Role of DWI MRI as functional imaging in assessment of treatment response of Targeted treatment of NSCLC.

Dr. Saly Zahra and Dr. Mahmoud Abdelsalam

Lung cancer is one of the most common cancers worldwide and the leading cause of cancer deaths in both developed and developing countries [1]. About 80% of the lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC), and their 5-year survival rate is only 18% [1, 2]. Recent medical advances have stimulated a huge increase in overall cancer survival, but this improvement has not been ideal for lung cancer because most NSCLC has a relatively poor prognosis. Studies have shown that early assessment of prognostic factors in NSCLC patients is of great significance in determining and adjusting treatment plans, improving patient outcomes, and enhancing patient quality of life [3]. In Canada, it is estimated that in 2024: 32,100 Canadians will be diagnosed with lung and bronchus cancer. This represents 13% of all new cancer cases in 2024. 20,700 Canadians will die from lung and bronchus cancer. This represents 23% of all cancer deaths in 2024 [4].

Targeted anticancer drugs block cancer cell growth by interfering with specific signaling pathways vital to carcinogenesis and tumor growth rather than harming all rapidly dividing cells as in cytotoxic chemotherapy. The Response Evaluation Criteria in Solid Tumor (RECIST) system has been used to assess tumor response to therapy via changes in the size of target lesions as measured by calipers, conventional anatomically based imaging modalities such as computed tomography (CT), and magnetic resonance imaging (MRI), and other imaging methods. However, RECIST is sometimes inaccurate in assessing the efficacy of targeted therapy drugs because of the poor correlation between tumor size and treatment-induced tumor necrosis or shrinkage. This approach might also result in delayed identification of response when the therapy does confer a reduction in tumor size. Innovative molecular imaging techniques have rapidly gained importance in the dawning era of targeted therapy as they can visualize, characterize, and quantify biological processes at the cellular, subcellular, or even molecular level rather than at the anatomical level [5].

The prognostic value of DWI-related parameters has been explored in patients with multiple cancer types who received targeted therapies, such as those with unresectable ICC receiving lenvatinib plus PD1 antibody,[6] recurrent glioblastomas receiving anti-VEGF monotherapy, [7] colorectal liver metastases receiving bevacizumab,[8] and NSCLC brain metastases treated with whole brain radiotherapy and gefitinib.[9] In general, a higher baseline or post-treatment percentage change of apparent diffusion coefficient (ADC) was associated with improved patient outcomes. [9-14] These

findings indicate that the pretreatment ADC value or post-treatment percentage change of ADC could accurately reflect the therapeutic efficacy of tumor-targeted therapies and predict patient survival. Therefore, the monitoring of ADC could potentially support the optimization of strategies in anticancer treatment.[10] If validated, DWI MRI could be integrated into routine oncology imaging to offer a non-invasive, early indicator of immunotherapy effectiveness, reducing reliance on invasive biopsies. This methodology outlines a structured approach to evaluating DWI MRI as a functional imaging biomarker for lung cancer immunotherapy response assessment, leveraging non-invasive imaging for precision oncology.

This study will be a prospective observational cohort study aimed at evaluating the efficacy of Diffusion-Weighted Imaging (DWI) MRI as a functional imaging tool for assessing treatment response in advanced or metastatic lung cancer patients undergoing targeted immunotherapy.

Study Population

Inclusion Criteria • Patients diagnosed with advanced non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) eligible for targeted immunotherapy. • Patients with measurable lesions as per RECIST 2.1 criteria. • No prior systemic therapy within the past 3 months. • Ability to undergo MRI scanning. Exclusion Criteria: • Patients with contraindications to MRI (e.g., pacemakers, metal implants). • Patients with severe pulmonary disease limiting imaging quality. • Patients who have undergone recent radiation therapy to target lesions.

Expected Outcomes & Significance

• Primary Outcome: To determine whether DWI MRI can serve as a reliable imaging biomarker for early treatment response assessment in lung cancer patients receiving targeted immunotherapy.

• Secondary Outcomes: Progression-Free Survival (PFS) and Overall Survival (OS). • Comparison with Standard Imaging (CT) to evaluate the added value of DWI MRI. • Correlation with Immunotherapy Response Markers: PD-L1 expression, Tumor Mutation Burden (TMB).

• Clinical Impact: If validated, DWI MRI could be integrated into routine oncology imaging to offer a non-invasive, early indicator of immunotherapy effectiveness, reducing reliance on invasive biopsies. This methodology outlines a structured approach to evaluating DWI MRI as a functional imaging biomarker for lung cancer immunotherapy response assessment, leveraging non-invasive imaging for precision oncology.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.

2.Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer. J Natl Compr Canc Netw. 2012;10(10):1236–71.

3.Im HJ, Pak K, Cheon GJ, et al. Prognostic value of volumetric parameters of (18)F-FDG PET in non-small-cell lung cancer: a meta-analysis. Eur J Nucl Med Mol Imaging. 2015;42(2):241–51.

4.Canadian Cancer Society. *Canadian Cancer Statistics 2024*. 2024. https://cancer.ca/en/research/cancer-statistics.

5. Jing-Wen Bai, Si-Qi Qiu and Guo-Jun Zhang. Molecular and functional imaging in cancer-targeted therapy: current applications and future directions. Signal Transduction and Targeted Therapy (2023) 8:89. https://doi.org/10.1038/s41392-023-01366-y.

6. Sheng, R. et al. Apparent diffusion coefficient MRI shows association with early progression of unresectable intrahepatic cholangiocarcinoma with combined targeted-immunotherapy. J. Magn. Reson. Imaging 57, 275–284 (2023).

7. Tang, L. et al. Non-Gaussian diffusion imaging with a fractional order calculus model to predict response of gastrointestinal stromal tumor to second-line sunitinib therapy. Magn. Reson. Med. 79, 1399–1406 (2018).

8. Ellingson, B. M. et al. Diffusion MRI phenotypes predict overall survival benefit from anti-VEGF monotherapy in recurrent glioblastoma: converging evidence from Phase II Trials. Clin. Cancer Res. 23, 5745–5756 (2017).

9. Liu, L. H. et al. Identifying response in colorectal liver metastases treated with bevacizumab: development of RECIST by combining contrast-enhanced and diffusion-weighted MRI. Eur. Radiol. 31, 5640–5649 (2021).

10. Ye, C. et al. Predictive effect of DCE-MRI and DWI in brain metastases from NSCLC. Open Med. (Wars.) 16, 1265–1275 (2021).

11. Zhu, H. B. et al. Prediction of therapeutic effect to treatment in patients with colorectal liver metastases using functional magnetic resonance imaging and RECIST criteria: a pilot study in

comparison between bevacizumab-containing chemotherapy and standard chemotherapy. Ann. Surg. Oncol. 29, 3938–3949 (2022).

12. Patel, K. S. et al. Diffusion Magnetic Resonance Imaging Phenotypes Predict Overall Survival Benefit From Bevacizumab Or Surgery In Recurrent Glioblastoma With Large Tumor Burden. Neurosurgery 87, 931–938 (2020).

13. Schell, M. et al. Validation of diffusion MRI phenotypes for predicting response to bevacizumab in recurrent glioblastoma: post-hoc analysis of the EORTC26101 trial. Neuro Oncol. 22, 1667–1676 (2020).

14. Wen, Q. et al. Comparison of ADC metrics and their association with outcome for patients with newly diagnosed glioblastoma being treated with radiation therapy, temozolomide, erlotinib and bevacizumab. J. Neurooncol. 121, 331–339 (2015).

DWI MRI Lung Impact Statement

Problem Statement

Conventional CT-based imaging to monitor treatment response can be inaccurate when assessing the efficacy of both targeted therapy and immunotherapy, which are increasingly used to treat lung cancer. This inaccuracy may delay identification of a response and cause misinterpretation of treatment effectiveness, adversely affecting oncologist decision-making and patient management. In lung cancer, where prognosis is relatively poor, timely and accurate response assessment is of critical importance.

Action Statement

Diffusion weighted magnetic resonance imaging (DWI) has been shown to increase capacity to elucidate the positive effects of treatment in some brain and colorectal cancers. This study of 20 patients will determine whether it improves assessment of the therapeutic efficacy of targeted therapy and immunotherapy, and/or improves prediction of patient survival in advanced or metastatic non-small cell lung cancer patients.

Benefit/Impact Statement

The positive impact of a DWI-based method which improves assessment of treatment efficacy, particularly as adoption of targeted therapy and immunotherapy continue to expand in oncology, will be felt across the entire lung cancer research community. As DWI technology is widespread and readily available, it has the potential for widespread adoption quickly. the positive impact will be felt across the entire lung cancer community. Accelerated identification of effective treatment regimens will aid oncologists in decision-making and patient management. For patients, it would result in better outcomes by maximizing time spent on the most effective treatments. At the institutional level, it will result in more efficient use of resources, with less time and money spent on less effective treatments. On a global scale, improved prediction of treatment efficacy in lung cancers will accelerate the development and clinical application of future anti-cancer treatments for this disease.

Implicated Personnel with roles and responsibilities

Dr. Saly Zahra, radiologist – will perform radiological assessements

Dr. Mahmoud Abdelsalam, medical oncologist – patient referral, advisory role

Dr. Maged Salem, medical oncologist – patient referral

Dr. Pierre O'Brien, medical oncologist – patient referral

Ian Chute, Oncology Research Manager – Administrative work

The Moncton Hospital, Horizon Health Network

Role of DWI MRI as functional imaging in assessment of treatment response of Targeted treatment of NSCLC.

– Public Non-scientific Summary

Dr. Saly Zahra and Dr. Mahmoud Abdelsalam

For oncologists and their lung cancer patients, no knowledge is as important as whether their treatment is working. The period between imaging assessments, when computed tomography (CT) scans show whether tumours have shrunk or grown, can be agonizing for patients. Assessing treatment response with imaging is imperfect and its accuracy has diminished when used to assess some of the latest, and more effective treatments. Although CT scans can discern the size of tumours, they are very limited in assessing their character. This means that although they can detect when tumours change in size, they are not able to see what is happening on the inside.

The evolution of cancer treatment has resulted in medications which attack tumours with more specificity than chemotherapy, such as targeted therapies and immunotherapy. The responses of patients to these new treatments are more variable and may not reduce tumour size quickly but instead cause internal changes to the tumour and sometimes even increase their size. Treatments may appear to be ineffective when observed using standard CT scans when in fact, they are causing the tumour to break down internally, or to enlarge as beneficial immune cells infiltrate the tumour. Immunotherapy can sometimes result in "pseudoprogression" which does not represent real progression of the cancer. This false assessment of treatment efficacy can mislead both the oncologist and the patient.

Diffusion- weighted magnetic resonance imaging (DWI) is an alternate imaging method that provides additional information about the structure of tumours and not just their size. This allows radiologists using DWI to look inside the tumour to see if it is being affected internally by the treatment, which can happen before any reduction in size. The earlier oncologists have information about whether the treatment is working, the more agility it provides for switching to another treatment regimen. DWI has been tested in some brain and colorectal cancers and it was shown to improve prediction of treatment efficacy and patient survival. For lung cancer patients with a poor prognosis, limiting time spent on an ineffective treatment is crucial to allow time for finding a more effective option.

In this study, we will be performing DWI alongside CT scans in 20 lung cancer patients. The imaging for each patient will be done before treatment and at 3, 6, 9 and 12 months after starting treatment. The goal will be to determine whether the DWI results in better prediction of treatment effectiveness and patient survival than CT alone. DWI may provide a better means of assessing the efficacy of more advanced and specific targeted treatment regimens. As magnetic resonance imaging is widely available, the benefits of this study with increased use of DWI could be quickly adopted by other institutions. If so, it will accelerate research and development of new, more effective treatments for lung cancer, while also providing oncologists and patients with greater confidence in their cancer care.

RÉSEAU DE SANTÉ Horizon HEALTH NETWORK

CORPORATE OFFICE/
BUREAU DE DIRECTION
Centre Woodbridge Centre
180, rue Woodbridge Street
Fredericton, NB E3B 4R3
Tel / Tél. : (506) 623-5500
www.HorizonNB.ca

RESEARCH SERVICES- BUDGET

Project Name: Role of DWI MRI as functional imaging in assessment of treatment response of Targeted treatment of NSCLC

Principal Investigator: Dr. Mahmoud Abdelsalam and Dr. Saly Zahra

Institutional Fees

Budget Item	**Fee**
1. REB Fees:	
Initial Review	$ 2,500
2. Human Research Protection Program (HRPP) Fee:	
Per study	$ 1,000

Outsourced Services Fees/ Salaries		
Budget Item	**Fees**	**Comment**
MRI	$20,000	5 MRIs per patient (Baseline, 3, 6, 9, 12 Months) 100 total
MRI Reading	$10,000	Radiologist Time for MRIs and CT scans (200 imaging reviews in total)
Administrative Cost (Protocol Writing, Data entry/analysis, Report Writing)	$2,000	Clinical research staff time (Research assistant)
TOTAL	**$35, 500**	*Estimated for 20 patients