# A recent application of fluoro-18-deoxyglucose positron emission tomography, treatment monitoring with a mammalian target of rapamycin inhibitor: an example of a patient with a desmoplastic small round cell tumor

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## Abstract

Several mechanisms may influence the enhanced glucose uptake in cancer cells, including upregulation of glucose transporters, increase in the hexokinase activity and the protein kinase B, also called Akt, which appears to play key role in the control of glucose metabolism together with proteins which are involved in the signal cascade pathway, such as the mammalian target of rapamycin (mTOR). It has been demonstrated in patients with gastrointestinal stromal tumors (GIST) and other sarcomas who received treatment with imatinib that PET with $^{18}$F-FDG is appropriate for treatment monitoring. Data suggest that $^{18}$F-FDG monitoring may be used for monitoring not only imatinib but also other kinase inhibitors. A 36-year-old female patient with metastasized desmoplastic small round cells tumor after a broad surgical resection of the tumor area and due to related enzyme findings, was treated with the mTOR-inhibitor everolimus (Certican®, Novartis, Basel, Switzerland) at an initial dose of 3×0.5 mg per day targeting at a blood level of >11 ng/ml. A baseline $^{18}$F-FDG-PET demonstrated an enhanced FDG uptake in three large liver metastases and in another metastatic lesion in the pelvic area. A dynamic $^{18}$F-FDG-PET study performed six weeks later, demonstrated non-response to the mTOR-inhibitor. Despite the antiproliferative activity of mTOR-inhibitors in experimental model systems, its antitumor activity in patients may be limited. *In conclusion,* $^{18}$F-FDG-PET seems to be a promising method for monitoring the therapeutic effect of mTOR-inhibitors.

*Keywords:* PET – FDG – m-TOR inhibitor – Treatment monitoring

## Introduction

The use of positron emission tomography (PET) for monitoring a therapeutic result in oncological patiens is well established [1-2]. The tracer of choice is still fluor-18-fluorodeoxyglucose ($^{18}$F-FDG), a glucose analogue. The biological background for that is based on the observation of Warburg, who first described an enhanced glycolysis under aerobic conditions, which is characteristic for malignant cells [3]. It is known, that FDG is transported by different glucose transporters by the cells and is then phosphorylated by hexokinases to the glucose-6-phosphate (FDG-6P). The FDG-6P is not a good substrate for further enzyme action and is therefore not further metabolized.

## Monitoring of protein kinase inhibitors

Protein kinases are enzymes that modify other proteins by phosphorylation. Phosphorylation usually results in a functional change of the target protein by changing the enzyme activity, cellular location or association to other proteins. Kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction, but also cell proliferation, cell movement and cell death (apoptosis). Kinases are turned on or off by phosphorylation. This occurs usually due to binding of activator proteins or inhibitor proteins or small molecules.

Several mechanisms may influence the enhanced glucose uptake in cancer cells, including upregulation of glucose transporters, increase in the hexokinase activity, oncogenic transformation as well as HIF1a activation.[4-5]. The protein kinase B, also called Akt, is a signal transduction protein with multiple functions, which appears to play key role in the control of glucose metabolism together with proteins which are involved in the signal cascade pathway, such as the mammalian target of rapamycin (mTOR). Therefore, $^{18}$F-FDG-PET is appropriate for monitoring treatment of protein kinase inhibitors. This has been demonstrated in patients with gastrointestinal stromal tumors (GIST) who received treatment with imatinib. GIST are characterized by a mutationally activated CD 117 (also known as c-KIT) receptor tyrosine kinase that is inhibited by imatinib. Cluster of differentiation (CD) molecules are markers on the cell surface used to identify cell type, stage of differentiation and activity of a cell. Follow-up studies with $^{18}$F-FDG demonstrated a significant reduction in the metabolism as early as one day after the first imatinib application. Furthermore, in a study with GIST and other soft tissue sarcomas, it was demonstrated that the decrease in $^{18}$F-FDG correlated to patient outcome [6]. These data suggest

that $^{18}$F-FDG may be used for monitoring not only imatinib but also other kinase inhibitors.

The mTOR is a large (serine/threonine) protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis and transcription [7]. Rapamycin is a bacterial natural product that can inhibit mTOR through association with its intracellular receptor immunophilin FK-506-Binding Protein- 12 (FKBP 12) [8]. Recent results show that mTOR integrates the input from multiple upstream pathways, including insulin and growth factors (like IGF-1 and IGF-2) [7].

## Desmoplastic small round cell tumors (DSRCT)

DSRCT are a highly aggressive tumors that mainly affect adolescent young and adults. In most cases a large abdominal mass with widespread peritoneal involvement is initially present. Histologically, they are composed of nests of small, undifferentiated round or oval hyperchromatic cells embedded in abundant desmoplastic stroma. Co-expression of epithelial, mesenchymal, and neural antigens in the same cell provides evidence of origin from a primitive pluripotent stem cell with multiphenotypic differentiation [9]. A multidisciplinary treatment including chemotherapy, surgery, radiation and myeloablative chemotherapy with stem cell rescue is in use for this rare disease. The prognosis is however still poor.

The following example demonstrates how $^{18}$F-FDG-PET can be used to monitor the therapeutic effect of an mTOR-inhibitor in a patient with DSRCT: A 36-year-old female patient with metastasized DSRCT was referred to the PET unit for a dynamic PET study with $^{18}$F-FDG. The primary tumor was located in the antrum of the stomach. A multivisceral resection was performed with an antrectomy, a mesocolon-resection, a resection of the processus uncinatus and a reconstruction by a Roux-Y anastomosis. Due to multiple liver metastases several chemotherapeutic protocols were given, however without response. Due to the age of the patient an experimental approach was considered. The histology of DSRCT was confirmed by fluorescence in-situ hybridization (FISH) and by the polymerase chain reaction method (PCR) showing the pathognomonic chromosomal t(11;22)(p13;q12) translocation. Protein extraction from snap-frozen biopsy material from a liver metastasis was performed and analyzed for activation of receptor tyrosine kinases and mitogen activated protein kinase (MAPk). This analysis revealed strong activation of ErbB2, insulin receptor, insulin growth factor receptor (IGF1R) and platelet-derived growth factor receptor (PDGFR) beta and strong activation of protein kinase B, also called Akt (PKB/AKT), glycogen-synthase kinase 3alpha, and MAPK ERK1 and ERK2. Due to these findings treatment with the mTOR-inhibitor everolimus (Certican®, Novartis, Basel, Switzerland) was initiated at an initial dose of 3×0.5 mg per day targeting at a blood level of >11 ng/ml. A written informed consent was obtained by the patient.

A baseline $^{18}$F-FDG-PET was performed, which demonstrated three large liver metastases, as well as a hypermetabolic area in the retropancreatic area and another metastatic lesion in the pelvic area ventrolateral of the bladder (Fig. 1). A dynamic $^{18}$F-FDG-PET study was performed six weeks after the initiation of treatment and demonstrated a non-response to the mTOR-inhibitor with increase of the $^{18}$F-FDG metabolism in the known metastases of the baseline study as well as the presence of new metastatic lesions (Fig. 2).

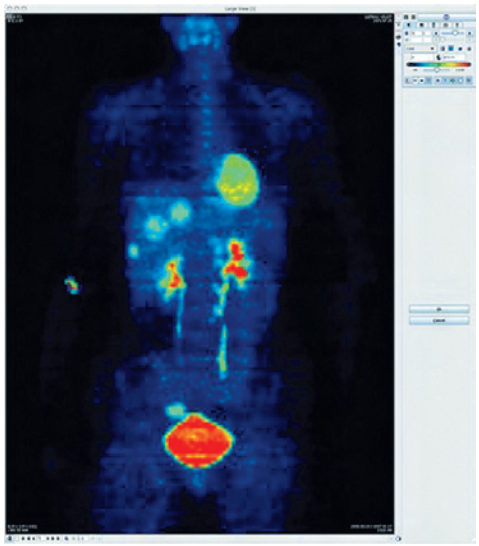

**Figure 1.** Maximum intensity projection (MIP) image of the $^{18}$F-FDG metabolism prior to the onset to mTOR-inhibitor treatment. The images demonstrate an enhanced tracer-uptake in three liver metastases as well as in the right pelvic region, ventrolateral of the bladder.

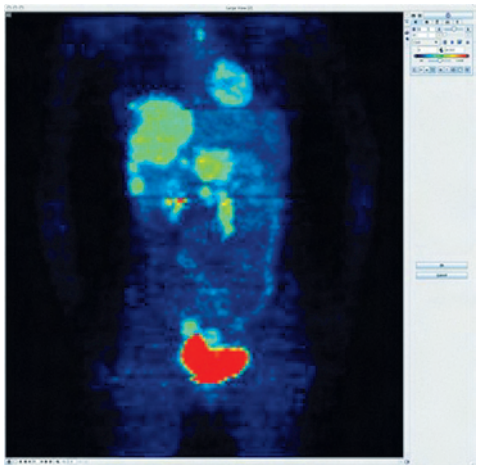

**Figure 2.** MIP-image of the $^{18}$F-FDG metabolism six weeks after the onset to mTOR-inhibitor treatment. The images demonstrate the presence of new metastatic lesions in the retropancreatic area, in the pelvic area and in the thoracic spine. The functional volume of liver metastases and all parameters of the $^{18}$F-FDG kinetics increased as compared to the baseline study.

## Discussion

Activation of phosphoinositide-3-kinase (PI3K)/Akt/mTOR signaling occurs in a majority of cancers and contributes to

deregulation of proliferation, resistance to apoptosis and changes in metabolism. This activation is regulated by upstream receptor tyrosine kinases, especially the insulin receptor and the IGF-1R. Recently, it could be shown that in DSRCT the fusion protein of chromosomal translocation might stimulate the expression of (IGF-1R) [10]. IGF-1R receptor is a potent antiapoptotic receptor tyrosine kinase that might play a role in the etiology of DSRCT. It was recently shown, that mTOR inhibition can induce IGF-1 expression and abrogate feedback inhibition of the pathway, resulting in Akt activation [11]. Furthermore, it was shown, that Akt demonstrates the ability to promote increased glucose utilization in tumors that is independent of the other effects on AKT on cell proliferation and apoptosis [12].

It was reported that despite the antiproliferative activity of mTOR-inhibitors in experimental model systems, the antitumor activity in patients may be limited [11]. This is in accordance with the presented case. One explanation of the increase of $^{18}$F-FDG-metabolism is due to the paradoxically induction of IGF-1R expression. It is known, that insulin facilitates the entry of glucose in tissue and this may lead to an enhanced uptake of $^{18}$F-FDG by stimulation of the glucose transporters. Kelley et al. reported on the effect of insulin on glucose transport and phosphorylation in normal sceletal muscle and found a 10-fold increase of FDG in normal muscle and significant increase in the rate constants for influx and phosphorylation. Furthermore, insulin increased by nearly twofold the number and area of sites labeling for GLUT-4 as measured by immunohistochemistry [13]. Activation of IGF-1R leads to mediation of insulin's effects, which can explain the increase in $^{18}$F-FDG-uptake. *In conclusion,* IGF-1R may reverse the antiproliferative effects of the mTOR inhibitor rapamycin. The same mechanism may be evident in the case of Certican, which is a rapamycin analogue (41-O-(2-hydroxy)-ethyl rapamycin). A combination treatment that ablates mTOR function and prevents Akt activation may improve antitumor activity. $^{18}$F-FDG-PET seems to be a promising method for monitoring the therapeutic effect of mTOR-inhibitors.

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