# TREATMENT: Improved therapy response assessment in metastatic brain tumors

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TREATMENT is an observational study addressing the need for knowledge and adequate diagnostic biomarkers in the response assessment of patients with brain metastasis. Reliable response assessment will be highly relevant in the coming years given the introduction of next-generation cancer drugs, including immunotherapy. This project uses advanced Magnetic Resonance Imaging (MRI) and Vessel Architecture Imaging (VAI) to better understand the response to traditional stereotactic radiosurgery (SRS) and immunotherapy.

Attributed in large by advances in treatment of primary tumors, there has been an explosive growth in patients with metastatic cancer over the last decades. Metastatic cancers, primary cancer that spread to another place in the body, are usually observed in bone, liver, lung and brain. The prognoses of patients with metastases to the brain are dismal with an overall survival from first diagnosis ranging from months up to a few years. The primary goal of treatment is to control tumor growth and standard-of-care usually includes chemotherapy, radiotherapy and surgery, depending on diagnosis and extent of disease. These treatments have been somewhat successful in the sense that treated patients live longer than untreated, but at the cost of clinical and neurological deficits. To this end, patients with metastatic disease represent an increasing demand on health care resources, especially for repeated therapeutic interventions and diagnostic work-up. The associated diagnostic methods for assessing treatment response follow the criteria formulated by the Response Assessment in Neuro-Oncology (RANO) working group, and are based on measuring the size of the enhancing lesion on contrast-enhanced T1-weighted MRI. Here, a complete or partial response requires a complete or ≥ 50% reduction in the enhancing target lesion for a minimum of 4 weeks with stable or reduced levels of vasogenic edema on MRI and sustained or reduced use of corticosteroids. Unfortunately, these criteria are challenged by high heterogeneity within-, and between, metastatic subtypes for both treatment response and time to progression.

The introduction of immunotherapy is widely viewed as the greatest advancement in cancer treatment in the last decade. Immunotherapy is the collective term of multiple treatment methods that uses the body's own immune system to help fight cancer. This is a highly promising therapy option that is now finally coming of age with some astonishing results of prolonged patient survival, especially for malignant melanomas. Unlike traditional cancer treatment, where the criteria for response assessment are given by RANO, the criteria for assessing treatment response after immunotherapy are not yet established.

Current diagnostic methods have been proven insufficient because the response to immunotherapy does not necessarily result in a simple reduction of tumor size. This treatment method, and even stereotactic radiosurgery (SRS) may, however, induce a temporary inflammatory reaction that manifest as increased contrast-enhancement and enlarged tumor volume on MRI. Figure 1 illustrates this problem after treatment by the means of SRS, but a similar response may also occur following immunotherapy.

The TREATMENT project will address the growing need for targeted biomarkers and gain important new knowledge on the diagnosis and the underlying response mechanisms following cancer treatment, thus paving the way for a more reliable response assessments. The study includes two patient cohorts, with brain metastasis from non-small-cell lung cancer (NSCLC) and malignant

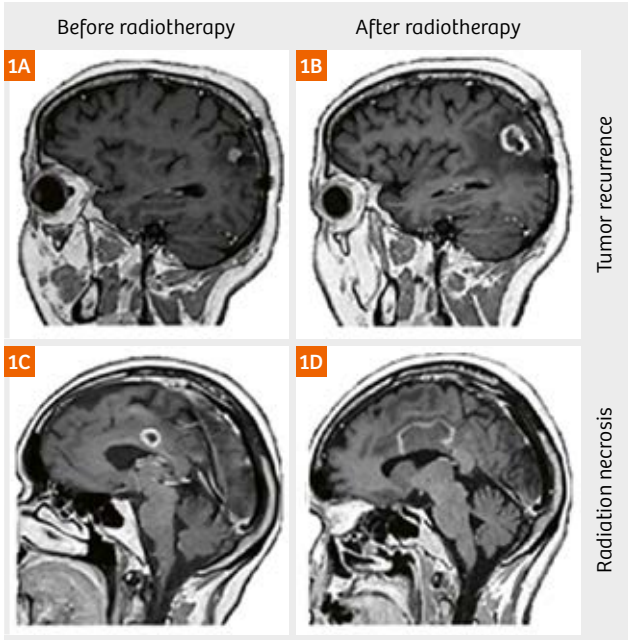


**Figure 1: Radiation necrosis vs. true progression**. Conventional MRI data from OUH showing a patient with a brain metastasis from breast cancer before treatment **(1A)** and with histologically confirmed tumor progression at 12 months **(1B)**. In contrast, MRI data of a patient with a non-small cell lung cancer metastasis **(1C)** show radiation necrosis at 15 months **(1D)** that eventually disappear. With dismal survival prognosis, biomarkers of early response are critical to differentiate patients responding to therapy from those patients who only suffer the side effects.

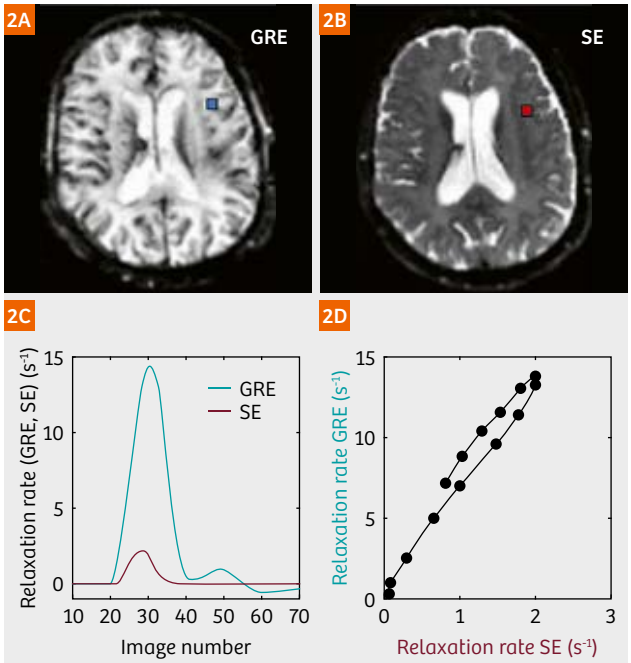


**Figure 2: Vessel Architectural Imaging (VAI).** The VAI-method is based on repeated acquisition of pair-wise gradient-echo (GRE) and spin-echo (SE) data. The acquisition are done simultaneously, thus yielding the corresponding relaxation rates from GRE (**2C**, blue curve) and SE (**2C**, red curve) following a single injection of contrast agent. The resulting vortex **(2D)** is characterized by its size, shape and direction, and reflects the underlying vascular properties in the target tissue.

melanomas (mal.mel). A unique diagnostic pipeline has been established at the Norwegian sites contributing to the project, in which targeted monitoring of patients with brain metastases receiving SRS and immunotherapy, are performed with repeated MRI every third month or until the patients is deemed unfit for continued imaging. Included in the MRI protocol is the new paradigm in cancer diagnostics; *Vessel Architecture Imaging* (VAI), developed by group leader Emblem and his associates at Massachusetts General Hospital [1]. This method uses repeated acquisition of pair-wise gradient-echo (GRE) and spin-echo (SE) data (Fig. 2). The GRE- and SE-data are acquired independently and simultaneously after the administration of a contrast agent by using Echo Planar Imaging (EPI) with the following key parameters: TR = 1500 ms, $TE_{GE}$(NSCLC/mal.mel) = 13/30 ms and $TE_{SE}$ = 104 ms. The acquired matrix size was 120 x 90 over a 240 x 180 (NSCLC) and 260 x 195 field of view with a scan time of 2 minutes and 36 seconds. The VAI-data are acquired pending a routine post-contrast T1-weigted image-series, thus utilizing this interim period without increasing the total scan time.

The general principle behind the VAI-method is based on the observation that GRE and SE signal-response following the administration of contrast agents depend on the microvascular properties of the tissue. By plotting the par-wise GRE- and SE-data, the resulting parametric curve forms a vortex. This vortex is then characterized by its size, shape and direction, which are further used to obtain measurements of the vessel size or caliber, vessel type and oxygen saturation ($\Delta SO_2$). Consequently, these novel measurements reveal new information regarding blood vessel types, vascular function and supply not obtainable by conventional dynamic MRI methods. The VAI-method has previously shown that anti-angiogenic treatment can improve microcirculation and oxygen saturation, as well as reduce vessel caliber in patients with primary brain tumors. Consequently, the TREATMENT study aim to investigate whether VAI may help identify patients benefiting from SRS and immunotherapy, as well as reveal underlying mechanisms that can contribute to new insights, and thus advancing response assessment. Given that the presence of sufficient oxygen is an important factor for achieving a good response to SRS

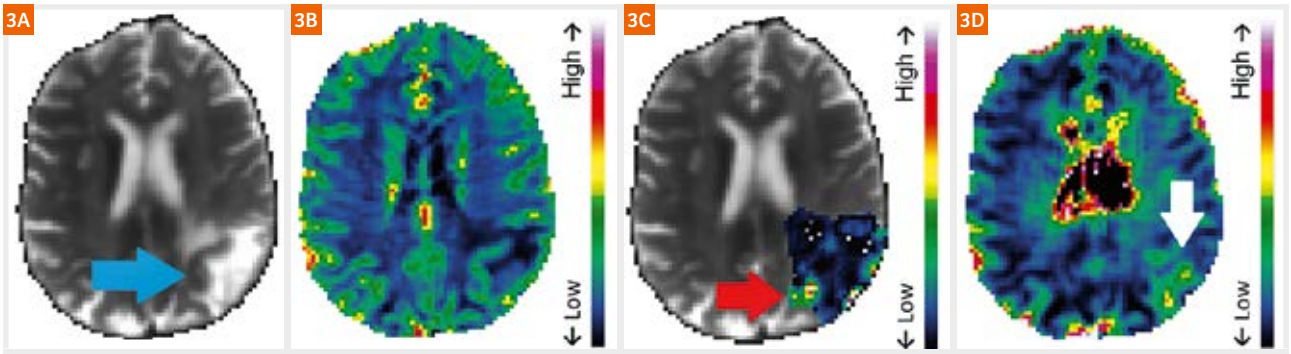


**Figure 3: Advanced pre-therapy MRI data of a brain metastasis from non-small-cell lung cancer.**
Based on conventional **(3A)** and even traditional perfusion MRI **(3B)**, it is difficult to depict tissue heterogeneity within the tumor region (blue arrow). In contrast, distinct regions of pathologic vasculature (**3C**; red arrow) and vessel calibers (**3D**; white arrow) are observed using VAI.

(and immunotherapy), it is hypothesized that VAI can identify patients with tumor profiles susceptible to such treatment (Fig. 3).

The two patient cohorts are further separated into different subgroups, depending on whether they receive SRS with or without combined immunotherapy. The goal is to include 100 patients with up to three-year follow-up. The initial finding suggests that immunotherapy directly affects the blood vessels and vascular function in the tumors, indicating that the new and advanced MRI methods may provide new insight into biological mechanisms relevant for response assessments.

As of today, clinicians face the challenge of insufficient and unreliable response assessment, and the criteria for identifying the correct response at an early stage in the treatment process is not obvious in many cancer patients. Consequently, there is an urgent need to improve the monitoring and management of cancer, especially with the introduction of new treatment methods. Hence, the radiological response criteria should not solely be based on the change in tumor size, but also reflect vascular and metabolic changes. The research group at OUH hopes that the TREATMENT project may aid overcome these challenges in the years to come.

**References**

1 Emblem et al. Vessel architectural imaging identifies cancer patient responders to anti-angiogenic therapy. Nat. Med. 19:1178–1183 (2013).

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The TREATMENT project (2016–2019) is led by Kyrre Eeg Emblem, Ph.D., at the Department for Diagnostic Physics, Oslo University Hospital (OUH), Norway, who has established a research group including oncologists, radiologists, radiographers, study nurses and physicists from OUH. In addition to being a national venture with contributors from OUH, Sørlandet Hospital Kristiansand (Birger Breivik, MD), Østfold Kalnes Hospital (Dag Ottar Sætre, MD) and St. Olav Hospital / Norwegian University of Science and Technology (NTNU) (Asta Håberg, MD), the project also collaborates with Massachusetts General Hospital and Dana-Farber Cancer Institute in Boston, MA, USA, both affiliated with Harvard Medical School, as well as the UT Southwestern Medical Centre in Dallas, TX, USA, and the University Medical Centre in Groningen, The Netherland. Managed by Emblem and his group at OUH, the researchers aim to acquire new knowledge that may help improve the current response assessment of traditional therapy and next-generation cancer drugs.