Abstract. Neuroendocrine tumours (NETs) may be fatal, though at a significantly slower pace than their exocrine counterparts. Nuclear medicine procedures for diagnosis and treatment of NETs are based on expression of somatostatin receptors. Radioguided surgery is a new method for diagnosing and treating many tumours and uses intraoperative gamma probes. The use and development of intraoperative gamma probes in the last 10 years has enabled the development of minimally invasive procedures in oncological surgery, with an improvement in both the survival rate and the quality of life. Systemic therapy with radiolabeled somatostatin analogues is a promising new tool in the management of patients with inoperable or metastatic NETs. In terms of tumour regression, the results obtained are encouraging.

Neuroendocrine tumours (NETs) are rare tumours. The term ‘neuroendocrine’ is used to define cells by their secretory products and some cytoplasmic proteins rather than by their localization and embryological derivation. Gastroentero-pancreatic (GEP) NETs may be fatal, though at a significantly slower pace than their exocrine counterparts. Most malignant NETs are slow-growing due to low mitotic activity in the mostly well-differentiated tumours. Nuclear medicine procedures for diagnosis and treatment of NETs are based on biological properties of these tumours: expression of somatostatin receptors.

Radioguided Surgery

Radioguided surgery or gamma probe-assisted surgery is a new method of diagnosis and treatment, where those in the areas of nuclear medicine, surgery, histopathology and sometimes radiology work close together (1). This method represents the use of radioactive substances for marking certain areas in organs or systems which are easily detected by intraoperative gamma probes and consequently surgically removed. A gamma probe is a small, portable and handy instrument useful for intraoperative localization of small tumours. A gamma-emitting radiopharmaceutical known for its affinity to a particular tumour is injected intravenously into the patient some time before the operation, depending on the effective half-life of the radiotracer used. During surgery, the tumour is identified as the area with the highest counting rate detected by gamma probe. This method of surgery allows a minimally invasive procedure because it allows a small area of tissue to be identified, that which is marked with a radioactive isotope, and removed, while a large area of the organ or the system remains unaffected. This means that the extent of the surgery is much less, with much lower morbidity.

Since its development from the end of 19th century until today, oncological surgery has been based on precision surgery excision of tumour with the minimal excision of healthy tissue, and this method of surgery was quickly and widely adopted. When the first commercial devices for the intraoperative detection of radioactivity with low energy (intraoperative gamma probes) became available, procedures implementing their use were rapidly developed. Radioguided surgery was clinically introduced in 1985 by Martin et al. (2). They began to utilise radioguided surgery in treatment of cancer of the colon and rectum. Later, radioguided surgery was used in the treatment of carcinoma of the ovary (3).
Today, gamma probes are widely used for localization of impalpable lesions in breasts, sentinel lymph nodes in breast cancer and malignant melanoma, for localization of parathyroid tumours and for intraoperative detection of NETs (4). The general characteristic of these procedures is the use of isotopes that bind to the areas which need to be removed at a level of activity that is detectable by intraoperative gamma probes. For such procedures, no additional radioactive protection is needed.

Nowadays, there are numerous intraoperative gamma probes available from different manufacturers. All are based on two principles: scintillation and semiconduction. Scintillation detectors are older; they are made of a scintillation crystal, a photomultiplier tube and an electronic counter. Semiconductor detectors are made of crystal with a semiconductor, amplifier and electronic device. Scintillation detectors are bigger and more sensitive, while semiconductor detectors are smaller and easier to handle. When choosing a detector, the following should be kept in mind: a) Sensitivity — this represents the number of gamma photons emitted by the source which are detected by the gamma probe. In general, the better the sensitivity, the better the gamma probe; b) Spatial resolution — this represents the minimal distance between two sources of radioactivity that are detectable by the gamma probe as two different sources. The better the spatial resolution, the better the gamma probe. This characteristic is especially important in biopsy of sentinel nodes, as the tumour is sometimes very close to the sentinel node and needs to be distinguished from it; c) Distinction of energy — this reflects the ability to detect different energy levels. This is needed when two different isotopes are used for two different sources; d) Feasibility — the shape, size and weight play an important role in the choice of the gamma probe. The smaller and lighter the gamma probe, the easier it is to use and manipulate during surgery.

There are at least nine main manufacturers of probes that differentiate by the characteristics named. The cadmium telluride probe has been designed for lower energy detection (i.e. 125iodine, 99mtechnetium) with an excellent energy and spatial resolution. It has a detection head of 11 mm diameter. The collimator is an integral part of the probe. The detector’s size is 5x5x3 mm³. The standard probe has an angled head to permit easier access. It is connected to the read-out module through a 3.5 m flexible cable. The probe’s milligram weight play an important role in the choice of the gamma probe. The smaller and lighter the gamma probe, the easier it is to use and manipulate during surgery.

There are two reports on the use of gamma probes and 99mTc for intraoperative localization of NETs: one from the University Medical Centre Ljubljana (7), the other from the Jagiellonian University Krakow, Poland (8). The Polish report discusses four patients with carcinoid of unknown origin and five patients with insulinoma. Intraoperative localization of tumours by gamma probes was successful in seven patients, false positive in one patient and one tumour not being detected. In a Slovenian study, intraoperative detection was successful in 20 out of 27 tumours (6). Because of the possibility of its in-house preparation, 99mTc-ethylenediamine-N,N’-diacetic acid-[pentetreotide] was used. New studies show that 111indium is not an ideal isotope for the detection of tumours by gamma probes because of its high gamma energy and long half-life. Gamma probes are best suited for the detection of sources of low gamma energy, such as 90SrTc.

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Radioguided surgery is a technically challenging method, requiring a high level of training in nuclear medicine and histopathology and a well-trained surgeon.

**Systemic Radionuclide Therapy**

Radionuclide therapy of NETs nowadays is considered predominantly palliative since the dose to the tumour is usually too low to cure. Indications for treatment with radiolabeled octreotide are the presence of inoperable, metastatic neuroendocrine carcinomas with high somatostatin expression confirmed by diagnostic 111In-[DTPA]-pentetreotide scintigraphy. Patients need to have normal bone marrow reserve (Hb >10 g/l, WBC >3.0×10⁹/l, platelets >100×10⁹/l) with no significant bone marrow metastatic disease. Previous unspecific systemic chemotherapy must also be taken into account. Renal
function needs to be adequate (serum creatinine <160 μmol/l, glomerular filtration rate (GFR) >40 ml/min), and the performance status good. Contraindications for the therapy are predominantly exceeding a dose limit due to previous therapy with radiopharmaceuticals, extensive hepatic involvement and pregnancy or lactation (10).

The uptake of radiolabeled somatostatin analogues depends on expression of somatostatin receptors on the tumour cell surface. Cold somatostatin analogue therapy is normally stopped before the treatment. Different radiolabeled peptides bind mostly to somatostatin receptor type 2. They have rapid blood clearance and low antigenicity. They are easy to synthesise, chemically modify and also easy to radiolabel. There is a physiological accumulation in some organs: kidneys, urinary tract, spleen, liver, gall bladder and intestines due to low hepatobiliary clearance, pituitary, and thyroid. The cells of renal proximal tubuli take up somatostatin analogues, therefore critical organs are the kidneys. The use of amino acid infusion together with radiolabeled octreotide will decrease renal activity by 30-40% (11). The side-effects of radiolabeled octreotide therapy are few and mostly mild, certainly when using renal protective agents. Serious side-effects such as renal failure and myelodysplastic syndrome are rare. Octreotide in therapeutic doses has also been shown to produce severe hypoglycemia in patients with insulinomas. Although not expected to exert clinically significant effects, as pentetetide is an octreotide analogue, it could potentially also produce hypoglycemia. Transient adverse effects of radiotherapy with octreotide occur in fewer than 1% of patients and include dizziness, fever, flushing and hypotension.

The therapeutic dose is limited by the dose to normal tissues. There is no radiopharmaceutical for systemic therapy of NETs commercially available at this time. Before targeted radionuclide therapy of NETs with radiolabeled somatostatin analogues is introduced into clinical routine, several issues need to be addressed to assure patient safety. These are physical properties of the radioisotopes (90)yttrium, 111In, 177lutezium). Individual correction factors for dose calibrators for correct measurement of radioactivity of each radionuclide need to be determined, taking into account the volume of radiopharmaceutical, and the type and size of the vial. Beta particles emitted by 177Lu have a shorter range in tissue than those emitted by 90Y and will frequently not reach the glomeruli, hence 177Lu causes less damage to the renal parenchyma (12). The median duration of the therapy response for 90Y-octreotide and 177Lu-octreotate is 30 to 36 months. Selection of the radiolabeled somatostatin analogue for use depends on its pharmacokinetics and range of beta particles. 90Y octreotide is more toxic for the kidneys, but possibly more effective due to its longer beta particle range in the tumour tissue, also killing cells by crossfire effect. Octreotide can be radiolabeled by the addition of carrier-free solution of 90Y or 111In and octreotate by addition of 177Lu solution. The mean absorbed dose of the tumour for 90Y-octreotide is comparable to that of 90Y-octreotate, but the dose to the kidneys is significantly less if octreotide is used (13). Lastly, quality of life improves significantly after treatment with both 90Y-octreotate and 177Lu-octreotate. These data compare favourably with the limited number of alternative treatment approaches, such as chemotherapy (14).

To determine dose to the organs at risk, as well as tumour uptake of the tracer by the organ, the length of time the isotope stays in the target organ and the size of the organ are needed. In the case of 90Y-octreotide, which is a pure beta emitter, it is injected together with 111In-octreotide for dosimetry measurements (15). Addition of 111In-octreotide is not needed if 177Lu-octreotate is used, since it also has gamma emission. Whole body images are taken at 1, 4, 24, 72 and 120 h in anterior and posterior projections to compensate for attenuation. They are used to estimate radiotracer uptake and the length of time the tracer is present for selected organs, and the dose is calculated using the organ volume derived from computed tomography (CT) and using OLINDA program (Organ Level INternal Dose Assessment code) by RADAR (RAdiation Dose Assessment Resource) (16). It is advised that serum creatinine levels and haemoglobin be followed for 12 weeks biweekly.

Further improvements may be expected by a combination of 90Y- and 177Lu-labelled compounds, up-regulation of somatostatin receptor expression, use of radiosensitizers, combined treatment approaches: surgery, radiofrequency ablation, chemotherapy, external beam radiotherapy, as well as with the development of new peptides, such as modified somatostatin analogues, gastrin/CCK, bombesin and possibly also use of alpha-emitting radionuclides: e.g. 211At. If more widespread use of radiolabeled somatostatin analogues is possible, such therapy might become the therapy of first choice in patients with metastatic or inoperable GEP NETs.

References


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