

The radioguided ^{111}In -pentetreotide surgery in the management of ACTH-secreting bronchial carcinoid

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Abstract. – Background and Objectives:

A correct intra-operative detection of the tumour and, therefore, the complete surgical resection is critical to success in ACTH-secreting bronchial carcinoids. To date, all available pre-operative and intra-operative procedures remain not entirely satisfactory. The use of intra-operative ^{111}In -pentetreotide detection could offer a potentially reliable and rapid tool of real time assessment to achieve a radical resection.

Materials and Methods: In two cases of ACTH-secreting bronchial carcinoids, after a preliminary ^{111}In -pentetreotide scan, radio-guided surgery was performed using a hand-held gamma probe 24 h after i.v. administration of the tracer.

Results: The ^{111}In -pentetreotide radioguided surgery with hand-held gamma probe, if compared with pre-operative ^{111}In -pentetreotide, significantly improved the intra-operative surgical management by detecting a millimetric nodule in one case; detecting mediastinal lymph node metastasis in both cases and ruling out any other disease localization.

Discussion: Intra-operative ^{111}In -pentetreotide detection appears to be safe and easy to perform. This technique allowed to achieve a complete resection of all the tumor locations, that would have been impossible to detect with conventional surgical approach.

On the basis of these results we advocate for a wider investigation of the potentialities connected with the radioguided surgery coupled with pre-operative ^{111}In -pentetreotide scan as a promising procedure in the management of ACTH-secreting bronchial carcinoids.

Key Words:

Carcinoid tumors, ^{111}In -pentetreotide, Octreoscan, Bronchial carcinoid, ACTH-secreting tumor, Intraoperative detection bronchial tumor.

Introduction

Carcinoid tumours account for approximately 1%-2% of all tumours of bronchial origin. They derive predominantly from the enterochromaffin (Kulchitsky) cells and often overexpress receptors for somatostatin. Because of the small size and indolent/slow growth of these tumours, symptoms (mostly cough, hemoptysis and recurrent infection) may persist for many years before the clinical diagnosis. The very well known "carcinoid syndrome" occurs in 5 to 10% of the cases and clinically develops when the vasoactive substances produced by carcinoid tumour escape hepatic degradation and gain access into the systemic circulation¹.

The Cushing's syndrome, as a result of the increased ACTH production, occurs in no more than 1% of patients with bronchial carcinoids. In contrast with other tumours source of ectopic production of ACTH, bronchial carcinoids are often difficult to detect with standard radiological procedures [computed tomography (CT), magnetic resonance imaging (MRI) and/or Positron Emission Tomography (PET-Scan)], due to their small size. Since somatostatin receptors are over-expressed in most neuroendocrine tumors, Krenning et al² firstly proposed the use of radiolabeled somatostatin analogs and external radionuclide scan to image carcinoids. Nowadays, the imaging standard is represented by somatostatin receptor scintigraphy with analog diethylenetriamine pentaacetic acid (DTPA)-D-Phe1- octreotide (pentetreotide), labeled with ^{111}In (OctreoScan; Mallinkrodt-Tyco; St. Louis, MO, USA). This procedure has proved to be of significant clinical value especially in the

assessment of small ACTH-producing bronchial tumors and their metastases which are often not detected by conventional imaging techniques³.

Even adopting Octreoscan, because of their small size, bronchial carcinoids appear to be less frequently visualized than other neuro-endocrine tumours. The rare lymph node metastases from these tumours are seldom visualised at all⁴.

For these reasons, the intra-operative ¹¹¹In-pentetreotide detection by handle-held gamma probe (previously used in the surgical management of gastro-entero-pancreatic neuroendocrine tumors and in medullary thyroid carcinomas⁵ to improve the intra-operative localization of small tumours or nodal involvement) has been recently proposed as an adjuvant in the surgical management of bronchial carcinoids and particularly in the ACTH-secreting ones^{6,7}.

Herein we report our experience by using ¹¹¹In-pentetreotide-guided surgery in two patients with ACTH-secreting bronchial carcinoids and discuss the benefits of this promising technique to further additional investigations.

Technique and Intra-Operative Tumor Localization

The expression of somatostatin receptors in the bronchial carcinoids is a precondition for the use of this technique. Therefore, a pre-operative radionuclide scan was always performed after i.v. injection of 6 mCi of the ¹¹¹In-pentetreotide.

The patient received the second administration the day before the operation and a low-dose (2,5 mCi) of ¹¹¹In-pentetreotide was chosen to reduce absorbed doses by patients and operators (better dosimetric values).

In the operating room, by a hand-held \square probe, have been identified both the area of the lesion and the surrounding tissues. The used tool was the Neo2000 – model 2200 (Neoprobe Corporation; Dublin, Ireland) (Figure 1), with a detector probe using an external collimator to decrease the Field Of View (FOV) and to increase the spatial resolution of the probe: this was made to easier distinguish between two radioactive sources that are close to one another. An energy threshold for ¹¹¹In was selected and a sterile surgical drape was used to ensure sterility (Figure 2).

Dosimetry of ¹¹¹In-Pentetreotide-Guided Surgery

For ¹¹¹Indium labelled radio-pharmaceuticals, no data on radiation exposure to surgical personnel is currently available in literature. However, in this re-



Figure 1. Radio-guided Surgery: the used tool was Neo 2000 – model 2200.

gard, limited data from one study reported that staff members and technologists involved in treating patients with somatostatin receptor positive tumours with a “therapeutic dosage” (216 mCi or 8000 MBq) of an ¹¹¹In-labeled somatostatin analogue (Mallinkrodt-Tyco; St. Louis, MO, USA) received a mean whole body dose equivalent of only 45 μ Sv per case⁸. We, moreover using a low dose for radioguided surgery, therefore assume that the staff exposure connected with the proposed technique is much lower and perfectly within acceptable ranges.

Clinical Experience

Case 1

A 39-years old woman came to our attention for the surgical treatment of a bronchial carcinoid

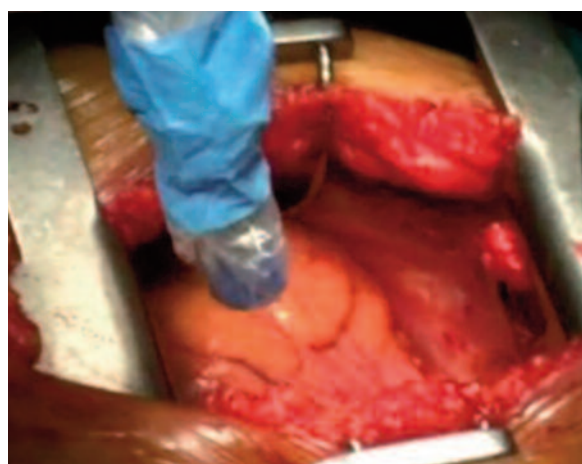


Figure 2. Radio-guided Surgery: the hand-held gamma probe.

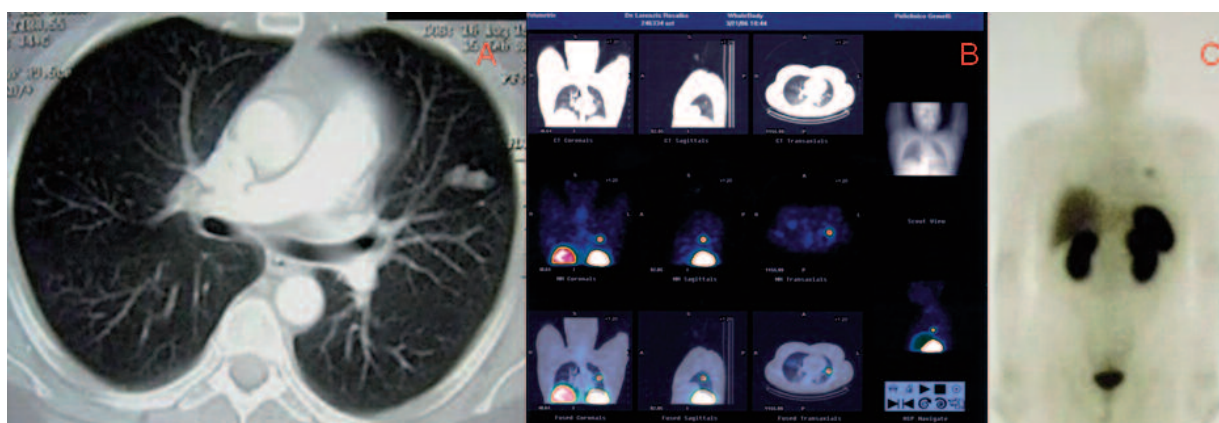


Figure 3. Preoperative findings: CT-Scan and ¹¹¹In-pentetreotide scan features.

secreting ACTH and causing a Cushing’s syndrome. A pre-operative CT-Scan (Figure 3 a) detected a polilobulated nodule in the anterior segment of the left upper pulmonary lobe. No enlarged lymph nodes were evident.

At ¹¹¹In-pentetreotide scan (Figure 3 b and c) two areas of increased uptake were pointed out in the left-upper pulmonary lobe and, slightly less evident, in the homolateral hilum, probably related to metastatic lymph node. Radio-guided surgery was scheduled 24 h after a low dose of 2,5 mCi of ¹¹¹In-pentetreotide. At surgery, the γ -probe pinpointed the small nodule in the upper lobe with a a tumour/normal tissue count ratio of 9,5; a lobectomy was performed. After the “first look”, an additional check of the operated region with the γ -probe pointed out a mediastinal 7-mm lymph nodal tissue in the aorto-pulmonary region (Figure 4) (target/normal tissue count ratio was 3,55). This tissue, correspond-

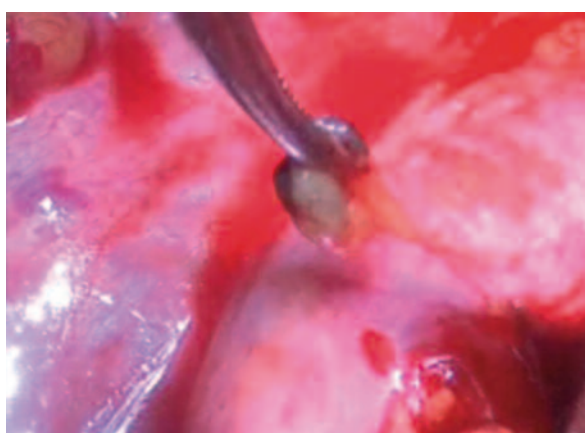


Figure 4. A metastatic lymph node in the aorto-pulmonary region detected by gamma-probe (target/normal tissue count ratio was 3,55).

ing likely to “the slightly less evident area” at pre-operative ¹¹¹In-pentetreotide scan, was removed.

No other uptakes in the tissue surrounding the tumor and in the pleural space were evidenced (median values of counts: 20 cps).

At definitive histological examination the lesion was confirmed as bronchial typical carcinoid while the lymph nodal tissue was formed by 4 millimetric conglobated metastatic lymph nodes immunohistochemical staining for ACTH.

At the moment of writing this report, the patient is completely disease free and asymptomatic with ACTH-levels in the normal range (Table I).

Case 2

A 32-years old man with persistence of Cushing’s syndrome after pituitary gland resection for a non-secreting adenoma was referred to our Center with the clinical suspect of ectopic secretion of ACTH. During the diagnostic work-up evaluation a very small hot area in the right pulmonary hilum was detected at ¹¹¹In-pentetreotide scan. No other localizations of disease were evident. The CT-Scan didn’t show any pathological findings in the hot area detected at the ¹¹¹In-pentetreotide scan.

Table I. Plasma ACTH values (picomoles per liter) at basal evaluation and after thoracic surgery.

Case	Baseline	After tumor resection
1	39	7,5
2	47	5

Plasma ACTH normal range, 2–11.5 pmol/liter.

Bronchoscopic evaluation showed only a slight *ab estrinseco* compression of the upper-right lobar bronchus (with minimal impact on the bronchial lumen shape and diameter). Histology on biopsy was non-diagnostic.

According with the ^{111}In -pentetreotide scan data, and upon the evaluation of the severity of the clinical condition, an explorative thoracotomy was scheduled 24 h after new i.v. administration of a low dose (2,5 mCi) of the tracer

At manual palpation no pulmonary nodules were detected while radioguided surgery allowed us to localize a hilar hot area (“*in vivo*”: target/normal tissue count ratio was 31,36; “*ex vivo*”: target/normal tissue count ratio was 16,67) corresponding with a thickening of the upper lobar bronchus wall (Figure 5). An upper lobectomy was performed and the intra-operative examination of a frozen section of the tumor was consistent with typical carcinoid tumor. The verification of the operated area with the gamma-detecting probe evidenced an other mediastinal hot area. We executed a systematic mediastinal lymph node dissection. No other uptake hot areas in the “tumor-bed” and in the remaining lung parenchyma were detected. Definitive pathology confirmed the carcinoid origin of the neoplastic tissue, clearly positive for ACTH at immunohistochemical staining. Moreover, one lymph nodal micrometastasis was found in the lymphatic tissue labeled as “upper paratracheal” whereas all the other specimens were tumour-free. The post-operative course was uneventful and plasmatic ACTH level rapidly decreased (Table I). Nine months after surgery no signs of disease recurrence were detected.

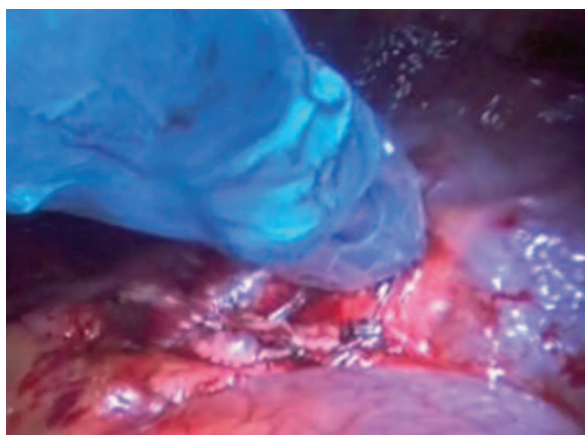


Figure 5. A hilar hot area corresponding with a thickening of the upper lobar bronchus wall (target/normal tissue count ratio was 31,36).

Discussion

Although typically painless, bronchial carcinoids are generally considered to be low grade malignancies, as shown by their ability to metastasize. Reportedly, the prevalence of node metastases in typical carcinoids ranges from 2.3 to 11%, figures that are lower than those reported for atypical carcinoids (27-66%)⁹. In this report both cases were typical carcinoids by standard definition. This finding seems to confirm the evidence reported by Shrager et al¹⁰ of a much greater metastatic potential for ACTH-secreting than for hormonally quiescent typical carcinoids but this hypothesis is not validated by other Authors⁴. Additionally, differently from non-secreting tumors, in ACTH-secreting bronchial carcinoids, the ACTH concentration might be used as a marker of persistence of disease after surgery. In all of our patients ACTH clearly decreased post-operatively to low or normal values (Table I), but a correct cut-off point for the interpretation of a post-operative ACTH value cannot be easily set.

Diagnosing an ACTH-producing bronchial carcinoid is difficult: standard imaging techniques (CT-Scan or MRI) are often sub-optimally accurate. The introduction of radionuclide scan techniques have improved the detection of these neoplasms due to the radiopharmaceutical tumour-specificity and the possibility of checking the whole body in one run. Nevertheless, to date, the intra-operative surgical assessment remains critical essentially for the size (consistently small) and the multi-focality of these tumours.

Moreover, an incomplete radical excision with a symptomatic persistence of the disease (Cushing's syndrome) often occurs because of the problematic intra-operative detection of all disease foci and lymph nodal metastases.

Only few reports exist in the literature describing radio-guided surgery with ^{111}In -pentetreotide for bronchial carcinoids. In 1997 Mansi et al⁷ reported a case of a 28 year old male patient with Cushing's syndrome from an adrenocorticotrophin (ACTH)-secreting bronchial carcinoid who, four days after receiving a 3 mCi i.v. injection of ^{111}In -DTPA-D-Phe1-octreotide, underwent radio-guided surgery with the assistance of a gamma detection probe. This procedure allowed for the achievement of an accurate localization and resection of a 1.8 cm tumour in the right lower lobe. Similarly, in 2005, Grossrubatscher et al⁶ reported

on a 28 year old female patient with Cushing's syndrome from an adrenocorticotrophin (ACTH)-secreting bronchial carcinoid who, two days after receiving a 4 mCi i.v. injection of ^{111}In -DTPA-D-Phe1-octreotide, underwent radio-guided surgery with the assistance of a gamma detection probe and which allowed for accurate localization and resection of multiple metastatic lymph nodes within the upper mediastinal region.

In the present report, we have described the use of intra-operative ^{111}In -pentetreotide detection in the surgical management of two cases of ACTH-secreting bronchial carcinoids.

In particular, this technique has been demonstrated to be a useful tool in:

- The accurate localization of the tumour (Case 2)
- The verification of the operated area (surgical bed, surrounding structures, Case 1 and 2)
- The accurate localization (and, therefore, the chance of excision) of millimetric lymph nodal metastases, already up-taking at preoperative ^{111}In -pentetreotide scan (Case 1)
- The detection of microscopic lymph nodal metastases undetected at the pre-operative ^{111}In -pentetreotide scan (Case 2).

In conclusion, intra-operative ^{111}In -pentetreotide detection appears to be a safe and "easy to do" technique in the management of ACTH-secreting bronchial carcinoids and a probably useful approach in all scintigraphically detectable bronchial carcinoids. By means of conventional approach we would have not been able to achieve the level of completeness we could obtain with this innovative approach. For this reason and based upon the data we have reported, we promote further investigations and warmly advocate the validation of this approach to be inserted in the clinical management procedures regarding carcinoids via a prospectively planned evaluation in larger series.

References

- 1) GOULD VE, LINNOILA RI, MEMOLI VA, WARREN WH. Neuroendocrine components of the bronchopulmonary tract: hyperplasias, dysplasias and neoplasms. *Lab Invest* 1983; 49: 519-537.
 - 2) KRENNING EP, BAKKER WH, BREEMAN WA, et al. Localization of endocrine-related tumours with a radioiodinated analogue of somatostatin. *Lancet* 1989; 1: 242-244.
 - 3) OLIARO A, FILOSSO PL, BELLO M, CASADIO C, ANGUSTI T, MASANEI I, MAGGI G, BISI G. Use of ^{111}In -DTPA-Octreotide scintigraphy in the diagnosis of neuroendocrine and non-neuroendocrine tumors of the lung. Preliminary results. *J Cardiovasc Surg (Torino)* 1997; 38: 313-315.
 - 4) LOLI P, VIGNATI F, GROSSRUBATSCHER E, DALINO P, POSSA M, ZURLENI F, LOMUSCIO G, ROSSETTI O, RAVINI M, VANZULLI A, BACCHETTA C, GALLI C, VALENTE D. Management of occult adrenocorticotropin-secreting bronchial carcinoids: limits of endocrine testing and imaging techniques. *J Clin Endocrinol Metab* 2003; 88: 1029-1035.
 - 5) ADAMS S, BAUM RP, HERTEL A, WENISCH HJ, STAIB-SEBLER E, HERRMANN G, ENCKE A, HÖR G. Intraoperative gamma probe detection of neuroendocrine tumors. *J Nucl Med* 1998; 39: 1155-1160.
 - 6) GROSSRUBATSCHER E, VIGNATI F, DALINO PJ, POSSA M, BELLONI PA, VANZULLI A, BRAMERIO M, MAROCCHI A, ROSSETTI O, ZURLENI F, LOLI P. Use of radioguided surgery with [^{111}In]-pentetreotide in the management of an ACTH-secreting bronchial carcinoid causing ectopic Cushing's syndrome. *Endocrinol Invest* 2005; 28: 72-78.
 - 7) MANSI L, RAMBALDI PF, PANZA N, ESPOSITO D, ESPOSITO V, PASTORE V. Diagnosis and radioguided surgery with ^{111}In -pentetreotide in a patient with paraneoplastic Cushing's syndrome due to a bronchial carcinoid. *Eur J Endocrinol* 1997; 137: 688-690.
 - 8) STOKKEL MP, BOOT IN, SMIT JW. Personal dosimetry of the staff during treatment of neuroendocrine tumours with a high dose of Indium-111 Octreotide. *Q J Nucl Med* 2002; 46: 331-335.
 - 9) KAYSER K, KAYSER C, RAHN W, BOVIN NV, GABIUS HJ. Carcinoid tumors of the lung: immuno- and ligando histochemistry, analysis of integrated optical density, syntactic structure analysis, clinical data, and prognosis of patients treated surgically. *J Surg Oncol* 1996; 63: 99-106.
 - 10) SHRAGER JB, WRIGHT CD, WAIN JC, TORCHIANA DF, GRILLO HC, MATHISEN DJ. Bronchopulmonary carcinoid tumors associated with Cushing's syndrome: a more aggressive variant of typical carcinoid. *J Thorac Cardiovasc Surg* 1997; 114: 367-375.
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