A straightforward way to improve local tumour control is to increase the radiation dose further, which is hampered by normal tissue constraints. Therefore, the concept of “dose painting” has been introduced, i.e. delivering a higher dose towards the more resistant tumour areas and reducing the dose towards the more sensitive area. Using this individualized strategy, the burden to the normal tissues can be kept constant;

Probably the most investigated methodology for visualizing *intra* tumour radio-resistance are hypoxia tracers. However, these tracers can have limitations, e.g. slow clearance of the unbound tracer in non-hypoxic areas, low test re-test performance, and low tumour to reference activity ratios can be observ. Also, as hypoxia is only one of several causes for radio-resistance, there is a lot of uncertainty about how specific these hypoxia tracers relate to radio-resistance;

Another important micro-environmental factor is tumour glucose metabolism, commonly assessed by the glucose analogue $^{18}$F-deoxyglucose (FDG) for PET imaging. FDG is the workhorse in the field of oncology for diagnostic and prognostic purposes that has led to improved clinical decision making in a large quantity of cancer patients. Many investigations have shown that high FDG uptake is prognostic for worse survival for patients both treated with radiotherapy and surgery. During the past decades FDG has become widely available and a lot of progress was made in standardisation and reproducibility of FDG-PET imaging, further improving the usability in the clinic.

The underlying biology for FDG uptake is complex as it measures the uptake of glucose in cells by ATP independent glucose transporters. This makes FDG uptake specific to the metabolic pathway although this pathway is known to influence numerous other processes to facilitate cancer. Consequently, in contrast to hypoxia tracers, FDG uptake in the tumour does not reflect a single biologic characteristic, but is correlated to, although certainly not specific for, radio-resistance, proliferation, cell density, hypoxia, mitochondrial dysfunction, and lipogenesis. Furthermore, in a pre-clinical investigation, it has been shown that an increase of radiation dose showed a higher local control for tumours with higher FDG uptake compared to tumours with lower FDG uptake, affirming the relation between FDG-uptake and radio-resistance. Another argument is that the locations of the patterns of relapse are associated with the pre-treatment high FDG uptake areas. Last year, our group has shown that the residual metabolic active areas after treatment show a high overlap with the high FDG uptake areas before treatment. This was confirmed in a study by the group of Dresden. These studies show that the location within the tumour with a high chance of metabolic relapse, and probably more radio-resistant, can be identified before treatment using a single FDG-PET-CT scan. Furthermore, it was shown that these high FDG uptake areas remain stable during a course of radiotherapy, making it possible to keep a similar dose painting plan during treatment.

As FDG corresponds to *several biologic characteristics* important for radio-resistance, due to the confirmed relation with the locations of relapse, the *wide availability*, the *standardized imaging protocols*, and the *stability of the uptake* patterns during RT, FDG is an attractive tracer for dose painting. Due to these favourable characteristics and because of sufficient improvements in the accuracy of imaging and dose delivery techniques, we believe that the time is right to more towards carefully designed clinical trials, by redistributing the dose towards the high pre-treatment FDG uptake areas. A randomized phase 2 trial in lung cancer started in 2010 in The Netherlands.