



REPORT

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CANCER

PRECIMET: PRECISION IMAGE FOR EVALUATION OF BONE METASTASIS

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1. Summary of the project

Bone is one of the most frequent sites of cancer metastases, particularly in some tumour types such as breast and prostate cancer. Up to 90% of patients with advanced disease present bone metastases, and very often bone is the only organ affected by the cancer. The response assessment to treatments against cancer is performed based on the evaluation of changes in tumour size by using medical images such as computed tomography (CT) and bone scans. The problem is that bone metastases are considered as non-measurable by CT or bone scan; thus, it is not possible to know if a patient with bone metastases is responding or not to treatment. The lack of information about the patient response may delay discontinuation of ineffective treatment, and it can delay starting a potentially beneficial treatment. Unfortunately, with the current tools, when there is enough evidence to switch the treatment, sometimes the disease has already progressed too much and the patient is clinically too unwell to try another treatment. New assays that inform about response to bone metastases based on new imaging techniques and advanced imaging analysis will allow us to know whether or not a patient is benefiting just a few days after starting treatment. Diffusion is a magnetic resonance imaging (MRI) technique that studies the movement of water molecules within a tissue and informs about tumour cell density. If a tumour responds to treatment, there will be a drop of tumour cells and this can be measured with diffusion MRI. Another advantage of MRI is that it does not require ionizing radiation, or the administration of any type of contrast (oral or intravenous), while these are necessary for CT or bone-scan image acquisition. We propose a study in patients with breast or prostate cancer and bone metastases that will start treatment with chemotherapy or hormone therapy, aiming to identify changes just a few days after starting treatment and define the change in diffusion MRI that differentiates a patient responding from non-responding to treatment. An early indicator of response in bone metastases will allow for advancing towards precision medicine, optimizing treatment switch, yes/no decisions and so on, improving cancer patient care. Moreover, this assay will facilitate acceleration of new anti-cancer treatments development by defining the efficacy of a tested drug earlier than we do nowadays, thereby reducing clinical trial time and costs.

2. Results

The PRECIMET Consortium has successfully completed a ground-breaking multicentre study, utilizing whole-body MRI to serve as a prognostic tool and a biomarker for assessing responses in patients with metastatic prostate and breast cancers. The outcomes for metastatic castration-resistant prostate cancer have already been disseminated. In a focused sub-study, we evaluated patients who were treated with either standard-of-care androgen receptor-targeting agents or taxane-based chemotherapy.

Our research, published in *European Urology* in March 2024, strongly endorses the application of whole-body MRI as an effective response biomarker. We employed multivariate models that include ADC and fat fraction metrics, which have shown a significant predictive value for patient outcomes. Furthermore, we observed that alterations in the volume of bone disease, as measured by whole-body MRI, are closely linked to patient outcomes, underscoring the method's value in clinical assessments. This study is particularly notable for its pioneering integration of MRI-based biomarkers and circulating tumour DNA (ctDNA) analyses as a combined response biomarker. The insights gained from our work pave the way for more precise monitoring of cancer progression in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases. This addresses a previously unmet need in evaluating responses to treatment in bone-related diseases and holds substantial promise for expediting the development of new drugs by providing a reliable intermediate endpoint.

3. Relevance with possible future implications

Impact in society and clinical implications of the study on whole-body multiparametric MRI as a response biomarker in bone metastases

Precision Imaging Towards Improving Healthcare Practice

This study introduces a pioneering response biomarker in breast and prostate cancer patients with bone metastases. It enables the early identification of responders and non-responders just a few weeks after initiating treatment. This early detection of

treatment efficacy or resistance is crucial for optimizing treatment sequences and minimizing risks to patients.

Given the current lack of reliable response indicators in patients with bone metastases, the findings of this project have the potential to revolutionize clinical response assessments. The results of the study are very promising, demonstrating the important role of whole-body MRI as an indicator of response in bone metastases, and its correlation with changes in tumour biopsies. Importantly, the reduction of malignant cells and their replacement with normal fat in the bone marrow serve as excellent indicators of response. We envision that this will become an essential tool in medical decision-making, thereby enhancing care for cancer patients. The results of this study are currently being evaluated in the prestigious scientific journal *European Urology*.

Accelerating Drug Discovery

Whole-body DWI has allowed us to identify areas of disease progression. In collaboration with the rest of the PRECIMET research team, image-guided biopsies of these areas have been performed. This approach has been instrumental in studying resistance mechanisms. We envision that this valuable information will foster the development of new drugs targeting these specific areas.

Additionally, this imaging technique promises faster response readouts in clinical trials, which could substantially reduce the duration and cost of drug development, leading to quicker market availability of new treatments.

Technological Development

The project was set to develop an automated MRI processing pipeline, culminating in the creation of software. We are currently working on fine-tuning this tool to enable automatic whole-body MRI analysis. This will facilitate the clinical implementation of MRI-based response biomarkers.

4. Generated scientific bibliography

Papers

- *Whole-Body Magnetic Resonance Imaging As A Treatment Response Biomarker In Castration Resistant Prostate Cancer With Bone Metastases: Ipromet Clinical Trial.* Alonso Garcia-Ruiz, Carlos Macarro, Francesca Zacchi, Rafael Morales-Barrera, Francesco Grussu, Irene Casanova-Salas, Francesco Sanguedolce, Macarena Gonzalez, Matias de Albert, Josep Garcia-Benet, David Marmolejo, Jacques Planas, Sarai Roche, Richard Mast, Christina Zatse, Josep M Piulats, Bernardo Herrera-Imbroda, Lucas Regis, Laura Agundez, David Olmos, Nahum Calvo, Manuel Escobar, Joan Carles, Joaquin Mateo, Raquel Perez-Lopez. *European Urology*. 2024 Mar 14:S0302-2838(24)02133-X. doi: 10.1016/j.eururo.2024.02.016. Epub ahead of print. PMID: 38490857.

Abstracts

- Tumour cellularity quantification from diffusion MRI associates with response in metastatic prostate cancer patients. A. Garcia-Ruiz, L. M. Atlagich, S. Cordoba, M. de Albert, T. Seibert, R. Mast, M. Escobar, F. Grussu, R. Perez Lopez. European Congress of Radiology (ECR) 2023. 10.26044/ECR2023/C-13864.
- Decomposition of clinical ADC into intracellular and extracellular-extravascular contributions in prostate cancer using histology. Alonso Garcia-Ruiz, Francesco Grussu, Snigdha Sen, Chen Jin, Alex Freeman, Aiman Haider, Shonit Punwani, Daniel C. Alexander, Raquel Perez-Lopez, and Eleftheria Panagiotaki. ISMRM Congress 2023. <https://www.ismrm.org/23m/>.
- Tumor cell density quantification using whole-body diffusion MRI in metastatic prostate cancer patients. Alonso Garcia-Ruiz, Luz Maria Atlagich, Sarai Cordoba, Camilo Monreal-Aguero, Marta Vidorreta, Matias de Albert, Tyler Seibert, Joaquin Mateo, Francesco Grussu, Raquel Perez-Lopez. Prostate Cancer Foundation Annual Meeting. 2022.