

Novel molecular imaging methods for cancer detection

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Valorization addendum

Imaging is a central player for patient selection with the ultimate goal of personalizing cancer treatment. Over the last decades, a plethora of new imaging techniques and imaging biomarkers are being developed and reported, demonstrating that imaging is a highly active field of research. The function of an imaging biomarker is the ability to quantitatively measure and also to provide spatial distribution of the target in the tumor. Additionally, imaging biomarkers might also provide prognostic information. However, the introduction of a new imaging biomarker into clinic practice is not straightforward. Because accumulation of a biomarker also depends on the tumor microenvironment thorough validation using for example correlations with pathology is required. The main aim of this thesis was to evaluate new imaging biomarkers for the detection of aggressive and invasive tumors and to acquire additional information of CT images in the concept of radiomics.

Clinical relevance:

Cancer is one of the dreadful diseases where the time of detection defines treatment option and outcome. If diagnosed in a too late stage for some cases of advanced cancers, treatment becomes mere palliative. Additionally, administration of drugs that are not effective is not only expensive but also degrades quality of life. With the development of new drugs and moving more and more towards the concept of personalized medicine, accurate selection and follow up of a specific treatment is of prime importance. Similar to the imaging biomarkers, the drug uptake in patients depends on multiple factors and therefore a simple biopsy might not be able to reflect the distribution of drug and the clinical outcome. Imaging thus can aid in patient selection and in monitoring treatment responses quantitatively as well as the spatial localization of the target molecule. Imaging can also provide prognostic information of the patient and therefore, can be beneficial to the clinician in making decisions. However, the use of the correct imaging technique is necessary and the imaging information should be reliable. Therefore, validation of an imaging technique/ tracer is required which means standardization of a procedure, the characterization of an imaging biomarker, overcoming the challenges with tumoral uptake and minimizing the background uptake. For this purpose, imaging has been an active field of research and numerous research studies are being conducted. Complementary information on tracer characteristics, time of imaging, influence of tumor microenvironment etc. (chapter 2, chapter 3 and chapter 4) can be attained by performing preclinical studies which aids in standardization of protocols in the clinic. For example, many new hypoxia tracers have been

developed such as FAZA, FMISO and HX4. However comparative studies in a same tumor model helps to characterize the tracers and to choose the correct tracer (chapter 2). In addition, choice of right tracer for a specific process is necessary.

Several FDA approved antibodies are currently used for the treatment of various cancers e.g. Bevacizumab (target VEGF), Cetuximab (target EGFR) and Trastuzumab (target HER2). However, not all patients screened for the presence of the target benefit from the treatment. For example, cetuximab has been a standard treatment for colorectal and head and neck cancer patients, it was reported that prior selection of patients based on EGFR expression was not beneficial. Preclinical studies using [⁸⁹Zr]-Cetuximab imaging in tumor models expressing different EGFR expression have verified that indeed a disparity exists between the EGFR expression and Cetuximab uptake. This disparity could be due to the influence of tumor microenvironmental parameters such as vessel density, hypoxia and necrosis (chapter 3). Thus, preclinical studies aid to validate findings and strengthen the information regarding drug development. [⁸⁹Zr]-Cetuximab imaging which is already in clinical trials has shown good correlations between the imaging and treatment responses. Hence, antibody based imaging accelerates development of therapeutic antibodies since these antibodies are already well characterized and the imaging information provides the actual distribution of the antibody in the tumors and hence can be used for theranostic purposes.

Small antibody fragments or chimeric antibodies have better reachability in the tumors due to their smaller size. In this thesis, we evaluated if a new antibody, which is produced in small immune protein format against MMP2 can be used for imaging purposes (Chapter 4). Several broad-spectrum inhibitors including Bisphosphonates, chemically modified tetracycline derivatives (e.g. col-3), hydroxomates (batimastat and its orally administrative analogue marimastat) have shown to be potent inhibitors of metastases and tumor growth in preclinical studies. However, the clinical trials were disappointing. The lack of knowledge on specificity of these broad-spectrum inhibitors and complexity of the nature of MMPs has been attributed to the failure of these inhibitors. Furthermore, patients with early stage cancers were excluded in clinical trials with broad-spectrum inhibitors while MMPs were also reported to play critical role in early stages of cancer development. Therefore, selection of patients based on presence of specific MMP activity is necessary. Furthermore, MMP2 activity is localized in the invasive front and therefore imaging using MMP2 antibody might help in identifying

intrusive tumor areas before spreading metastases. Although further research is warranted with aMMP2-SIP as an imaging biomarker, the accurate detection of MMP2 activity despite the decreased levels of MMP2 protein makes it a promising tool for imaging MMP2. In the second part of the thesis, CT imaging has been used to understand the molecular patterns within tumors. CT imaging is widely used in clinic and is less expensive than PET imaging. Imaging features extracted from CT images using Radiomics, an advanced image analysis platform, has been proven to be prognostic in patients. However, little is known about the direct relationship between these image features and gene patterns. Therefore, the research conducted in second part of the thesis is to evaluate further in-depth to understand whether tumor heterogeneities and molecular patterns influence image features. Once, the direct relationship is established, these CT imaging features can deliver both anatomical and molecular information.

Road to the market:

Imaging with therapeutic antibodies has the benefit of faster translation to clinic, as the antibodies are prior validated for safety and biodistribution in therapeutic settings. However, tagging the antibody can sometimes change the properties of the antibody. Therefore preclinically and clinically the safety profile needs to be tested. [⁸⁹Zr]-Cetuximab imaging has shown improved therapeutic results. Validation of the tracer including parameters that can influence an uptake can give additional information for the clinician. New antibodies take lot more time for translation into clinic as several steps such as timing of imaging and tracer characteristics needs to be optimized like. aMMP2-SIP is directed towards active MMP2 and is proven to detect MMP2 activity even when MMP2 protein levels are reduced. However, the main goal is to validate the antibody as an invasive biomarker. Therefore, further research is warranted using orthotopic models to detect the invasive front. On the other hand, CT imaging is widely used in clinic to detect cancer. Therefore, the application of radiomics in clinical settings is easier. However, strong external validations are required when extrapolating the imaging features from preclinical to clinical cases, as the patient tumors are more complicated. More relevant models such as orthotopic or spontaneous models could be used for better translation into clinic.

Societal Benefit:

Detection of cancerous tissue accurately saves time and treatment costs for the patient. For instance, after a surgical tumor resection, the specimen needs to be tested for any intrusive tumor cells. If there is any invasive tumor tissue, a second surgery might be needed. Under the guidance of proper imaging tool (e.g. MMP2 imaging) invasive areas of tumor could be detected noninvasively and hence cost-effectiveness will be improved. During and post treatment using this theranostic approach helps to avoid unnecessary treatments. If a patient has high EGFR expression but low Cetuximab uptake, he/she will not benefit from Cetuximab treatment. Prior selection and follow up using Zr^{89} -Cetuximab imaging can help not only the patient but also the doctor in making right decisions. In most of the cancer centers, PET/CT imaging is performed. While PET gives molecular information and CT gives anatomical information, deriving imaging features from both using Radiomics gives additional information for better treatment. This adds valuable information to the doctor and no additional costs to the patient.