

Intraoperative and Postoperative Gamma Detection of Somatostatin Receptors in Bone Invasive “En Plaque” Meningiomas

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Abstract:

Objective: Scintigraphy with radiolabeled somatostatin analogue ([111In-DTPA] octreotide), detects the somatostatin receptors that are found in vitro in all meningiomas. Previous studies have proved the benefit of radioimmunoguided surgery with a handheld gamma probe, for the assessment and the removal of neuroendocrine tumors. We conducted a study to determine whether intraoperative radiodetection of somatostatin receptors is feasible and could increase the probability of complete meningioma resection, especially for bone invasive “en plaque” meningiomas that are difficult to control surgically.

Methods: Eighteen patients with “en plaque” sphenoid wing and skull convexity meningiomas were studied for pre and post-operative somatostatin receptor scintigraphy. In 10 of them, intraoperative radiodetection using a handheld gamma probe was performed 24 hours after the intravenous administration of [111In-DTPA] octreotide. This procedure was combined with a computer-aided navigation system.

Results: All pre-operative scintigraphies were positive. Intraoperative gamma probe detection was possible for invaded bone, dura, and periorbit of sphenoid wing meningiomas. The average tumor/non-tumor counting ratio was 2:1 with a maximum of 12:1, allowing precise detection capable of defining the tumor margins. In three cases of sphenoid wing meningiomas, post-operative scintigraphies were helpful for the determination of recurrences that MRI failed to detect.

Conclusion : These preliminary data show that intraoperative radiodetection of somatostatin receptors using a handheld gamma probe is feasible and may be helpful to guide the surgical removal of bone invasive “en plaque” meningiomas. Pre and postoperative scintigraphy may be useful for the management and follow-up of these tumors.

Key words : bone invasion; intraoperative radiodetection; meningiomas; somatostatin receptor scintigraphy.

Introduction:

High-affinity somatostatin receptors have been identified on numerous tumors, especially on neuro-endocrine tumors of the gastrointestinal tract and on medullary thyroid carcinomas (22, 24). The effectiveness of the surgical treatment of these tumors has been improved by the use of an intraoperative handheld gamma probe to localize occult tumor locations or metastasis after the administration of [Indium –111-diethylenetriaminepentaacetic acid (DTPA)–D-Phe1] pentetreotide, an analogue to somatostatin (1).

Additionally, somatostatin receptors have been detected *in vitro* and *in vivo* in virtually all meningiomas (23). These findings have increased the interest of using somatostatin analogues in the treatment of these tumors with controversial results (5, 7, 14). Receptor scintigraphy with the radioactive somatostatin analogue [111In-DTPA] octreotide has been used to detect the receptors and assist in the pre-operative diagnosis or postoperative follow-up of these tumors (12, 16).

In the present study, we tested the intraoperative efficacy of tumor localization using a probe after injection of [111In-DTPA] octreotide. In 1989, Reinhardt demonstrated the benefit of intra-operative probe detection of radiolabeled brain tumors after ³²P (radiophosphorus) infusion, especially for meningiomas (21). Perioperative gamma detection of meningiomas radiolabeled with somatostatin analogue may help ensure complete tumor resection as this remains the most important risk factor for recurrence (11). The use of such a probe is particularly useful in the resection of bone invasive or “en plaque” meningiomas as it is sometimes difficult to estimate the tumor limits intraoperatively. The feasibility of this procedure is evaluated with the simultaneous use of a computed assisted neuronavigation system. In addition, we discuss the benefit of post-operative scintigraphy in the follow-up of invasive meningiomas.

Subjects and Methods:

Patients:

18 patients with convexity or sphenoid wing “en plaque” meningiomas were selected for a pre- and post-operative somatostatin receptor scintigraphy analysis. All patients were female with a mean age of 51.6. All patients underwent preoperative brain MR imaging and CT scanning with acquisition of bone windows to assess the extent of bone invasion by the tumor prior to somatostatin receptor scintigraphy. There were three “en plaque” meningiomas of the skull convexity, two with invasion into the mastoid process, and thirteen sphenoorbital meningiomas with sphenoid wing bone osteosclerotic invasion. Surgery attempted to remove the involved osteosclerotic bone, dura mater, in addition to the intracranial component of the tumor. In cases with periorbital tumor involvement, affected tissues were also resected. In four cases of sphenoid wing meningiomas, there was a minor amount of tumor extension into the cavernous sinus that was not surgically resected.

Intraoperative gamma probe detection was employed in 10 of the 18 patients. Patient selection was based on tumor location, and on the likelihood of attempting a complete resection that might utilize the intraoperative gamma probe. Six patients had “en plaque” sphenoid wing meningiomas without any cavernous sinus involvement; the four remaining patients had meningiomas that invaded the skull convexity or mastoid process.

The patients not included in the intraoperative gamma probe detection study were the three “en plaque” sphenoid wing meningiomas that invaded the cavernous sinus. The remaining five patients (one skull convexity meningioma and four bone invading sphenoid wing meningiomas) were included before the intra-operative analysis to assess the feasibility of the pre- and post-operative somatostatin receptor scintigraphy in the management of the follow-up images of these invasive meningiomas.

Radiopharmaceutical Kits and Operative Gamma Detection Probe:

The somatostatin analog, pentetreotide (Octreoscan), was obtained from Mallinckrodt (France) in lyophilized form and radiolabeling was performed by adding 111 MBq ^{111}In chloride according to the manufacturer's instructions.

Several weeks before surgery, the radiolabeled pentetreotide was administered intravenously. Multiple planar overlapping anterior, posterior, and lateral images of the head were performed using a medical energy collimator adapted for indium 111 at 4 and 24 hours to confirm the presence of somatostatin receptors (Gamma Camera: DSTXL, Sofa Medical Vision, France). A second injection was administered the day before surgery, but no more than 24 hours, to be correctly detected during the surgical procedure. A gamma detection scintigraphy was obtained four hours after this new injection to assess the good uptake of the receptors.

The Tec probe 2000 consists of a cesium-iodide crystal (diameter 9.5mm; length 15mm), a photomultiplier (diameter 10mm), and a collimator with aperture of 8 mm and a length of 10 mm. Three channels were available for the different radionuclides (e.g. ^{111}In , $^{99\text{m}}\text{Tc}$). The probe was connected to an electronic unit providing both visual and audible indication of the counting rate (range 0-25000 counts per second (cps)) as the tumor was approached (figure 1). Sterile latex covers from a surgical glove were used to ensure sterility during surgery.

The probe was used to compare the counting rates of the invaded bone and of normal skull distant from the meningioma site. Counting ratios were then calculated to help define the tumor margins. At the end of surgical resection, the probe was used again to estimate the counting rates of the bony margins.

Computer-aided navigation procedures:

The surgery was performed with a computer-aided navigation using CT images to define the extent of bone invasion by the meningiomas (Surgiscope® (ISIS, France)). Each measure of the gamma probe was paired with its corresponding registration point on the computer-aided navigation system.

Post-operative scintigraphy:

All 10 patients having undergone perioperative detection and 8 additional patients with en plaque meningiomas were post-operatively evaluated with both somatostatin receptor scintigraphy and postoperative MRI and CT scanning. These were compared to the pre-operative images. The scintigraphy was used to assess the degree of resection and to rule out a recurrence.

Results:**Preoperative scintigraphy and intraoperative gamma probe detection:**

Somatostatin receptor scintigraphy detected all tumors. Images corresponded well with the MRI findings except in one case where scintigraphy detected a second lesion that MRI failed to identify.

The results of intraoperative counting rates (cps) for both tumor-invaded skull and normal skull are listed in Table 1. Detection was possible on invaded bone and on dura, especially in the case of convexity meningiomas. Detection of dural or periorbital involvement of “en plaque” sphenoid wing meningiomas was more difficult due to the size of the device. The probe was not used on soft tumor or at the brain interface as residual tumor under these circumstances may be easily resected under direct vision, and the size of the probe presented unnecessary potential risk.

The average tumor to non-tumor counting ratio was at least 2:1 with a maximum of 12:1. The cumulative maximum counting rates were significantly higher in invaded bone compared with normal bone ([figure 2](#)). Using computer-aided neuronavigation, the margins of the invaded bone on CT corresponded to a relatively high level of radioactivity in 6 cases helping to guide the extent of bone and dural resection.

Postoperatively, the gamma detection was useful in confirming that the counting rates for bone or dura were similar to those from distant normal bone or dura ([figure 2](#)). However, it was easier to confirm that the resection was complete for “en plaque” convexity meningiomas than for sphenoid wing tumors. Indeed, the intraoperative gamma counting of the temporal skull base always remained higher than the normal skull, despite a surgical resection that seemed to be complete based on computer-aided surgery guidance.

Postoperative [¹¹¹In-DTPA] octreotide scintigraphy:

The median follow up period for all 18 cases was 2.5 years (6 months- 3 years). Eight of the ten patients operated using intraoperative gamma probe underwent postoperative scintigraphy, which proved negative. The remaining two cases had a slight detection three months after the surgical removal that was potentially secondary to inflammatory tissue.

In three cases of “en plaque” sphenoorbital meningiomas, the MRI and the CT were inconclusive regarding recurrence as an abnormal signal was present that may have represented post-operative scar tissue. However, new onset exophthalmus resulted in a scintigraphic evaluation revealing an elevated ¹¹¹In Octreotid uptake. One patient had removal of an intra-orbital recurrence followed by stereotactic radiotherapy, while the two other patients had radiotherapy alone. In these cases, the last somatostatin receptor gamma scintigraphy interestingly revealed a remarkable decrease in the uptake index (illustrative case: [figure 3](#)).

Discussion:**The somatostatin receptor scintigraphy in meningiomas:**

Since the discovery of somatostatin receptor activity in primary cultures of meningiomas, the biological and clinical interest of these receptors has increased (4, 7, 13, 14, 23). The somatostatin receptors have been identified in almost all meningiomas and the most frequent receptor subtype to be identified was the sst2 receptor (17, 25, 26). In vivo detection of these receptors is possible using a somatostatin analogue labeled with ¹¹¹Indium ([¹¹¹In-DTPA] octreotide) scintigraphy (15). Octreotide appears to be very sensitive and provides excellent contrast, as it is very specific for somatostatin receptors. There is no uptake in the brain, in the skull or other structures (except the pituitary gland). As a result, it is much better than less specific tracers such as [18F]FDG (Fluoro Deoxy Glucose) that are strongly retained in brain tissue. In the skull, only meningiomas are able to bind octreotide at a significant level, providing a high specificity.

The high somatostatin receptor expression level in nearly all meningiomas provides a very high negative value of the Octreoscan® imaging which is very useful for the preoperative diagnosis or in cases of persistent abnormalities on post-operative MRI. Other brain tumors (high grade gliomas, ependymomas,..) and skull metastasis from somatostatin positive primary tumors may also have a significant positive uptake. However, the diagnosis of meningioma can be established with the help of an Octreoscan® imaging in addition to the other conventional images. The diagnosis of tumors can be confirmed in cases where other benign tumors of the skull base that do not have somatostatin receptors are suspected (schwannoma, for example).

The postoperative utility of somatostatin receptor scintigraphy has already been discussed (9, 12). We illustrate here that it may be particularly helpful for speno-orbital “en plaque” meningiomas where remnants in the cavernous sinus or in the superior orbital fissure are

sometimes difficult to differentiate from postsurgical scar tissue on MRI. Furthermore, the ^{111}In -labelled octreotide uptake decreased after radiation therapy in two patients without clear evidence of MRI changes. This illustrates the interest of this biological marker in the management of brain tumor and especially meningiomas.

The interest of intraoperative gamma probe detection:

Peri-operative gamma probe detection of somatostatin receptors is currently used during surgery of slowly growing neuroendocrine tumors (medullary thyroid carcinomas or gastroenteropancreatic tumors) that frequently metastasize to regional lymph nodes or the liver (1). Using a handheld gamma probe, the surgeon is able to localize small metastases that are not palpable and thus not identifiable at the time of surgery, despite being identified on preoperative conventional images or on somatostatin receptor scintigraphy (18). As bone invasion by meningiomas is a risk factor for recurrence, it has been hypothesized that using computer aided navigation, a “biological” device might be beneficial to improve the radical resection of tumors (2, 11).

Using a miniature semiconductor probe, intraoperative measurements of radiophosphorus (^{32}P) tumor marker have been proposed to improve the discrimination between normal brain and neoplastic tissue (21). The best results have been found in meningiomas where small tumors within the matrix zone could be detected. We have shown here that intraoperative detection of somatostatin receptors of meningiomas is also a non-invasive method that may be useful in situations where a local radical tumor removal is important. This method offers the benefit of detecting specific meningioma markers with low radiation exposure to the patient. Additionally, the physical properties of the ^{111}In are excellent for the intraoperative detection using a small probe (19). However, the size of the probe may sometimes be too large in comparison to the topography of the tumor margin

tested, especially in the drilled out depths of an affected temporal skull base. In this particular topography, the gamma probe in our study detected a high counting rate even after an apparently complete resection. This is due to the proximity of the pituitary gland that also binds the [^{111}In -DTPA] octreotide (6).

In “en plaque” convexity meningiomas, the computer aided navigation system helped define the limits of the tumor, as it was difficult to visually define the interface between affected bone that had been drilled and normal bone. In this case, the intraoperative gamma probe still detected significantly high counts at the tumor margin that led to complete surgical resection of an otherwise nonappreciable distant invasion. Thus, intraoperative gamma-probe detection may increase the probability of complete tumor resection.

Recently another labeled somatostatin analogue, Tc-99m depreotide (8), was shown to be more easily detected in meningiomas than the [^{111}In -DTPA] octreotide. Future developments of radiotracers (68 Ga DOTATOC with PET scan for example (10)) or of the gamma probe design would also increase the feasibility of intraoperatively assessing the degree of resection of invasive meningiomas. Recently, the development of a camera that provides intraoperative images of the tumors may be even more beneficial assessing the degree of tumor resection than the probe used in the current study (20).

Conclusion:

As radical removal of meningiomas remains the best means of providing the best chance for long-term recurrence free survival, intraoperative surgical technologies have been developed to improve the completeness of local tumor removal (computer aided surgery or intraoperative MRI, for example)(3). Intraoperative gamma detection of somatostatin

receptors in meningiomas is a simple, non invasive method that is feasible and may be useful in the removal of invasive meningiomas, especially those involving the bone. This is particularly effective for “en plaque” convexity meningiomas. Unless the precision to delineate the tumors is difficult to achieve, this method may also help assess the degree of resection for invasive sphenoid wing tumors.

Other tumors of the brain can have somatostatin receptors. However, the pre-operative use of the scintigraphy after [¹¹¹In-DTPA] octreotide injection can add informations for the diagnosis of meningioma. The post-operative scintigraphy still remains a very useful adjunct in the follow-up of these particularly invasive meningiomas, particularly when post-operative images are difficult to interpret.

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Figure 1: Picture of the gamma probe (Tec probe 2000) used for the intraoperative detection of somatostatin receptors of bone invasive meningiomas. The probe has a diameter of 10 mm, and a length of 15mm. The electronic unit provides both visual and audible indication of the counting rate (cps).

Figure 2: Diagram of the maximal uptake (in counts per second) of somatostatin receptors determined during the surgical removal of the invaded bone of 10 “en plaque” invasive meningiomas. This was measured using an intraoperative handheld gamma probe on the invaded skull before its removal (Tumoral bone : measurements in the center of the tumor) and after the tumor resection, on the margins of the resection (Post resection). These were compared with the data obtained at distant normal skull bone (Non tumoral bone). Mean values are indicated with a bar. Statistical analysis of the different data are calculated (Mann Whitney, non parametric double sided). (Cps: counts per second)

Figure 3: This 66 years old woman complained of exophthalmus and visual loss. A large “en plaque” sphenoid wing meningioma associated with a second frontal meningioma was discovered. The uptake of the tumors on pre-operative somatostatin receptors scintigraphy was high (A). Three months after an extensive resection the scintigraphy (B) confirmed the complete removal demonstrated on MRI. One year later, the exophthalmus recurred with no clear evidence of recurrence on conventional images, but the scintigraphy was demonstrative (C). After radiation therapy, the somatostatin receptor uptake decreased (D). (E: preoperative MR image; F: one year post-operative MRI. The arrow head points out a possible remnant or recurrence at the orbital apex.)

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