Treatment monitoring with ^{18}F-FDG PET in metastatic thymoma after ^{90}Y-Dotatoc and selective internal radiation treatment (SIRT)

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Abstract

A 39 years old male patient with a history of an unresectable thymoma and synchronous liver metastases was referred tor our position. The patient had been originally treated with systemic chemotherapy followed by imatinib (Glivec) and sunitinib (Sutent). Since the therapeutic response was unsatisfactory, a gallium-68 (^{68}Ga)-Dotatoc-positron emission tomography (PET) was performed and demonstrated an enhanced SSTR 2 expression in the primary tumor but not in the liver metastases. Three cycles of yttrium-90 (^{90}Y)-Dotatoc were then administered. Outcome after treatment was monitored by ^{18}F-FDG-PET and CT and showed a response only of the primary tumor. Selective internal radiation treatment (SIRT) with ^{90}Y microspheres was then applied for the liver metastases. ^{18}F-FDG uptake showed that metabolism in the liver metastases decreased after SIRT. MRI of the liver demonstrated a decrease in vascularization and a modest decrease in tumor volume. Therefore, surgical resection of the primary thymoma was initiated.

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Case description

A 39 years old male patient with a history of an unresectable thymoma and synchronous liver metastases was referred to our position. A surgical resection of the primary tumor was not considered due to multiple liver metastases. The patient had been originally treated with systemic chemotherapy and had received imatinib (Glivec) as well as sunitinib (Sutent) later as an experimental treatment. Imatinib is the first member of a new class of agents, which act by inhibiting in particular tyrosine kinase enzymes and was primarily used for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST) but is also used for the treatment of other malignancies, such as thymomas [1]. Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor, which inhibits cellular signaling by targeting all receptors for platelet-derived growth factor (PDGFR) and vascular endothelial growth factor (VEGFR) and plays a role in both angiogenesis and proliferation. Furthermore, it inhibits other receptor tyrosine kinases (e.g. like CD 117 and flt 3). Sunitinib was primarily used for the treatment of renal cell carcinoma and imatinib-resistant GIST, but is also administered for other malignancies. After progression of liver metastases under imatinib treatment, therapy with sunitinib was initiated. An ^{18}F-FDG scan was performed for staging and clearly demonstrated an enhanced uptake in multiple liver lesions as well as in the primary thymoma. Furthermore, a ^{68}Ga -Dotatoc positron emission tomography (PET) was additionally performed and demonstrated an enhanced SSTR 2 expression in the primary tumor but not in the liver metastases. Due to the enhanced Dotatoc-uptake in the primary tumor, a radionuclide treatment consisting of three cycles (12GBq) of yttrium-90 (^{90}Y)-Dotatoc was then administered in order to control the primary thymoma. Sunitinib therapy was continuously applied (50mg/d) to prevent a progression in the liver metastases. Interestingly, the thymoma showed a decrease in fluorine-18 fluorodesoxyglucose (^{18}F-FDG) metabolism following the radionuclide treatment. As expected, liver metastases did not show any response to this treatment. Outcome after treatment was monitored by ^{18}F-FDG-PET and CT.

Ultimately, progression of the liver metastases after sunitinib therapy was noted, and selective internal radiation treatment (SIRT) with ^{90}Y microspheres (2.3GBq) was applied. ^{18}F-FDG-PET and magnetic resonance imaging (MRI) were performed prior and following SIRT treatment to monitor the therapeutic effect. Histological studies of one liver metastasis prior to SIRT based on a fine needle aspiration biopsy demonstrated a poorly differentiated carcinoma with strong expression of DC117/c-KIT on immunohistochemistry (Fig. 1).

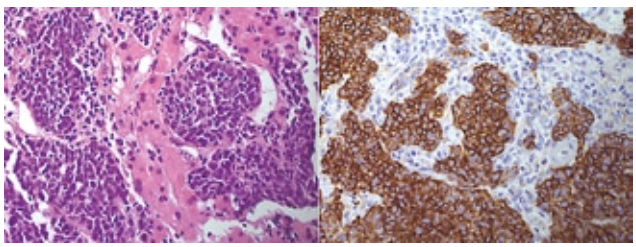

Figure 1. Histological image of the liver metastasis prior to SIRT. Conventional Hematoxylin and Eosin (H&E) staining shows morphology of a poorly differentiated carcinoma (left panel) with strong expression of CD117/c-KIT on immunohistochemistry (right panel).

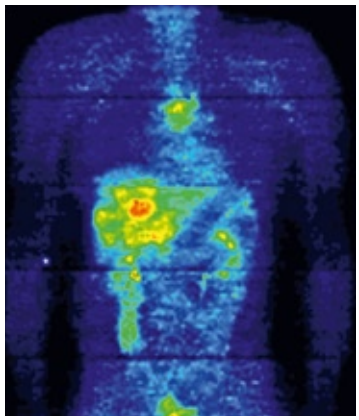

Figure 2a. ^{18}F-FDG-PET image prior to SIRT. Enhanced ^{18}F-FDG-uptake in multiple liver metastases. Increased ^{18}F-FDG-uptake in the primary thymoma.

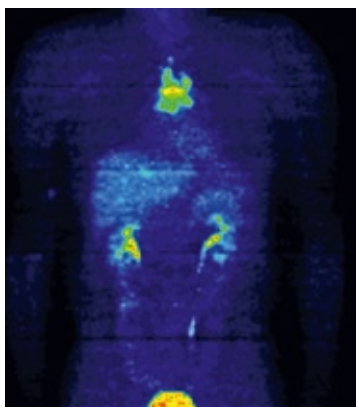

Figure 2b. ^{18}F-FDG-PET image three months following SIRT. Clearly decrease of the ^{18}F-FDG-uptake in the liver metastases. Still enhanced ^{18}F-FDG-uptake in the primary thymoma.

The ^{18}F-FDG-PET study prior to SIRT showed a clearly increased ^{18}F-FDG uptake in multiple liver metastases located in both liver lobes with mean standardized uptake values (SUV) varying between 3.8 and 6.8 (Fig. 2a). Inhomogeneous ^{18}F-FDG-metabolism with high phosphorylation was shown in the segments 4-8 and also in segment 2. Immediately after SIRT the SUV was decreased in the liver metastases. Finally, only one lesion located in segment 8 was still active with an average SUV of 5.4. A follow-up ^{18}F-FDG-PET three months after SIRT showed a further decrease in ^{18}F-FDG uptake and the liver metastases could not be delineated (Fig. 2b). The MR images of the liver demonstrated multiple hypervascularized liver lesions as shown in Figure 3a. Following SIRT MRI demonstrated a decrease in vascularization and a modest decrease in tumor volume (Fig. 3b). As the FDG metabolism and the vascularization of the liver metastases decreased under SIRT, a surgical resection of the primary thymoma was indicated.

Radionuclide therapy with ^{90}Y -Dotatoc is an experimental therapy used in patients with tumors, which show an enhanced SSTR2 expression. Prerequisite for an ^{90}Y -Dotatoc therapy is an enhanced ^{68}Ga -Dotatoc uptake in the tumors prior to therapy [2]. The idea for using ^{90}Y -Dotatoc in this patient was an experimental approach due to failure of conventional chemotherapy. Therapeutic effect was expected only for the SSTR2-positive lesion, which was the primary tumor. Bertagna et al. reported on a patient with medullary thyroid carcinoma and right ventricular cardiac metastasis who was treated with ^{90}Y -Dotatoc with a good therapeutic result. This patient demonstrated a stable disease based on RECIST and WHO criteria [3]. Stoeltzing et al. reported on the value of neoadjuvant ^{90}Y -Dotatoc -therapy in neuroendocrine tumors with advanced liver metastases. In a one-year follow-up, they did not found any recurrence of tumor or other metastases [4].

Selective internal radiation treatment is similar to chemoembolization but uses radioactive microspheres. The treatment uses the radioactive isotope ^{90}Y inside resin emboligen microspheres to deliver radiation directly to the tumor. Each sphere is about the size of five red blood cells. The spheres are

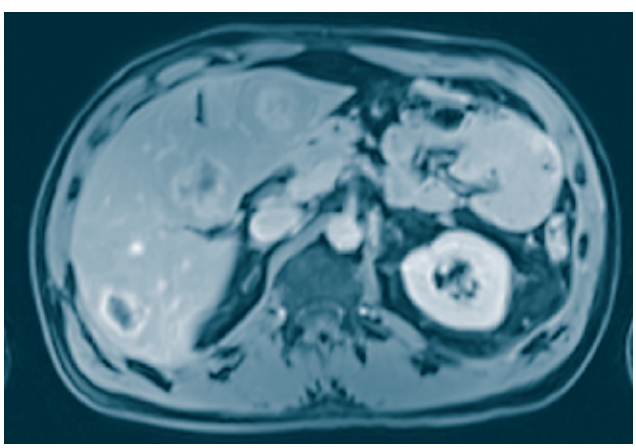

Figure 3a. MRI of the liver prior therapy: T1 weighted image (VIBE-sequence) demonstrates three vascularized nodules in both liver lobes with enhancement in the margin as well as in the centre.

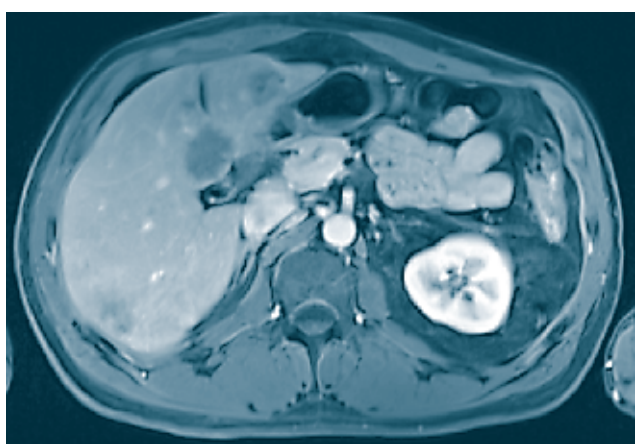

Figure 3b. MRI of the liver four months after SIRT: T1 weighted image (VIBE-sequence) demonstrates a decrease in the vascularization of the three nodules and a modest regression in size.

applied by a laminar flow procedure through a catheter selectively introduced into the right and left artery, which supplies the liver metastases in most cases. This technique allows for a higher local radiation dose to be used for the treatment of the liver metastases without subjecting the normal surrounding tissue. First introduced in the 1980's, the use of SIRT-therapy in liver metastases has been reshown by Gulec et al. in 2009. In the present case, the preoperative treatment with ^{90}Y - microspheres resulted in tumor downsizing and aspired as an effective liver-directed therapy with favorable therapeutic ratio [5]. One has to be aware of potential side effects of SIRT. Moroz et al. identified the risk of developing a subclinical portal hypertension in patients treated with SIRT and hepatic arterial chemotherapy because of significant increase of portal vein diameter and spleen size 12 months after treatment [6]. Fortunately, this was not the case in this patient.

The evaluation of the therapeutic effect of SIRT with anatomic imaging alone is suboptimal. Changes in tumor size are less sensitive and do not provide information on early therapeutic effects [7-10]. ^{18}F-FDG-PET imaging is more sensitive in the evaluation of early response to SIRT by showing early changes in metabolic activity of lesions [11]. Anovazzi et al. showed, that changes in metabolism as measured by ^{18}F -FDG-PET are more sensitive than changes in tumor volume as measured by CT-imaging in non-endocrine neoplastic disorders of the gastrointestinal tract. Therefore, metabolic imaging using FGD-PET should be used for monitoring liver metastases of thymomas [12]. Wong et al. demonstrated a significant decrease of tumor metabolism by FDG-PET after SIRT in 19 patients with metastatic liver lesions. The results demonstrated a significant change in the total liver SUV in the response group [13]. Also Pöpperl et al. showed in 23 patients with nonresectable liver tumors a decrease in tumor size, an increase of survival time and a drop of tumor markers after performing SIRT [14]. In another study, Wong et al. used SIRT in 46 patients with surgically unresectable and chemotherapy-refractory liver metastases of different solid tumors and demonstrated a significant decrease in the FDG metabolism of liver tumor after the treatment [15].

However, this example clearly demonstrates that individualization of treatment including combination of different therapeutic protocols is necessary to achieve a good therapeutic result. A dedicated therapy monitoring including a combined functional and anatomic imaging is also necessary for the quantitative assessment of the therapeutic result. In this case of metastatic thymoma, only the combination of different experimental therapies, including ^{90}Y -Dotatoc, Sunitinib and SIRT led to a good therapeutic result.

Bibliography

1. Ströbel P, Hartmann M, Jakob A et al. Thymic Carcinoma with Overexpression of Mutated *KIT* and the Response to Imatinib. *N Engl J Med* 2004; 350: 2625-2626.
2. Miederer M, Seidel S, Buck A et al. Correlation of immunohistopathological expression of somatostatin receptor 2 with standardized uptake values in 68Ga-DOTATOC PET/CT. *Eur J Med Mol Imaging* 2009; 36: 48-52.
3. Bertagna F, Giubbini R, Savelli G et al. A patient with medullary thyroid carcinoma and right ventricular cardiac metastasis treated by ^{90}Y-Dotatoc. *Hell J Nucl Med* 2009; 12: 161-164.
4. Stoeltzing O, Loss M, Huber E et al. Staged surgery with neoadjuvant ^{90}Y-DOTATOC therapy for down-sizing synchronous bilobular hepatic metastases from a neuroendocrine pancreatic tumor. Langenbecks Arch Surg. 2009; DOI 10.1007/s00423-009-0520-x.
5. Gulec SA, Pennington K, Hall M, Fong Y. Preoperative ^{90}Y microsphere selective internal radiation treatment for tumor downsizing and future liver remnant recruitment: a novel approach to improving the safety of major hepatic resections. *World J Surg Oncol* 2009; 7:6.
6. Moroz P, Anderson JE, Van Hazel G, Gray BN. Effect of selective radiation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume. *J Surg Oncol* 2001; 78: 249-252.
7. Bienert M, McCook B, Carr BI et al. ^{90}Y microsphere treatment of unresectable liver metastases: change in ^{18}F-FDG uptake and tumor size in PET/CT. *Eur J Nucl Med Mol Imaging* 2005; 32: 778-787.
8. Lin M, Shon IH, Wilson R et al. Treatment response in liver metastases following ^{90}Y SIR-spheres: an evaluation with PET. *Hepatogastroenterology* 2007; 54: 910-912.
9. Dierckx R, Maes A, Peeters M, Van de Wiele C. FDG PET for monitoring response to local and locoregional therapy in HCC and liver metastases. *Q J Nucl Med Mol Imaging* 2009; 53: 336-342.
10. Torizuka T, Tamaki N, Inokuma T et al. Value of fluorine-18-FDG-PET to monitor hepatocellular carcinoma after interventional therapy. *J Nucl Med* 1994; 35: 1965-1999.
11. Szyszko T, Al-Nahhas A, Canelo R et al. Assessment of response to treatment of unresectable liver tumors with ^{90}Y microspheres: value of FDG PET versus computed tomography. *Nucl Med Commun* 2007; 28: 15-20.
12. Anovazzi A, Peeters M, Maenhout A et al. 18-Fluorodesoxyglucose positrone emission tomography in non-endocrine neoplastic disorders of the gastrointestinal tract. *Gastroenterology* 2003; 125: 1235-1245.
13. Wong CY, Quing F, Savin M et al. Reduction of metastatic load after intraarterial hepatic yttrium-90 radioembolization as evaluated by [^{18}F]fluodeoxyglucose positron emission tomographic imaging. *J Vasc Interv Radiol* 2005; 16: 1101-1106.
14. Pöpperl G, Helmberger T, Münzing W et al. Selective internal radiation therapy with SIR-Spheres in patients with nonresectable liver tumors. *Cancer Biother Radiopharm* 2005; 20: 200-208.
15. Wong CY, Savin M, Sherpa KM et al. Regional yttrium-90 microsphere treatment of surgically unresectable and chemotherapy-refractory metastasic liver carcinoma. *Cancer Biother Radiopharm* 2006; 21: 305-313.