

University of Groningen

## Molecular imaging to guide clinical decisions on targeted treatment of solid tumors

Oosting-Lenstra, Sjoukje Femmy

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2014

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Oosting-Lenstra, S. F. (2014). *Molecular imaging to guide clinical decisions on targeted treatment of solid tumors*. [Thesis fully internal (DIV), University of Groningen]. s.n.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

## **Chapter 9**

### **General discussion and future perspectives**

## **Molecular imaging on the way to personalized medicine in oncology**

Over the last decade, an explosion of new targeted therapy options have become available for treatment of cancer patients. In 2012 alone, ten new targeted drugs were approved by the United States Food and Drug Administration (FDA) for cancer treatment, and for five targeted agents indication was expanded.<sup>1</sup> Several agents are approved for specific subgroups of patients based on tumor characteristics that predict treatment efficacy, such as vemurafenib for BRAF mutated melanoma and crizotinib for patients with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer.<sup>2,3</sup> However, for other drugs such as sorafenib (for advanced radioactive iodine refractory differentiated thyroid cancer) and abiraterone (for advanced castration resistant prostate cancer) no predictive biomarkers are available and selection of patients who benefit from targeted treatment remains a challenge. Molecular imaging with PET can provide insight in availability of a drug target, tumor distribution of a drug, and biologic changes after start of systemic treatment. This information could be useful to identify patients who will experience a meaningful increase in overall survival or quality of life. Another strategy to reach this goal for individual patients, are initiatives where tumor biopsies are screened for characteristics that predict response to existing drugs.<sup>4</sup> Although this patient centered approach is attractive, it will probably be hampered by heterogeneity between and within tumor lesions and by changes over time where repeat biopsy is burdensome for patients.

### **<sup>18</sup>F-FDG PET for evaluation of imatinib treatment in GIST patients**

Early after discovery of imatinib as an active agent for treatment of GIST, results of small imaging studies indicated that imatinib can induce a rapid and dramatic decrease in <sup>18</sup>F-FDG tumor uptake and that PET responders had a better progression free survival than non-responders.<sup>5,6</sup> Based on these observations, we adopted the routine practice of performing <sup>18</sup>F-FDG PET before, and 1 week after start of imatinib in GIST patients at our institute. We evaluated whether PET response predicted primary imatinib resistance, but found a false negative rate that was too high for decision making on discontinuation of imatinib. Although the confidence interval was broad because of the small size of the study, we concluded that increasing the study population was not meaningful, as PET results were highly unlikely to add significant predictive information to the upfront 85% chance of clinical benefit. The routine practice of performing repeated <sup>18</sup>F-FDG PET scans after one week of imatinib treatment in GIST patients was therefore abandoned at our institute. This retrospective study demonstrates the importance of critical evaluation of predictive value of biomarkers. An association with progression free survival does not support the use of imaging if its results do not impact on clinical decision making.

### **<sup>89</sup>Zr-bevacizumab PET no prognostic biomarker in VHL patients**

VHL patients frequently have multiple disease manifestations. Their chance to develop hemangioblastomas is 60-80% and up to 60% of the patients is diagnosed with RCC, at a mean age of 39 years.<sup>7</sup> Extensive serial imaging, ocular, blood and urine examinations are

recommended to enable early diagnosis and timely treatment of disease manifestations that pose a threat to the patient. Increased vascular endothelial growth factor A (VEGF-A) production is an important downstream consequence of loss of functional von Hippel-Lindau protein.  $^{89}\text{Zr}$ -bevacizumab did accumulate in about one third of the disease manifestations, but visibility and SUVmax was not prognostic for the behavior of a lesion. Read out of other downstream effects of VHL loss, especially hypoxia inducible factor (HIF)-independent functions such as regulation of apoptosis and stabilization of microtubules, might still be able to predict progression of lesions.

### Heterogeneity

The clinical studies that we report in this thesis using  $^{89}\text{Zr}$ -bevacizumab PET, show heterogeneity in tracer accumulation in lesions at baseline on 3 different levels: between different diseases, between patients with the same disease, and within patients.

In VHL patients, 30.8% of the lesions  $\geq 10$  mm were visualized whereas in sporadic metastatic RCC patients 56.7% of lesions were visible, with at least 1 lesion in every patient. In contrast, four out of 14 metastatic NET patients had a negative scan and in the remaining patients only 19% of the tumors  $\geq 10$  mm were detected on PET. In a previous study in breast cancer patients, 25 out of 26 primary tumors were visualized with  $^{89}\text{Zr}$ -bevacizumab PET.<sup>8</sup> The amount of tracer uptake in breast tumors (mean SUVmax 1.85) was much lower than in NET and RCC with a median SUVmax 5.8 (range 1.7 – 15.1) and 6.9 (range 2.3 – 46.9) respectively.

Heterogeneity in tumor  $^{89}\text{Zr}$ -bevacizumab uptake between patients with the same disease may reflect a meaningful difference in biology. Especially for VHL disease, where patients have both alleles of the VHL gene mutated in all lesions, the heterogeneity in tracer uptake in disease manifestations we observed is remarkable. A possible explanation is a difference in the remaining decreased capacity of VHL protein to target HIF-1 $\alpha$  for degradation, determined by the combination of the type of germline and somatic mutation.

Inpatient heterogeneity in  $^{89}\text{Zr}$ -bevacizumab uptake was unanticipated but when we were struggling with the interpretation of the results of the RCC study, the paper on mutational heterogeneity by Gerlinger et al. was published, offering clonal evolution as a possible explanation for our imaging results.<sup>9</sup> Additional mutations may affect the dependence on VEGF-A pathway activation as a driver of tumor progression. In RCC patients however, the amount of tracer accumulation also differed according to the localization, with the highest uptake in renal masses and low uptake in lung metastases, suggesting a location or organ specific effect of the microenvironment on the behavior of RCC lesions. Indeed tracer accumulation is not only dependent on extracellular VEGF-A concentration, but also on tumor perfusion and vascular permeability. Unfortunately, the relative contribution of each of these factors could not be determined in our studies. Combination of  $^{89}\text{Zr}$ -bevacizumab PET with dynamic contrast enhanced CT or MRI, or  $^{15}\text{O}$ -water PET in future studies could shed light on the relation between perfusion, permeability and tracer accumulation.

Finally, heterogeneous tumor response on  $^{89}\text{Zr}$ -bevacizumab PET was demonstrated for different antiangiogenic treatment strategies. Bevacizumab plus interferon induced a

consistent decrease in tumor tracer accumulation in metastatic RCC patients while sunitinib resulted in a decrease in the majority of the lesions but also a striking increase in an important subset of metastases. From daily clinical practice, medical oncologists and radiologists know that different lesions in a single patient can respond differently, therefore also during sunitinib treatment heterogeneity in  $^{89}\text{Zr}$ -bevacizumab tumor uptake may reflect a difference in biology. For bevacizumab treatment we assume that vascular changes play a major role in the decrease of tumor  $^{89}\text{Zr}$ -bevacizumab uptake. Also during treatment it would be interesting to investigate simultaneously tumor perfusion, permeability and  $^{89}\text{Zr}$ -bevacizumab accumulation to determine the contribution of vascular changes to the PET results.

Our findings, together with the molecular heterogeneity demonstrated by Gerlinger et al.<sup>9</sup> explain why treatment of metastatic disease with an agent targeting a single tumor characteristic is unlikely to control metastatic renal cell carcinoma at all localizations for a long period of time. Also for GIST it is known that additional acquired mutations can result in imatinib resistance.<sup>10</sup> Rational combinations of targeted treatment can add to the solution, but overlapping toxicity frequently hampers this approach. An approach that seems worthwhile to explore is combining targeted therapy with local treatment such as stereotactic radiotherapy, radiofrequency ablation or metastasectomy for tumors sites that are not responsive.

### **$^{89}\text{Zr}$ -bevacizumab PET is a potential predictive biomarker for antiangiogenic treatment**

Findings in the two VHL patients that we describe, and the study in patients with sporadic RCC, suggest that patients with high tumor  $^{89}\text{Zr}$ -bevacizumab uptake can derive prolonged benefit from treatment with angiogenesis inhibitors. Also the observation of low tracer uptake in breast cancer is interesting. Recently FDA approval for bevacizumab has been withdrawn for this indication because of lack of significant activity. This contrasts with the fact that angiogenesis inhibitors are an important component of standard of care for metastatic pancreas NET and RCC. The predictive value of  $^{89}\text{Zr}$ -bevacizumab PET for efficacy of angiogenesis inhibitors could be further explored with a single baseline  $^{89}\text{Zr}$ -bevacizumab PET scan in a randomized trial comparing treatment regimens with and without an angiogenesis inhibitor, by using the PET result as a stratification factor.

### **Molecular imaging**

For this thesis we investigated PET imaging, which is a non-invasive test evaluating whole body tumor characteristics. PET scans result in radiation exposure. For patients with metastatic disease and limited life expectancy the radiation exposure of a PET scan is not clinically relevant. However, for patients with a disease that can be cured or has a favorable prognosis, radiation exposure should be kept to a minimum to avoid secondary cancers. PET scans are relatively expensive, however, if 2 months of futile treatment with a targeted agent can be avoided by doing a PET scan, this strategy can not only spare the patient unnecessary side effects but also save costs.

With PET one tumor characteristic can be investigated at the time. However, different features can be studied by injecting different tracers. For example in metastatic breast cancer patients estrogen receptor expression can be visualized with  $16\alpha$ -[ $^{18}\text{F}$ ]-fluoro- $17\beta$ -oestradiol ( $^{18}\text{F}$ -FES) as a tracer, and human epidermal growth factor receptor 2 (HER2) expression with  $^{89}\text{Zr}$ -trastuzumab.<sup>11,12</sup> In lung cancer patients Van der Veldt et al. studied docetaxel distribution and perfusion with  $^{11}\text{C}$ -docetaxel and  $^{15}\text{O}$ -water PET scans.<sup>13</sup> Other molecular imaging modalities have been developed such as optical imaging with antibodies labeled with a near infra red dye<sup>14</sup> and ultrasound imaging with antibody coated microbubbles.<sup>15</sup> These new imaging techniques may facilitate better selection of patients and more accurate evaluation of cancer treatment outcome in the future. They do not result in radiation exposure, but whole body imaging is not feasible. An advantage of optical imaging is that in principle distribution of different tracers, labeled with fluorophores of different wave lengths, can be studied simultaneously. A disadvantage however is the limited penetrance of light, which requires close proximity of the camera. For evaluation of angiogenesis inhibitors early during treatment, measurements of vascular characteristics with sophisticated MRI and ultrasound techniques is also promising.<sup>16,17</sup> In conclusion, molecular imaging with PET evaluates the combined effect of different mutations and microenvironmental changes on a relevant tumor characteristic, and can be used to demonstrate distribution of a treatment target, distribution of a drug and biological changes over time. Information obtained with PET imaging is therefore complementary to immunohistochemic and genomic analysis of tumor biopsies. Combining both approaches in future studies will facilitate investigations to bring the right drug to the right patient. Recent progress in extracting tumor DNA from the plasma of cancer patients enables non-invasive serial mutation analysis.<sup>18</sup> It is currently unknown if circulating tumor DNA represents all tumor lesions of a patient. The relevance of a specific mutation in a signaling pathway across all tumor lesions in a patient could potentially be examined with molecular imaging. This strategy in which a tumor biopsy is combined with molecular imaging and serial mutation analysis of circulating tumor DNA in cancer patients may be worthwhile to be explored in small and smart designed contemporary studies. Such studies would generate a lot of information and improve our understanding of cancer biology. This potentially brings personalized cancer treatment a step closer.

**References**

1. [www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm](http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm)
2. Chapman PB, Hauschild A, Robert C, ET AL. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507-16.
3. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012; 13:1011–9.
4. Von Hoff DD, Stephenson JJ Jr, Rosen P, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol* 2010;28:4877-83.
5. Stroobants S, Goeminne J, Seegers M et al. <sup>18</sup>F-FDG-positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). *Eur J Cancer* 2003;39:2012-20.
6. Jager PL, Gietema JA, van der Graaf WTA. Imatinib mesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG PET. *Nucl Med Commun* 2004;25:433-8.
7. Lonser RR, Glenn GM, Walther M, et al. Von Hippel-Lindau disease. *Lancet* 2003;361:2059-67.
8. Gaykema SBM, Brouwers AH, Lub-de Hooge MN, Pleijhuis RG, Timmer-Bosscha H, Pot L, et al. <sup>89</sup>Zr-bevacizumab PET imaging in primary breast cancer. *J Nucl Med* 2013;54:1014–8.
9. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012;366:883-892.
10. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res* 2005;11:4182-90.
11. Van Kruchten M, de Vries EG, Brown M, et al. PET imaging of oestrogen receptors in patients with breast cancer. *Lancet Oncol* 2013;14:e465-475.
12. Dijkers EC, Oude Munnink TH, Kosterink JG, et al. Biodistribution of <sup>89</sup>Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Ther* 2010;87:586-92.
13. Van der Veldt AA, Lubberink M, Bahce I, et al. Rapid decrease in delivery of chemotherapy to tumors after anti-VEGF therapy: implications for scheduling of anti-angiogenic drugs. *Cancer Cell* 2012;21:82–91.
14. Terwisscha van Scheltinga AG, van Dam GM, Nagengast WB, et al. Intraoperative near-infrared fluorescence tumor imaging with vascular endothelial growth factor and human epidermal growth factor receptor 2 targeting antibodies. *J Nucl Med* 2011;52:1778-85.
15. Korpany G, Carbon JG, Grayburn PA, Fleming JB, and Brekken RA. Monitoring response to anticancer therapy by targeting microbubbles to tumor vasculature. *Clin Cancer Res* 2007;13:323-30.

16. Batchelor TT, Gerstner ER, Emblem KE, et al. Improved tumor oxygenation and survival in glioblastoma patients who show increased blood perfusion after cediranib and chemoradiation. *Proc Natl Acad Sci U S A* 2013;110:19059-64.
17. Lassau N, Koscielny S, Albiges L, et al. Metastatic renal cell carcinoma treated with sunitinib: early evaluation of treatment response using dynamic contrast-enhanced ultrasonography. *Clin Cancer Res* 2010;16:1216-25.
18. Murtaza M, Dawson SJ, Tsui DWY, et al. Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature* 2013;497:108-13.



