Research Protocol

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Advanced image analyses of dynamic FDG-PET/CT from patient-derived mouse models of endometrial cancer

Background

Endometrial cancer (EC) is the most common gynecological cancer in industrialized countries and the incidence is increasing [1]. Although EC is formally surgiopathologically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system [2], imaging plays a central role in the management of EC patients. Preoperative imaging findings guide primary surgical treatment and are especially useful to stratify high-risk patients for lymphadenectomy, which is a major clinical challenge [3].

Transvaginal ultrasound and/or magnetic resonance imaging (MRI) is typically performed preoperatively to assess local tumor extent. Computed tomography (CT) alone or CT combined with positron emission tomography (PET-CT) are useful to assess both abdominal spread to pelvic- and paraaortic lymph nodes as well as distant spread [4]. PET imaging in oncology is most often performed using ^{18}F-labeled glucose, fluorodeoxyglucose (FDG). Malignant cells are metabolically characterized by elevated energy demands and will normally have an increased uptake of glucose. Cancers will therefore typically exhibit high uptake of FDG generating contrast in PET images. In addition to elevated FDG uptake in metastatic lymph nodes, primary EC are also typically highly FDG avid [5].

Clinically, PET images are usually acquired by conventional static scanning, typically one hour post-injection for FDG, and analyses are based on the semi-quantitative and variation-prone parameter standardized uptake value (SUV) [6, 7]. In order to delineate and segment a tumor from normal surrounding tissue a fixed threshold of >2.5 SUV is typically applied to include all putative tumor voxels in a volume of interest (VOI). Several additional segmentation methods exists including manual-, boundary and region-based techniques and the chosen approach will be dependent for the outcome [8]. In EC the 2.5 SUV threshold-based method is commonly used, and the mean and maximum uptake is reported (SUV_{mean}/SUV_{max}) though the documented usefulness of these parameters is limited [9].

Intrinsically, one of the main advantages of PET technology is the possibility to perform absolute quantification by dynamic imaging. Pharmacokinetic parameters derived from dynamic imaging can potentially yield functional tumor information beyond that represented

by SUV and better characterize tumor heterogeneity and monitor therapeutic response [10]. Patlak modelling, a linear regression analysis technique suited for PET tracers with irreversible uptake like FDG, has shown to be a useful model in the analyses of dynamic PET in oncology [11].

Preclinical imaging of patient-derived tumor xenograft (PDX) mouse models represents a useful tool for unravelling new imaging biomarkers for prediction and evaluation of treatment response that eventually can be translated into the clinic [12, 13]. We have established a multimodal imaging platform similar to that routinely employed at EC primary diagnostic work-up in the clinic, and we have shown increased FDG uptake in EC PDX mouse models using small-animal PET [14]. Advanced image analysis of tumors in clinically relevant animal models using advanced imaging methods represents an ideal research platform for testing and validation of imaging cancer biomarkers prior to potential implementation in the clinic.

Objectives

In a recent preclinical EC imaging study from our group (Espedal et al, manuscript in preparation) we found that the clinical >2.5 SUV segmentation threshold may be suboptimal for mice. We want to explore alternative segmentation methods in a systematic manner to develop an optimal method for our PDX models. Furthermore, we want to investigate if parameters derived from dynamic imaging outperforms that of static parameters for capturing clinically relevant in tumor characteristics and predicting treatment response.

<u>Main aims:</u>

1) We will optimize and standardize the tumor segmentation protocols in our mouse model database of dynamic FDG-PET (n>200) in order to provide a basis for future PET image analyses.
2) Using the method obtained in 1), we will compare dynamic and static image parameters. Static parameters will include SUV_{mean}, SUV_{max}, metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Dynamic images will be analyzed using Patlak-modeling and influx of FDG (K_i) will be calculated.
3) Compare static and dynamic image parameters to assess treatment response in a subset of mice that has received chemotherapy following tumor implantation.

Material and methods

This retrospective study will include >200 mice with orthotopically implanted PDX EC of different stage and histology. All mice have undergone a one-hour dynamic FDG PET-CT scan between 2013 and 2020. A cohort of mice within the database have received chemotherapy and this treatment study will also be included in the analyses.

Prior to image analysis all PET acquisitions will be reconstructed into standardized time frames using Nucline software. For the segmentation study, the last 30 minutes of the 1-hour scan (static) will be used. Advanced image analysis of the dynamic FDG-PET scans will be carried out using two different software: Interview Fusion (visualization, segmentation) and PMOD (segmentation, kinetic modeling).

Statistical analysis will be carried out using SPSS and Prism.

The student's role and plan for education

The student is expected to work independently following software training by the main supervisor. The results will be discussed with both supervisors and within the research group. The candidate will start her full-time research year autumn 2021, but the initial training can start earlier as part of the candidate's elective course spring 2021.

Project plan

	2021		2022		2023	
	1	2	1	2	1	2
Software training and literature search	**x**					
Image reconstruction and analysis		**x**	**x**			
Data analysis and structuring of results		**x**	**x**			
Manuscript preparation			**x**	**x**	**x**	
Publication						**x**

Planned publication

The goal of this project is to yield novel results that may be presented in a manuscript that will be submitted to an international, peer-reviewed journal specializing in preclinical imaging. It is realistic that a first draft can be started towards the end of the first research year. Follow-up studies implementing results from the primary work are possible and dependent on whether the research student is interested in pursuing a PhD afterwards.

Education

The student will enroll in the mandatory courses MEDMET1 and FORMIDL901. Additionally, it is recommended that the student sign up for LAS 301/302 (Course in animal research) as the material in this project is based on mouse studies. Additional courses such as a statistics course (Legeforeningen online course) and a seminar series for research dissemination (CCBIO901) is also encouraged to sign up for.

Approvals

All animal experiments and the images that were collected for use in this study has been approved by Mattilsynet/FOTS (FOTS ID: 4036, 6080, 6710, 6735, 18798)

Finance

Expenses related to imaging software licenses and data analyses will be financed by the project (Precision imaging in gynecologic cancer; headed by Prof. Haldorsen) at Mohn Medical Imaging and Visualization Centre (MMIV) to which the research student will be affiliated. The group will also cover potential costs associated with compulsorily or elective courses to attend when regarded necessary.

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