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Tyrosine positron emission tomography and protein synthesis rate in pituitary adenoma: different effects of surgery and radiation therapy

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Abstract

Introduction Positron Emission Tomography (PET) using amino acid tracers is able to establish biochemical tumour characterization *in vivo*. The use of PET in the follow-up of non-functioning pituitary adenomas (NFA) and growth hormone producing pituitary adenomas (GHA) after surgery and radiation treatment is not yet clear.

Methods To determine the value of PET before and after transsphenoidal neurosurgery in NFA and GHA, we investigated 12 patients with pituitary adenoma (9 NFA and 3 GHA) before and 4 months after surgery with magnetic resonance imaging (MRI) and tyrosine PET (TYR-PET). Three years after radiation therapy TYR-PET was used to document residual activity in 6 of these patients (4 NFA and 2 GHA). Tumour size was quantified by computerized MRI measurements. In TYR-PET, tumour activity was assessed by computerized measurements of the hot spot and by determination of protein synthesis rate (PSR).

Results In response to surgery, MRI showed a median tumour volume reduction of 58% ($P < 0.01$). TYR-PET demonstrated 62% volume reduction ($P < 0.02$), but no change in PSR ($P > 0.30$). After radiation therapy the MRI-volumes of the residual pituitary adenomas did not change but the volume of the hot spot on TYR-PET-imaging was reduced by 58% ($P = 0.02$), and PSR decreased in 5 of 6 patients ($P = 0.12$)

Conclusion Amino acid PET tumour activity is reduced parallel with MRI volume changes after surgery. The decrease in TYR-PET activity after radiation therapy, despite unaltered MRI tumour volume, supports the concept that it is possible to follow biological tumour activity with this technique. The diagnostic merit of this tracer technique, predicting pituitary adenoma regrowth, needs to be validated in a large prospective study.

Introduction

In view of the high recurrence rate in case of residual pituitary adenoma after surgery alone the accurate evaluation of post-operative residual pituitary adenoma by imaging techniques is essential^{1,2}. The detection of residual pituitary adenoma after surgery by magnetic resonance imaging (MRI) and/or computed tomography (CT) is frequently hampered by postoperative tissue remodelling^{3,4}. It is particularly difficult to distinguish residual vital adenoma tissue from operative changes in sellar structures, and to discriminate between vital and non vital tissue after radiation therapy. Moreover, it is obvious that the diagnostic yield of hormonal assessment is mostly restricted to those tumours which abnormally secrete anterior pituitary hormones, like growth hormone, adrenocorticotrophic hormone and prolactin. Therefore an additional imaging technique is necessary which enables to document the biological behaviour of the tumour.

Pituitary adenomas are characterized by a high amino acid metabolism⁵⁻⁸. Consequently, positron emission tomography (PET) with radio labeled amino acids may be a suitable method for accurate detection of the activity of these tumours in response to medical and surgical treatment and radiation therapy. Accordingly, it has been shown in prolactinoma and growth hormone producing pituitary adenoma (GHA)⁹, that amino acid metabolism changes in response to medical treatment⁵, but treatment responses after surgery and radiation therapy in NFA and GHA have not been reported so far.

L-[1-¹¹C]-tyrosine is suitable for calculation of protein synthesis rates, since this tracer has a small pool of free tyrosine in plasma and tissue and a rapid high incorporation into protein, which is not hampered by the blood brain barrier. This allows not only visualization but also quantification of the protein synthesis rate (PSR), which is higher in metabolically active and proliferating pituitary adenoma than in normal brain tissue^{5,10,11}.

We hypothesized that after surgical tumour reduction TYR-PET tumour volume would decrease parallel with MRI tumour volume changes, without affecting PSR. In view to the efficacy of radiation therapy to prevent re-growth of residual pituitary adenoma¹, we expected that this treatment would, in contrast, affect biological tumour activity, as determined by TYR-PET tumour volume and/or PSR. The present study was therefore initiated to demonstrate the feasibility of pituitary TYR-PET imaging and measurement of protein synthesis rate after neurosurgical intervention and in response to radiation therapy.

Patients and methods

Patient characteristics

The study was approved by the medical ethics committee of the University Medical Center Groningen, and all participants provided informed consent. In all patients, hormonal

evaluation was carried out to determine hormonal deficiencies using pre-specified cut off values for hormonal deficiencies¹². Before entry in the study, they had received replacement therapy with thyroid hormone and glucocorticoids if necessary. In case of suspected acromegaly, growth hormone excess was established by an elevated level of growth hormone during a glucose tolerance test and an elevated level of insulin-like growth hormone-1 in plasma. None of the patients was considered to have prolactinoma or Cushing's disease. In all patients transsphenoidal surgery was carried out and the pituitary tumour classified as NFA or GHA on histopathological grounds (9 NFA and 3 GHA). In 6 of these patients (4NFA and 2 GHA) MRI and PET-images were performed 3 years after radiation therapy.

PET acquisition and imaging analysis

TYR-production

TYR was produced via a modified microwave induced Bücherer-Strecker synthesis. The radiochemical purity was over 99%. A mean dose of 300MBq (range 55-375MBq) of TYR was injected intravenously. The procedures were protocolized to assure a maximum pharmaceutical quality. Radiochemical and chemical purity were verified by high performance liquid chromatography.

Blood sampling

All quantitative PET sessions included placement of a catheter in the radial artery for sampling blood radioactivity. During the sessions, blood samples were taken at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.25, 2.75, 3.75, 4.75, 7.50, 12.50, 17.50, 25.00, 35.00, 45.00 minutes after injection.

Camera

PET sessions were performed with an ECAT 951/31 camera (Siemens/CTI, Knoxville, USA). A transmission scan of 20 minutes to correct for attenuation was obtained immediately before the emission scan. The spatial resolution of the camera was 5 mm. in the center of the field of view. TYR was administered as a one minute bolus via a MEDRAD MCT Plus infusion pump. Axial images with a slice thickness of 3mm. were made of the head and neck area. A region of interest (ROI) was drawn around the hot spot in the sella turcica by hand on the relevant planes and the volume of the ROI and the PSR in the ROI were calculated.

All PET-measurements were determined twice, immediate after imaging and at the time of completion of this study, with no discrepancies in measured volumes and PSR between the first and second measurements.

MRI acquisition and imaging analysis

Tumour size on MRI (1.5T Siemens; slice thickness of 3 mm) was quantified by computerized measurements on coronal T1-weighted (TR/TE 650-800/20) contrast-enhanced images and a restricted field of view (20 × 20 cm), after identification of the tumor boundaries by one neuro-radiologist (AMvdV). The major criteria used for pituitary adenoma detection on MRI were or no enhancement or delayed contrast enhancement after injection of gadolinium. MRI-images and PET-images were evaluated separately, each investigator being blinded for the results of the other technique.

Statistical analysis

Data are given in medians (ranges). Data before and after intervention were compared using the paired Wilcoxon test. Relationships between variables were determined by Spearman's rank correlation analysis. A two-sided P-value < 0.05 was considered significant.

Results

We studied 12 patients with pituitary macroadenomas (9 patients with NFA and 3 with GHA) who were evaluated before transsphenoidal surgery and 4 months after. Before and shortly after neurosurgery all GHA patients had biochemical evidence of growth hormone hypersecretion, but they were not treated with somatostatin analogues, pegvisomant or dopamine-agonists. This group included 9 men and 3 women with a median age of 46 (range 25 - 68 years). As determined by MRI, tumour volume decreased by 58% (median) from 4.85 (1.4-13.9) cm³ to 2.6 (0-12.2) cm³ postoperatively (P < 0.01). Using TYR-PET, metabolic tumour volume decreased by 62% from 5.05 (1.1-8.0) to 2.05 (0-6.6) cm³ (P < 0.02). Figure 1 demonstrates TYR-PET imaging results pre- (A) and postoperatively (B) in a representative NFA patient. The tumour volume as determined by TYR-PET was not significantly different from its volume by MRI, both pre- or postoperatively (combined-data set, n = 24, P > 0.30). The relationship between MRI tumour volume and TYR-PET tumour volume also did not differ either between the pre- and postoperative situation. In the combined data-set, these measures of tumour volume were positively correlated (r = 0.58, P < 0.01). PSR was 35.3 (28.4-63.8) mmol/ml/min pre-operatively, and remained unchanged after transsphenoidal surgery (33.4 (0-62.4) mmol/ml/min, P > 0.30; median change -3.3%).

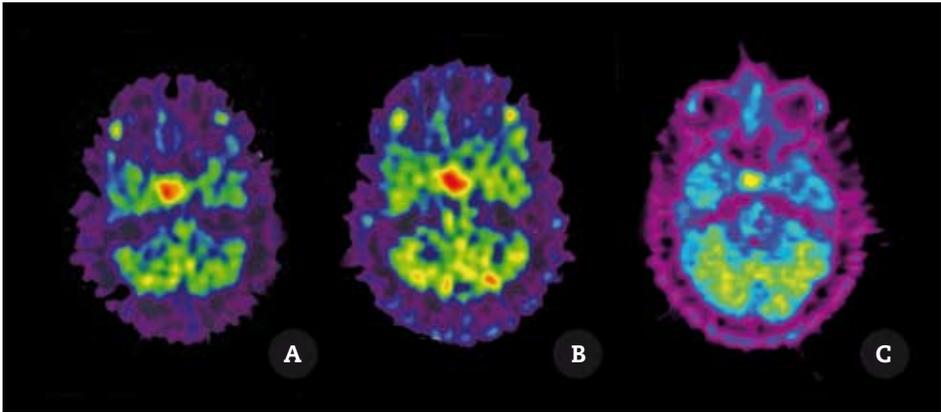


Figure 1 A representative axial PET-image of one NFA patient before (A) and 4 months after surgery before radiation therapy (B) and 3 yrs after radiation therapy (C)

To determine the effect of radiation therapy on pituitary TYR-PET characteristics, we studied 6 patients before and approximately 3 years after this treatment. This group comprised 4 patients with NFA and 2 patients with GHA, who also participated in the neurosurgical intervention protocol. In these patients the pituitary tumour was not completely removed by surgery or active acromegaly had persisted after this treatment. Fractionated radiation therapy was applied with 1.8 Gray daily dose to a total of 45 Gray in 5 weeks, using a three to five field technique, and was given 6 months after transsphenoidal surgery. This group included 5 men and 1 women with a median age of 48 (range 37- 60) years. In these patients, tumour volume by MRI was very similar before (1.95 (1-4.9) cm³) and after radiation therapy 1.95 (1-4.9) cm³, $P = 1.0$; median change 0%). In contrast, TYR-PET tumour volume decreased by 58% from 2.05 (1-3.7) to 1.0 (0-1.9) cm³ ($P = 0.02$) (Figure 2), whereas PSR decreased in 5 patients (total group: 67% change from 33.4 (2.6-40.8) to 13.2 (0-46.2) mmol/ml/min, $P=0.12$) (Figure 3). Figure 1 demonstrates TYR-PET imaging results before radiation therapy (B) and 3 years after radiation therapy (C) in a representative NFA patient.

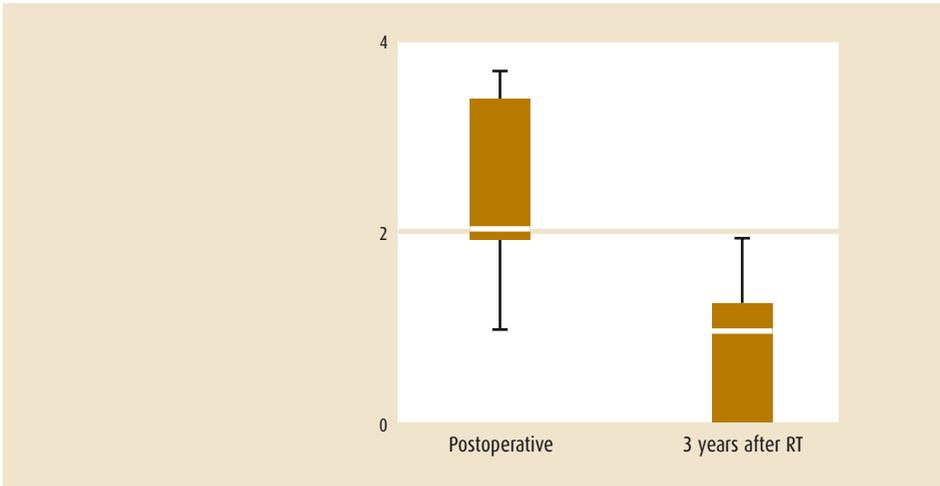


Figure 2 PET-volumes (cm^3) of the pituitary adenomas 4 months after surgery before radiation therapy and 3 years after radiation therapy. Medians, interquartile ranges and 5% and 95% ranges are shown in the boxplots.

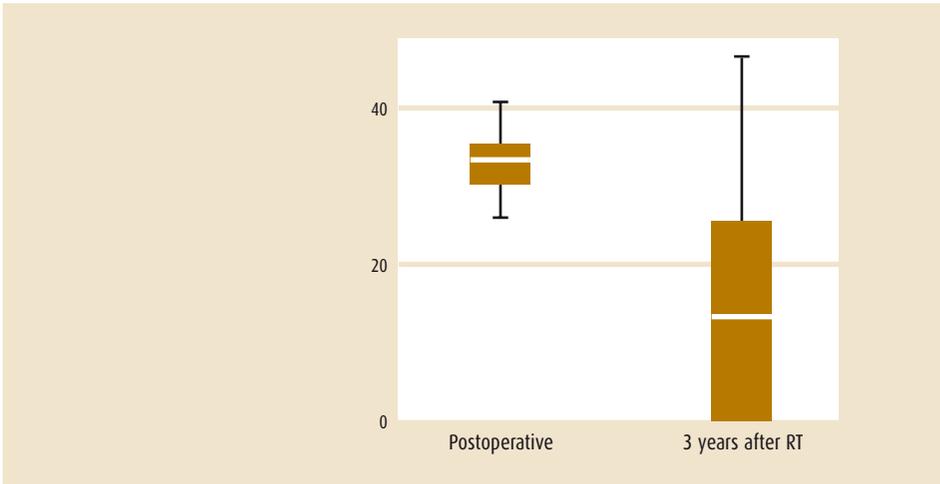


Figure 3 PSR values (mmol/ml/min) of the pituitary adenomas 4 months after surgery, but before radiation therapy and 3 years after radiation therapy. Medians, interquartile ranges and 5% and 95% ranges are shown in the boxplots.

Discussion

This study has demonstrated that in all untreated NFA and GHA patients tested abnormal TYR-PET uptake is present and PSR can be determined. Our findings therefore suggest, that PET imaging using amino acid as tracer is a feasible technique to document amino acid metabolism in these tumours *in vivo*. The volume of the TYR-PET uptake decreased parallel with the MRI tumour volume reduction after transsphenoidal surgery. In response to radiation therapy however, the volume of the TYR-PET uptake decreased but the MRI tumour volume did not show any change. These findings support the concept that this technique bears clinical potential to detect changes in biological activity of these tumours.

Several amino acid tracers, including ^{14}C -Methionine have been used so far to detect biological activity of pituitary adenoma. In this study, we used L-[1- ^{14}C]-Tyrosine as tracer, because Tyrosine has a higher incorporation into proteins and a lower amount of metabolites than methionine in brain and tumour tissue¹¹, and this tracer is not incorporated to a relevant extent in normal pituitary tissue and in brain tissue, as documented in PET-imaging studies of glioma patients^{13,14}. Furthermore, in animal models a radiation dose-dependent reduction of tracer uptake has been reported, which correlated with the changes in tumour volume¹⁵. In the present study, its incorporation in NFA and GHA was found to be sufficient for imaging. Thus, all NFA and GHA were well visualized because the high ratio of uptake in the adenoma compared to the surrounding structures.

MRI is considered to be the imaging modality of choice for the diagnosis and follow-up of pituitary disorders, because of its adequate soft tissue contrast⁴. In our study, there was considerable agreement between TYR-PET and MRI tumour volumes, and tumour volume measured by MRI was not significantly different compared to its TYR-PET volume. It seems that heterogeneity of tracer uptake within adenoma or its remnant was not large enough to result in measurable differences in tumour volume between these imaging techniques. Indeed, in agreement with our hypothesis that radiation therapy would affect TYR-PET uptake and/or PSR, we observed that TYR-PET but not MRI tumour volume decreased after radiation therapy, which can be expected to diminish protein metabolism in remaining tumour tissue⁶. TYR-PET imaging may therefore provide a clinically relevant imaging technique which is complementary to MRI. In particular, the presence of residual pituitary adenoma after surgery has therapeutic consequences¹, and our study raises the possibility that abnormal amino acid PET imaging and metabolism in pituitary adenoma after neurosurgical intervention could be helpful to target additional therapy. However, we could not perform fusion of MRI with TYR-PET scanning with the presently used imaging modalities, and it was not possible to document abnormalities in pituitary anatomy precisely with TYR-PET imaging. Finally, our

report should be regarded as a proof of concept study. A limitation is its small sample size, which precludes to determine the value of PET in NFA compared to hormone secreting tumours, such as GHA, ACTH-producing adenomas and prolactinomas.

In conclusion, the present preliminary study results suggest that TYR-PET may yield complementary information regarding biological tumour activity in NFA and GHA. The diagnostic value of this tracer technique to predict pituitary adenoma behaviour needs to be validated in a larger long-term study.

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