Imaging of tumor hypoxia with PET

VALORISATION ADDENDUM

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Tumor hypoxia is a property of cancer with a negative impact on the prognosis of the patient. In this thesis the possibilities to visualize, monitor and target tumor hypoxia are described. Since cancer is one of the leading causes of death in the Netherlands and its incidence is expected to rise due to an increased life expectancy of our elderly population, the scientific results of this thesis can be of benefit for the general society.

Social relevance

The treatment of cancer patients is continuously improving, with the aim to tailor cancer treatment to the needs of each individual patient. The presence of tumor hypoxia is known to have detrimental effects on the ability to control the disease. The non-invasive detection of tumor hypoxia provides the opportunity to individualize anti-cancer treatment by the ability (1) to improve the prediction of the response to treatment, (2) to monitor the response to treatment and (3) to select patients for additional anti-hypoxia treatment.

There are several **prediction** models available which estimate the chances of survival or local recurrences in cancer patients based on their general health and tumor characteristics. Several studies have shown that hypoxia is an important prognostic marker for treatment response. The addition of hypoxia PET parameters to already existing prediction models could improve the accuracy of these predictions. In the future these models can be used to intensify treatment in patients with a high chance of local recurrences.

The visualization of tumor hypoxia during treatment allows us to **monitor** the response to the given treatment and provides the ability to act on this information. This window-of-opportunity trial design might be very useful in the development of anti-hypoxia treatment strategies. The effect of hypoxia targeting by visualization before and after the treatment shows the effect of the (additional) treatment and its potential to target hypoxia. These studies are very effective, because with a limited amount of patients the effect of the treatment can be visualized, since each patient acts as its own control.

In addition, hypoxia imaging before treatment and the effect of anti-hypoxia treatment in the individual patients can be used for **patient selection**. Only patients with tumor hypoxia will have additional gain of anti-hypoxia treatment. Also the anti-hypoxia treatment should cause a decrease in hypoxia in the individual patient. Therefore patients that do not have significant hypoxia before the start of treatment, or patients that do not have a response to the additional treatment, could be excluded from unnecessary anti-hypoxia treatments.

Besides the clinical benefit, the ability to stratify patients based on their hypoxia status also provides economical benefit, since additional treatments to counteract hypoxia can be applied to only those patients who benefit from it, increasing their prognosis. Therefore, also unnecessary treatment, with additional costs and potential side-effects, can be omitted in the patients with no clinical benefit.

Target groups

Patients and their doctors could benefit from the implementation of hypoxia imaging and targeting. An optimized and individualized treatment can be given, with less recurrences and a longer life expectancy. In addition, in the current health care environment patients are more and more involved in the treatment decisions. Improved prediction models and treatment monitoring will guide the doctors and patients in their treatment decisions.
Last, the opportunity to visualize tumor hypoxia can be of general interest to all health care companies which develop hypoxia targeted agents. The hypoxia PET tracers allow in an early stage to detect, in vivo, the effect of a hypoxia targeting drug, which can guide them in the development.

Activities and products

In this thesis the included number of patients is still limited. However, patient accrual is still ongoing in the described clinical trials and new clinical trials are initiated. As soon as sufficient data are gathered, the additional value of hypoxia PET imaging to the current prediction models can be evaluated. There are already several prediction models available (for example on www.predictcancer.org). Hypoxia PET imaging data could be integrated into these prediction models. The current data might provide additional information improving the response prediction.
At Maastro there is a research group investigating the potential of quantitative features from medical images (RADIOMICS) to monitor the response to treatment http://www.radiomics.org/. At the moment research is performed mainly on CT and [^{18}F]FDG PET imaging. Hypoxia PET imaging could be integrated in this extensive image analysis, and analysis are planned for the near future.

Innovation

The detection of tumor hypoxia is not new. However the clinical use of hypoxia PET imaging to monitor or predict the response to treatment is limited. Also, treatment selection based on hypoxia PET imaging is not yet implemented. In this thesis we mainly describe the use of the hypoxia PET tracer HX4, this is a relative new PET tracer for hypoxia PET imaging. Comparing this tracer with the alternative hypoxia PET tracers on the market showed beneficial characteristics which motivated the use of this tracer in clinical trials. We showed the ability of HX4 PET imaging to monitor the response to radiotherapy, in patients with head and neck cancer, and the response to TH302 treatment in preclinical setting.

Planning and realisation

The research described in this thesis is the basis of several new initiatives to implement hypoxia PET imaging. The follow-up data of all patients described in this thesis will provide information on the ability to predict the response to treatment. This information on tumor hypoxia will be implemented in the available prediction models. To perform the research described in this thesis, a close collaboration with Threshold Pharmaceuticals was started.

This led to new opportunities regarding clinical trials. The next step is a phase I trial investigating the use of TH302 in combination with radiotherapy in patients with esophageal cancer. In this setting HX4 PET imaging will be used to monitor the effect of the treatment. Also, preclinical trials are performed investigating radiotherapy dose escalation based on HX4 PET imaging, in comparison to FDG-PET imaging. The information from these studies will be essential for the clinical implementation of hypoxia boost trials. Last, the use of hypoxia PET imaging in the RADIOMICS project will be started in the near future, which will show us if hypoxia PET imaging provides additional information to the image features derived from standard CT (and FDG-PET) imaging for response prediction.

To summarize, this thesis provides valuable information on the use of hypoxia HX4 PET imaging. The implementation of hypoxia PET imaging in our clinical trial setting is optimized and based on the results of this thesis new initiatives are taken, with the aim to improve our cancer treatment. This thesis was therefore an important step to individualized cancer treatment.