



# PHYSICS

## PhD Research Report

# Assessment of cancer aggressiveness by functional magnetic resonance imaging (MRI)

### Abstract

There is a continuing lack of prognostic and predictive biomarkers for the optimisation of treatment for the individual patient in cancer diagnostics. Magnetic resonance imaging (MRI) is the standard tool for staging rectal cancer, and with many functional MRI methods available, these represent a promising tool to obtain knowledge about the tumour microenvironment. The vasculature of the tumour may be particularly important to differentiate aggressive tumours, as it is widely known that tumour cells that do not have access to enough oxygen for their requirements can become hypoxic, and as a result, the tumour becomes treatment resistant and highly likely to metastasise.

In my PhD, I investigated functional MRI methods as a possible approach for the collection of biomarkers in two patient cohorts. In the first cohort, we performed a retrospective analysis of 27 rectal-cancer patients for whom we had diffusion-weighted MRI (DWI) with three b-values. We investigated whether it was possible to extract from these limited data both the diffusion and the perfusion fraction through use of the so-called intravoxel incoherent motion (IVIM) method. Both parameters were then evaluated to find out whether they could be used to predict tumour regression grade after neoadjuvant treatment and/or overall survival rates.

In the second patient cohort of 94 rectal-cancer patients, we combined a multi-echo dynamic contrast MRI with an extended DWI sequence in addition to the standard diagnostic MRI. The multiple echoes gave us the opportunity to extract both the  $T_1$  and the  $T_2^*$  signals from the dynamic contrast curve. The  $T_1$  contrast curve, or dynamic contrast enhanced (DCE) MRI, is more sensitive to the leakage, or permeability, of the vasculature than the  $T_2^*$  curve. The less-used  $T_2^*$  contrast curve, or dynamic susceptibility contrast (DSC) MRI, is more sensitive to the bulk flow, or perfusion, of the tissue than the  $T_1$ . Both are shown in Figure 1. Combination of these data with the IVIM method gave us a range of parameters that were associated with the vasculature of the tumour.

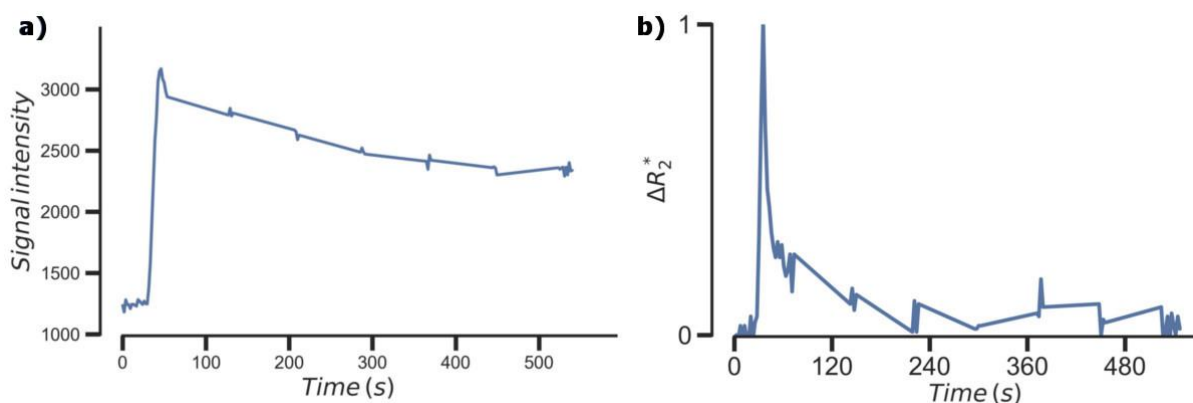


Figure 1: Illustration of the difference between the signals. The  $T_1$ -curve a) is more sensitive to leakage, while the  $T_2^*$ -curve b) is more sensitive to the bulk flow. (The  $T_2^*$ -curve is inverted as the susceptibility effect is negative; illustration is not to scale.)

First, we investigated the relationship between all these parameters. Some relationships we found were as expected; for example, the pseudo-diffusion from IVIM was related to the perfusion. However, some relationships that we expected to find were not

present in our data. For instance, the perfusion fraction from IVIM was not related to either perfusion or the vascular space that was estimated from DCE MRI.

Secondly, we looked at the relationship between these parameters and the clinical outcomes. We found that the tumour perfusion or blood flow (BF) was the most significant parameter by far in the determination of the aggressiveness of the disease in the patients. We found that tumour BF was highly related to progression-free survival rates (Figure 2), where most of the progressive events were metastatic disease. This indicates that low BF in tumours is a risk factor for a disease that is on its way to metastasise. Low tumour BF was also an indicator of poor treatment response to chemoradiotherapy. Figure 3 shows example images from the study.

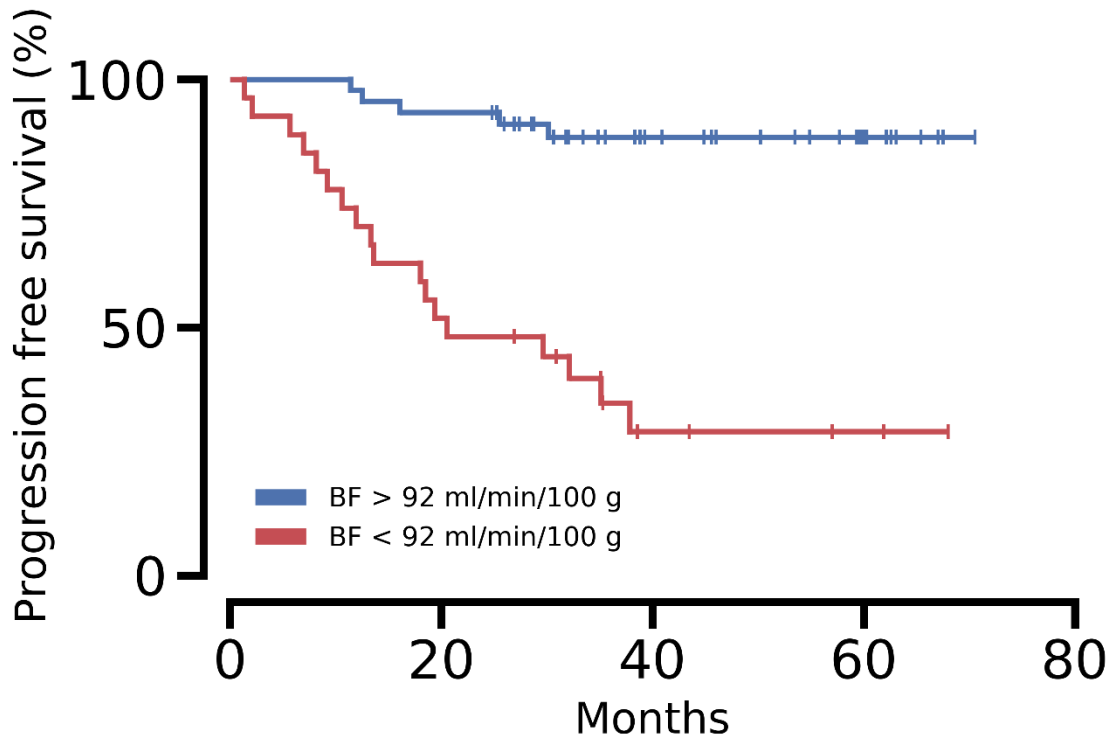


Figure 2: Low tumour blood flow (BF) was associated with shorter progression-free survival than moderate tumour blood flow (Bakke et al., Radiology 2020)

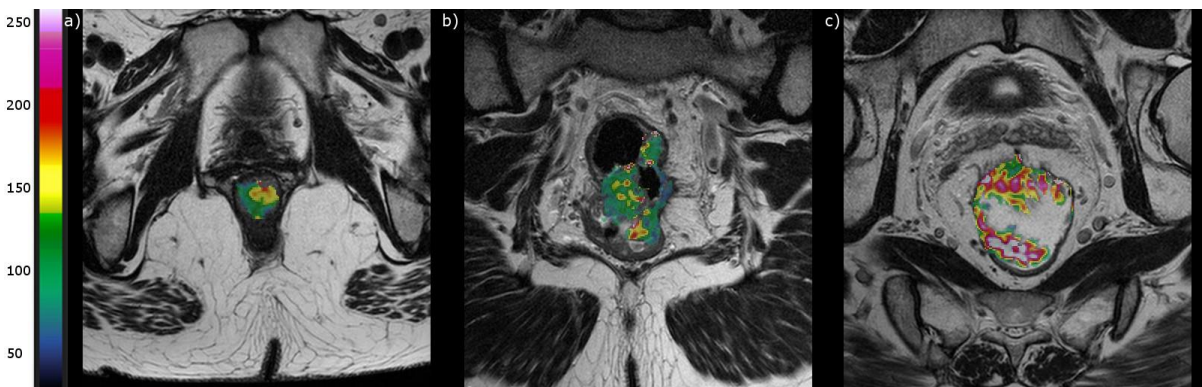


Figure 3: T<sub>2</sub>-weighted images with the BF-map as an overlay on the tumour. a): images of rectal cancer in a patient with stage-1 disease and a mean BF of 67 ml/min/100 g. At time of surgery the patient was discovered to have an infected lymph node, and at 14 months the patient was diagnosed with lung metastasis. b) and c): both these patients had stage-3 disease. Patient b had a mean BF of 82 ml/min/100 g and was diagnosed with liver metastasis after 12 months; patient c had a mean BF of 139 ml/min/100 g and was declared disease free at last follow-up at 63 months. (Bakke et al., Radiology 2020)

Surprisingly, we found that there was a difference in BF between men and women at higher disease stages (Figure 4). Results of analysis of serological factors from the same cohort indicated a relationship of blood flow to levels of vascular endothelial growth factor and lactate dehydrogenase. However, these results need further investigation to deconvolve.



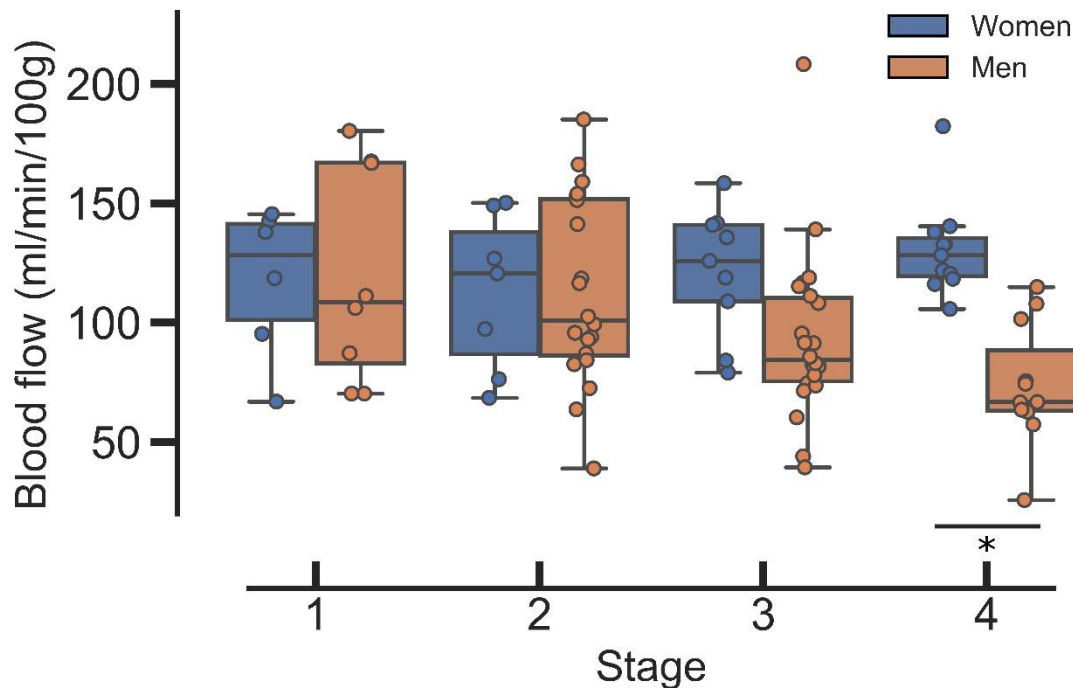


Figure 4: Blood flow in tumours in women was significantly higher than in men at more advanced disease stages. (Bakke et al., Radiology 2020)

Our results have been published in three papers:

Kine Mari Bakke, Knut Håkon Hole, Svein Dueland, Krystyna Kotanska Grøholt, Anne Hansen Ree, Therese Seierstad, Kathrine Røe Redalen. Diffusion-weighted magnetic resonance imaging of rectal cancer: tumour volume and perfusion fraction predict chemoradiotherapy response and survival. *Acta Oncologica*, 2017; 56:813-818; DOI: [10.1080/0284186X.2017.1287951](https://doi.org/10.1080/0284186X.2017.1287951)

Kine Mari Bakke, Endre Grøvik, Sebastian Meltzer, Anne Negård, Stein Harald Holmedal, Lars Tore Gyland Mikalsen, Lars Gustav Lyckander, Anne Hansen Ree, Kjell-Inge Gjesdal, Kathrine Røe Redalen, Atle Bjørnerud. Comparison of intravoxel incoherent motion imaging and multiecho dynamic contrast-based MRI in rectal cancer. *Journal of Magnetic Resonance Imaging*, 2019; DOI: [10.1002/jmri.26740](https://doi.org/10.1002/jmri.26740)

Kine Mari Bakke, Sebastian Meltzer, Endre Grøvik, Anne Negård, Stein Harald Holmedal, Kjell-Inge Gjesdal, Atle Bjørnerud, Anne Hansen Ree, Kathrine Røe Redalen. Sex Differences and Tumor Blood Flow from Dynamic Susceptibility Contrast MRI Are Associated with Treatment Response after Chemoradiation and Long-term Survival in Rectal Cancer. *Radiology*, Sept 1 2020; DOI: [10.1148/radiol.2020200287](https://doi.org/10.1148/radiol.2020200287)

## ***What was the motivation for the topic of your PhD work?***

More knowledge about the biology of tumours is of increasing importance as personalised cancer therapy with multiple treatment options that include biologically targeted molecular- and radiotherapy is more readily available. Increased understanding about the biology behind metastasising tumours is also of importance, as this often is the threshold at which point cancers go from curable to incurable. We believe that MRI is an important tool for the depiction of the biology and heterogeneity of tumours and that this information is valuable for optimal adaptation of personalised cancer treatment.

## ***What were the main findings of your PhD?***

Our main finding was that the tumour blood flow, which could be discovered through use of the infrequently applied DSC MRI method, was associated with treatment response and long-term-survival. In addition, we discovered that blood flow differed between sexes, which we found surprising but very interesting from a biological perspective.

## ***Can you comment on the impact of your work to the field?***

I think the main point to draw from my work is that DSC MRI, which is usually reserved for brain imaging, should be investigated more widely as an imaging tool for use outside the brain. Also, I think that the differences we discovered in blood flow between

the sexes are a reminder of how important it is to remember basic biology during analysis of these images, and that biological research often should be stratified based on sex.

### ***What was the most challenging part of your PhD?***

Finishing 😊.

### ***Who or what inspired you most during your studies?***

I think all the work that goes into this type of clinical study; the patients who gave up their time, and the work of the radiographers, radiologists and the other medical staff that inspired me to contribute my part and make the most out of the data that I was given.

Also, my research group and colleagues have a good work environment with a cheer-you-on attitude.

### ***Will you stay in the field? What are your plans for the future?***

I hope to stay on as a researcher in the field for some more years.

### ***Which institution were you affiliated to during your PhD?***

The University of Oslo, Department of Physics, and Akershus University Hospital, Department of Oncology, in Norway.

### ***When did you defend your thesis and who was your supervisor?***

I defended my thesis on Friday, 13 December, 2019. My main supervisor was Kathrine Røe Redalen, professor at Norges teknisk-naturvitenskapelige universitet (NTNU) (Norwegian University of Science and Technology) and former senior scientist at Akershus University Hospital; also a member of the young European Society for Radiotherapy and Oncology (ESTRO) committee

## **About the author**

Dr Bakke received a bachelor's degree in physics in 2010 and a master's degree in biophysics and medical physics in 2012, both from the University of Oslo. She then worked as a research assistant at Akershus University Hospital for six months, before taking up a position as a service engineer at a preclinical Bruker 7 Tesla MRI scanner at the Norwegian Radium Hospital. After three years of imaging mice, she returned to Akershus University Hospital as a PhD student. She currently works as a post-doctoral fellow at the Institute of Clinical Medicine at the University of Oslo after receiving her PhD degree in December 2019.



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