with technetium radiocompounds.

Each radionuclide has its own physical properties to consider such as physical half-life, photon yield (emission probability per decay) and principal γ-photon radiation emission (or emissions, in case of multiple radiations). Additionally, the γ-photon radiation emitted from each radionuclide can be defined as low-energy within a 0–150 keV range, medium-energy for values between 150 and

400 keV and high-energy emissions for values greater than 400 keV [7, 9, 26–31].

The choice of a radiopharmaceutical for a RGS procedure has to be done on the basis of either radionuclide's physical properties or pharmacokinetics of the radiotracer, to achieve the highest lesion to background ratio.

With respect to radiolabeled somatostatin analogs (SSAs), various radiopharmaceuticals have been used for intraoperative localization of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including ^{111}In-pentetreotide (OCT), ^{125}I-Tyr3-octreotide, ^{123}I-MIBG, and ^{99m}Tc-EDDA/HYNIC octreotate. Although, in the presence of a high gastrointestinal background creating unfavorable conditions in RGS of GEPs, OCT proved to be the most efficient [32–34].

The choice of this agent is supported by the shorter physical half-life compared to ^{125}I (approximately 2.80 days versus 60 days), which implicates less radiation safety issues related to both storage and disposal of radioactive materials. Furthermore, its intestinal clearance can be partially overcome by the administration of laxatives, whereas ^{125}I-Tyr3-octreotide is excreted via hepatobiliary system, thus leading to a more considerable amount of intestinal activity. Thirdly and most importantly, OCT allows the achievement of the highest tumor-to-background ratio (TBR), up to 4:1 and more, providing the best intraoperative results. Although the worst energy spectrum and dosimetry of ^{111}In in comparison with the corresponding radiopharmaceuticals labeled with ^{123}I or ^{99m}Tc, OCT remains the favorite radiotracer for RGS using SSA, being easier to be managed and more reliable for this surgical procedure. Nonetheless, all the aforementioned radiocompounds have been successfully used to localize either primary or metastatic lesions from multiple GEP-NETs, including gastrinomas, carcinoids and insulinomas [35].

Gamma-detection probe systems are the most represented in clinical applications, however, since γ radiation has a high penetrating potential and can pass through large amounts of tissue, any nearby tracer uptake represents a non-negligible background level, which can reduce the TBR and undermine the feasibility of this technique. Therefore, in order to widen RGS application field, a newer approach with β^- emitting radioisotopes has been suggested.

Promising results in RGS have been published using β^+ emitting radiopharmaceuticals, such as ^{18}F-Fluorodeoxyglucose (^{18}F-FDG), although its intra-operative utilization should be limited or carefully regulated because of concerns regarding exposure of operating room personnel to radiation [36–38]. Nevertheless, being absent a clinical usefulness for ^{18}F-FDG in patients with NETs undergoing surgery, because of the high rate of false negative results, a higher interest is connected to the use of β^- probes, presenting technical advantages in RGS respect to γ emitters. In fact, β^- radiation only penetrates up to few millimeters of tissue, with insignificant background activity due to secondary radiation. This feature allows administration of radiopharmaceuticals with lower activity, development of more accessible and compact probes, which are preferred by surgeons and may provide higher TBRs, that could help in the definition of lesion's extension and margins. In addition, thanks to the lower absorbed dose and the short range of electrons, there is a negligible radiation exposure for medical personnel, which could therefore allow a larger number of RGSs per year for surgeon [39].

Another possible field of application, that has been analyzed also in the field of NETs, takes advantage of the application of specific monoclonal antibodies (MoAb) to RGS setting the basis for the modern development of the radio-immuno-guided surgery (RIGS), already used in the past, but without effective results, because of the availability of unsatisfactory antibodies. In this context, either whole MoAbs or monoclonal antibodies fragments (FAbs) can be used in RIGS, with possible different indications, to target antigens expressed on the surface of tumor cells or within the extracellular environment surrounding the tumor. In fact, thanks to their smaller molecular weight, more rapid tumor penetration and clearance rate, monoclonal antibody fragments may provide higher TBRs, thus improving tumor detection. The drawback can be found in the possibility of a greater kidney accumulation of such fragments, which may hamper the assessment of the abdomino-pelvic area, for the detection of tumors within or surrounding the kidneys or the bladder. In general, the most important characteristics of an ideal MoAb include high affinity (i.e. the initial ability to bind the antigen) and high avidity for its antigen (i.e. the ability to retain the binding over an extended period), rapid penetration into the tumor tissue, rapid clearance from the bloodstream and minimal accumulation within normal tissues. However, the production of such radiolabeled MoAb is not a simple task and indirectly favors the utilization of "regular" agents such as SSA radiopharmaceuticals. In fact, for example, the conjugation of a radionuclide to an antibody may potentially change the specific binding properties of the MoAb itself reducing its affinity and/or avidity for the intended target antigen and thus undermining its clinical efficacy [40–42].

With respect to radionuclides and radiopharmaceuticals, there is another important key-point that needs to be evaluated in order to keep a safe work environment for all personnel, represented by the assessment of occupational radiation exposure to those involved in RGS. This has been done for several nuclides, including ^{125}I, ^{111}In, ^{99m}Tc, and, ^{18}F. In particular, the United States Nuclear Regulatory Commission (USNRC) set the annual occupational exposure limit for adults as a total effective dose equivalent of 50,000 μSv; whereas the International Commission on Radiological Protection (ICRP) has set a limit of 20,000 μSv per year, averaged over a five year period (100,000 μSv in five years) [43, 44].

Clinical applications of RGS with radiolabeled somatostatin analogs

Neuroendocrine tumors

The employment of RGS in neuroendocrine tumors (NETs) has not been standardized yet due to the application of different protocols, including radiopharmaceuticals, doses and time intervals between injection and acquisition. At present, five subtypes of somatostatin receptors (SSTRs) have been characterized: SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5. They are expressed with a certain degree of tissue specificity; however, SSTR2 is the most represented [45]. ^{111}In-pentetreotide scan (Octreoscan®, OCT) has been recognized for several years as the gold standard technique in diagnostic imaging studies for NETs and is yet the most diffuse SSA either for RGS and for SPECT. The reasons for its success, also at the present, lay in the high sensitivity and reliability of this method, recently improved thanks to the availability of hybrid SPECT/CT, for both tumor localization and staging and in follow-up [46–49].

Even if great strides have been made in preoperative imaging technology, the intraoperative evaluation still represents a demanding task for surgeons, in presence of a reported rate of negative laparotomy up to 30% for patients with gastroenteropancreatic NETs (GEP-NETs) [50–52]. For this reason, a RGS approach, which may take advantage of the gamma-detection probe to localize intra-operatively such tumors, could reduce significantly the negative laparotomy rates. In particular, the selective radiopharmaceutical-receptor binding to SSTR2, which is expressed in more than 90% of GEP-NETs, suggests a possible application with intraoperative γ-detection of the tumor. Unfortunately, abdomen is not the ideal site of application for detecting neoplastic sites with OCT, due to the "physiological" presence of the radioisotope in liver, spleen, kidneys and bowel thus resulting in a scattering and disturbing effect which, in most cases, compromises the assessment of the region (because of a decrease in TBR) [53–56].

Another aspect to consider in the decisional diagnostic process is tumor differentiation that can be used as selection criteria of which radiolabeled SSA should be preferred for GEP-NETs staging. In particular, OCT appears more sensitive than ^{18}F-FDG for well-differentiated tumors, whereas ^{18}F-FDG demonstrates superior sensitivity for undifferentiated lesions [57]. In this sense, being patients positive at ^{18}F-FDG inoperable, there is no role for RGS with ^{18}F-FDG in patients with NETs.

Recently, a new family of PET radiolabeled SSAs, synthesized through a chelation with ^{68}Ga, has been proposed for NET imaging. Gallium-68 may be linked to different SSAs through a chelating agent, as DOTA (1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid), which is the agent of choice because of its ability to form stable complexes with different radiotracers of the metal group like ^{111}In, ^{68}Ga, ^{64}Cu, ^{90}Y and ^{177}Lu, with the last two radioisotopes used for radionuclide therapy.

SSAs radiolabeled with ^{68}Ga are used in the so called DOTA-PET, which significantly improved quality and diagnostic accuracy of NETs imaging respect to scintigraphy or SPECT with OCT, thanks to better performances of PET, in presence of a great *in vivo* stability, good pharmacokinetic properties and a high and specific receptor-mediated tumor uptake. In line with such good premises, ^{68}Ga-DOTA-Tyr3-octreotate (^{68}Ga-DOTA-TATE) has been proposed as a potential agent for RGS in GEP-NETs [58, 59]; however, further studies are still required to assess its role in this field and evaluate its clinical cost/effectiveness, also because of the radiation dose to the surgical staff [50, 60, 61].

At the present, the most used procedure for RGS of GEP-NETs is therefore based on the intravenous injection of OCT, with a dose ranging from 3 to 6 mCi (110–220M Bq), followed by a 4-hour and 24-hour whole body acquisition, integrated with a SPECT imaging.

The actual surgical exploration, instead, which can be preceded by a specific patient preparation in order to minimize the background radiation from physiologic bowel excretion of ^{111}In, is generally performed between 48 and 72 hours post-injection. As soon as the probe detects an area with high levels of activity, the γ-detection system is held stationary to obtain the number of counts in a time typically of 10 seconds. The localization of the high value in a little area is crucial to calculate the TBR, which has to be greater than 1.5 for confirmation of the neoplastic tissue localization, considering that "physiological" bowel uptake is spread to larger areas [62, 63]. Adams and Baum reported how the use of such system with γ-detection probe and OCT increased the intra-operative detection of GEP-NETs. Thanks to the localization of small tumor sites accumulating OCT, smaller than 5 mm in greatest dimension, they managed to identify 57% more lesions when compared to the "palpating finger" of the surgeon. In addition, it has to be considered that when dealing with recurrences, much of the operative field is obscured with scar tissue compromising surgeon localization with palpation. In this scenario, RGS proved its value distinguishing cancerous tissue from scars, thus helping in the surgical dissection of all sites of tumor. As a result, RGS improved long-term outcomes for patients with GEP-NETs with primary or recurrent/metastatic disease thus representing a valuable alternative in the management of these patients [54].

Lung tumors

Another possible application of RGS with OCT can be found in operable lung tumors, including either pulmonary NETs and non-small cell lung cancer (NSCLC), being the primary surgery in patients with small cell lung cancer (SCLC) very rarely indicated. Interestingly, while SSTRs are *in vitro* expressed either by NETs and SCLC, they are not expressed by NSCLC. Nevertheless, a high OCT's uptake has been observed *in vivo* in these tumors, due to the increased uptake at the level of activated reactive cells surrounding the neoplasm [64, 65]. Being absent an OCT's uptake in normal lung, a high TBR may be obtained, although a more difficult evaluation in lesions adjacent to the diaphragm has been verified, due to scatter radiations deriving from liver and spleen. It has to be however pointed out that better technical conditions may be obtained in RGS of lung neoplasm respect to GEPs, mainly affected by the unfavorable physiological concentration of ^{111}In in the bowel. By taking advantage of previous experiences in NETs, Mansi et al. showed how useful RGS may be at thoracic level in patients with operable lung tumors, in which an *in vivo* high TBR for OCT is demonstrated at diagnostic scintigraphy. OCT may effectively guide surgical resection improving intra-surgical staging and better defining tumor extension, with main reference to the parietal involvement. No information has been obtained in their series in evaluating lymph node staging. In this context unreliable results could be obtained, being possible false positive results at the level of actively inflamed lymph nodes [66].

Brain tumors

The application of RGS in brain tumors is based on the systemic administration of radiopharmaceuticals which may allow the intraoperative localization and total resection of neoplasm highly concentrating the radioactivity, in presence of a low concentration at background level. After the excision, taking advantage of the three-point counting principle, the interested area is probed again to check for potential residual activity. At present, very limited data are available on RGS, and even less on the application of OCT, in brain tumors.

Bhanot *et al.* [67] evaluated the role of RGS by studying 19 patients with brain tumor, showing a high uptake at SPECT-CT. They concluded that the use of RGS provided additional information in the real-time intraoperative identification of the tumor and in terms of surgical radicality assessment, helping in the differentiation between tumor and normal brain. This aspect can be crucial in patients with

tumors like gliomas, in which the survival outcome is directly connected with the completeness of tumor excision.

From a technical point of view, best results of RGS are strictly related to the achievement of a high TBR.

Using OCT, as seen in NSCLC, an increased OCT's uptake may be obtained independently from the "specific" expression of SSTRs in the neoplasm. Furthermore, with respect to background, even though SSTR expression has been proved in the human brain, its *in vivo* targeting is highly difficult because, in normal conditions, radiolabeled SSAs are unable to cross the intact blood-brain barrier (BBB). Conversely , an *in vivo* uptake has been observed in meningioma and glioma, as well as in tumors of pituitary and pineal glands.

Kiviniemi A et al. demonstrated that ^{68}Ga-DOTA-peptides accumulate in gliomas and that uptake is associated with disrupted BBB [68]. In 2005, Gay et al. [69] studied with OCT 18 patients with "en plaque" meningiomas, either located in the sphenoid wing or in skull convexity. They also investigated the use of a γ-probe to determine whether intraoperative detection of SSTR is achievable and could increase the probability of a complete resection, by helping in the definition of tumor margins. In all patients, a pre-operative scintigraphy was performed to demonstrate desirable uptake values in the tumor respect to background. Intra-operatively, the elevated affinity of OCT for SSTR in meningiomas provided high TBRs with a mean value of 4.4:1, which enabled the probe also to discriminate tumor invasion on bone and dura matter. A peri-orbital involvement may be also individuated in case of sphenoid wing meningiomas, although with difficulty, due to the background contamination from the normal pituitary gland, concentrating OCT. The authors concluded that RGS is not only feasible but also useful in the removal of invasive meningiomas, especially those involving the bone and skull convexity, rather than sphenoid wing tumors. While many studies reported a substantial uptake of SSA in meningiomas [70–72], a smaller body of evidence has demonstrated the presence of SSTR in high-grade gliomas (HGG). Heute et al. used ^{68}Ga-DOTATOC to allow a pre-therapeutic assessment of patients with high grade glioma (HGG) undergoing a treatment with ^{90}Y-DOTATOC [73].

In a population including 11 patients with meningioma and 12 with HGG, Collamati *et al.* [16] evaluated a possible approach to RGS with β^- emitters. As concerning meningioma, all patients, but one with an atypical extracranial tumor, showed high uptake of ^{68}Ga-DOTATOC, with a TBR greater than 10 in almost all cases and usually above 20. They reported instead a significantly worse uptake in HGG, with a TBR slightly higher than 4, a value still acceptable for RGS purposes, although the more limited receptivity requires longer probing times (about 5–6 s) to discriminate between lesion and healthy tissue.

Breast tumors

With respect to breast lesions, since the introduction of national screening programs the incidence of non-palpable breast cancer has increased. The main challenge of resecting such lesions consists in correct margins definition in order to minimize the involvement of nearby healthy tissues and to reduce cosmetic damage. At present, there are three different techniques commonly used intraoperatively: wire (WGL), ultrasound, and radioguided localization, more commonly performed with radiocolloids (ROLL).

In this context, radiolabeled SSA may play a role in detection and treatment of breast lesions. As concerning scintigraphic localization of either primary or metastatic breast lesions, various experimental and clinical studies support the role of radiolabeled SSAs in breast cancer; nevertheless, due to the heterogeneous SSTRs expression in breast tumors and/or to the small number of evaluated patients, the full potential of scintigraphy and/or PET with radiolabeled SSA has not been revealed yet [74]. In 2005, Kumar et al. analyzed the expression of SSTRs in primary human breast cancer, correlating their data with tumor pathology. In particular, they indicated SSTR2 as the main subtype expressed in breast tumors even though multiple receptors were identified, with different expression within the same tissue. Furthermore, they suggested a possible positive correlation of SSTR1, SSTR2 and SSTR4 with estrogen receptors (ER) and of SSTR2 with progesterone receptors (PR) [75]. For all the aforementioned reasons, the initial determination of SSTR levels and subtypes may be crucial to assess the responsiveness to a therapy with cold or radiolabeled SSA.

In several studies, OCT identified between 50% and 94% of breast tumors, with a lower accuracy in high grade or large tumors, probably due to SSTR down-regulation [76–80].

As accessory information, demonstrating the possible role of radiolabeled SSA in therapy of breast cancer, *in vitro* studies on human breast MCF-7 carcinoma cells demonstrated how octreotide might be of practical value not only in the development of tumor radiotracers, but also as a carrier of cytotoxic antitumor drugs, such as paclitaxel, via binding to SSTRs [81]. In addition, in MCF-7cells, which express multiples SSTRs, SSA may exert both cytostatic and cytotoxic effects, inhibiting tumor cellular growth and promoting apoptosis [82]. Unfortunately, there is no evidence of such activity *in vivo*. Bontenbal *et al.* [83], in post-menopause patients with metastatic breast cancer, comparing first line endocrine therapy with tamoxifen combined with antiprolactin and octreotide versus tamoxifen alone, didn't show differences in overall post-relapse survival between the two arms. Similarly, Bajetta *et al.* [84], in a phase III multicenter randomized controlled trial in 203 patients with locally recurrent metastatic ER- and/or PR-positive breast carcinoma analyzed the performance of long-acting release octreotide pamoate plus tamoxifen, as a first line therapy for advanced breast carcinoma. They concluded that because of similar response rates and median time to progression there is no indication for adding SSA to tamoxifen, thus stopping the trial at the interim analysis.

With respect to intraoperative tumor detection, it is well known that the use of OCT shows its value mainly in tumors expressing high amounts of SSTRs. However, even though breast cancers express such receptors, each tumor type has a different pattern of SSTR expression, with lower receptor density and higher heterogeneity of SSTR subtypes compared to GEP-NETs, showing high-density regions adjacent to regions virtually without SSTRs [3, 85]. Hence, there is no doubt that further studies are required to assess the role and effectiveness of RGS with radiolabeled SSA in patients positive at scintigraphy or DOTA-PET.

Conclusions

In the last few years, RGS using γ-detection probes witnessed an enormous expansion, becoming a consolidated technique and a valuable asset for every surgery team. Research is cur-

rently focusing on surgical guidance based on β^- emitters and has already showed promising results. However, a critical point in the development of new RGS procedures, which has to be considered, is the radiation exposure of the medical personnel that may restrict, especially with high-energy isotopes, the clinical application. With respect to neuroendocrine tumors, the favorable TBR granted by the selective radiopharmaceutical binding to SSTR encouraged the use of RGS, which proved its value in a challenging task such as GEP-NETs. Helping in the surgical dissection of all sites of tumor, improved long-term outcomes of patients with primary or recurrent/metastatic disease may be obtained. As concerning the possible application of RGS at thoracic or brain level and the employment of ^{68}Ga-DOTA-peptides or β^- emitters, they are still under evaluation even if there are all the makings of future transition to clinical practice, particularly if further research and development are done to improve the performance of detection systems. Finally the possible role of RGS with radiolabeled SSA in breast cancer has to be further evaluated to better understand the possibility of a reliable total resection aided by RGS, in presence of a non-homogeneous distribution of SSTR.

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