THE ROLE OF NUCLEAR MEDICINE IN LYMPHOMAS – A FOCUS ON PROGNOSTIC EVALUATION OF DIFFUSE LARGE B-CELL LYMPHOMA WITH POSITRON EMISSION TOMOGRAPHY

Ph.D thesis booklet

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1. Introduction

Vast evidence has accumulated supporting the diagnostic superiority of 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) in the staging of diffuse large B-cell lymphoma (DLBCL) and further studies support its prognostic utility in early treatment response evaluation, termed interim PET (iPET). To enable semiquantitative evaluation of FDG uptake, standardized uptake value (SUV) had been introduced that normalises the measured activity concentration for injected activity and body weight. Most commonly, SUV_{max}, the SUV of the most intense voxel within a volume of interest (VOI) is used. VOIs encompassing lymphomatous tissue on PET define metabolic tumour volume (MTV) and this metric is getting recognised as an additional prognostic biomarker in DLBCL, however, there is no consensus regarding which segmentation method should be utilised and about the optimal cut-off point. Visual criteria using the Deauville-score (DS) system in evaluating iPET response are robust, but still face challenges, especially with its low positive predictive value (PPV). To improve the ordinal DS system, continuous-scaled prognostic values have been introduced, as the ΔSUV_{max}, the quantitative PET (qPET), and the ratioPET (rPET) method. Recently, the use of texture analysis or

radiomics have been applied to PET/CT scans in the prognostic estimation of DLBCL but these studies are heterogeneous in endpoint and methodology.

2. Objectives

The general aim of the two research studies in this thesis was to investigate potential roles of existing FDG-PET/CT prognostic parameters in DLBCL and to establish new or modified methods which are both easy to implement in routine workflows and yield more accurate results than the current ones, with special focus on the following questions:

1. How is the prognostic accuracy of baseline volumetric PET parameters influenced by different segmentation methods and is there an additive value in standardising to body weight?

2. What is the prognostic efficacy of different baseline and iPET parameters in a prospective, multi-centre study?

3. What is the prognostic value of baseline clinical, volumetric, and radiomics-based textural parameters individually and in a combined analysis with a machine learning algorithm in a retrospective, single-centre study?

4. Is there an additive value of the newly introduced MTVrate parameter?

3. Methods

3.1. Study A – *Prognostic parameters on baseline and interim FDG-PET/CT in DLBCL patients (Objectives 1-2)*

Data of 107 DLBCL patients from a multicentre, prospective trial were used for analysis of baseline volumetric values (MTV and total lesion glycolysis [TLG], also normalised for body weight) segmented with three different methods (glob4: SUV>4.0; 41pc: 41% isocontour VOI around the local maximum point; grad: a vendor-specific gradient-based lesion growing algorithm) and interim parameters (DS, ΔSUV_{max}, modified qPET [mqPET], and rPET method). 24-month progression-free survival (PFS) was the clinical endpoint and receiver operating characteristics (ROC) analyses were performed to define optimal cut-off points for continuous parameters. The PFS of low- and high-risk groups were compared with log-rank and Cox-regression analysis.

$$\Delta SUVmax = \frac{SUV_{max}(interim) - SUV_{max}(baseline)}{SUV_{max}(baseline)}$$

$$mqPET = \frac{SUV_{peak}(lesion)}{SUV_{mean}(liver)} \qquad rPET = \frac{SUV_{max}(lesion)}{SUV_{max}(liver)}$$

SUV_{peak}(lesion): average SUV in the hottest virtual volume of 1 cm^3

SUV_{mean}(liver): average uptake in 3 cm diameter spheric VOI positioned in the right liver lobe

3.2. Study B – *Volumetric and textural analysis of PET/CT in patients with DLBCL, introducing the importance of novel MTVrate feature (Objectives 3-4)*

Retrospective analysis of baseline PET/CT scans of 50 DLBCL patients from one centre was performed to investigate textural PET features and the newly defined MTVrate value (the quotient of the largest lesion's volume and total body MTV), alongside MTV and clinical data with 24-month PFS serving as the clinical endpoint. MTV was segmented with the SUV>4.0 method and the VOI of the largest lymphoma lesion was used to extract first-, second-, and higher-order textural features, 44 in total. ROC analyses were performed to define optimal cut-off points for continuous parameters. The PFS of low- and high-risk groups were compared with log-rank analysis.

Furthermore, a machine learning algorithm was used to build a prognostic model based on logistic regression. To avoid overfitting, we utilised elastic net regularization. After preprocessing, repeated cross-validation was used to train the model in three cycles, randomly splitting the patient population 70% : 30% into training and test. The model cleared the redundant parameters and gave the remaining ones relative importance. At the end, ROC-analysis was performed with the model to determine its prognostic value.

4. Results

4.1 Study A – *Prognostic parameters on baseline and interim FDG-PET/CT in DLBCL patients (Objectives 1-2)*

In the analysis of Study A, good to excellent correlation was observed among MTV and TLG values segmented by glob4, 41pc and grad methods (Pearson correlation coefficients above 0.84). However, optimal cut-off points were markedly different, 122.5 with glob4, 257.5 with 41pc, and 334.9 with grad segmentation for MTV and 714.7 with glob4, 1207 with 41pc, and 2112 with grad segmentation for TLG.

Greater variability in sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy was seen, mostly among the same volumetric parameters acquired by different segmentation methods, rather than between traditional and body weight-adjusted MTV or TLG.

Regarding interim PET parameters, optimal cut-off points on ROC analyses were -71.22%, 1.32, and 1.54 for ΔSUV_{max}, mqPET, and rPET, respectively.

Highest hazard ratio was shown for rPET (HR=9.09), and it was also an independent predictor of PFS (p=0.041; HR=9.15) in a multivariate Cox-regression model (Figure 1).

A combined analysis showed that patients with high ΔSUV_{max} and high MTVglob4 formed a group with distinctly poor PFS (35.3%).

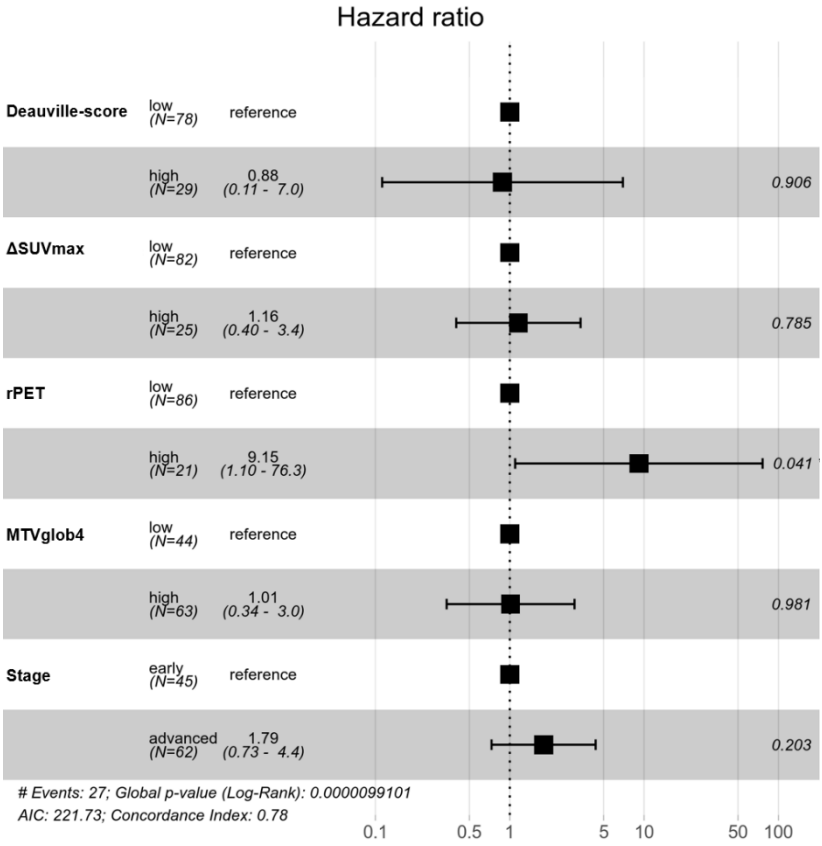

Figure 1. Multivariate Cox-regression model of progression-free survival including Deauville-score, ΔSUV_{max}, rPET, MTV, and clinical stage

SUV_{max}: maximum standardised uptake value; rPET: ratio PET; MTV: metabolic tumour volume

4.2. Study B – *Volumetric and textural analysis of PET/CT in patients with DLBCL, introducing the importance of novel MTVrate feature (Objectives 3-4)*

Among the single-centre data, individual analysis showed the highest AUC on ROC analysis for MTVrate at 0.74 (Figure 2), followed by LDH, MTV, and skewness, with areas-under-the-curve (AUCs) of 0.68, 0.63, and 0.55, respectively, and these parameters were also able to differentiate the PFS.

A combined analysis including MTV and MTVrate identified a subgroup with particularly low PFS at 38% where patients had high MTV and low MTVrate.

The machine learning-based model had an AUC of 0.83 and the highest relative importance was attributed to five textural features (features contrast, long-zone low grey-level emphasis, zone percentage, skewness, and maximum lesion diameter) and both MTV and MTVrate (Figure 3).

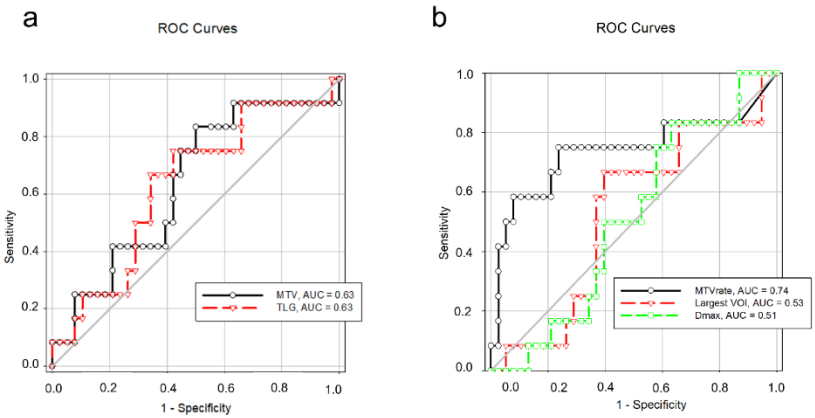

Figure 2. Receiver operating characteristic curves for 24-month progression-free survival (PFS) for a) metabolic tumour volume (MTV) and total lesion glycolysis (TLG); b) MTVrate, maximum lesion volume (Largest VOI), and maximum lesion diameter (Dmax).

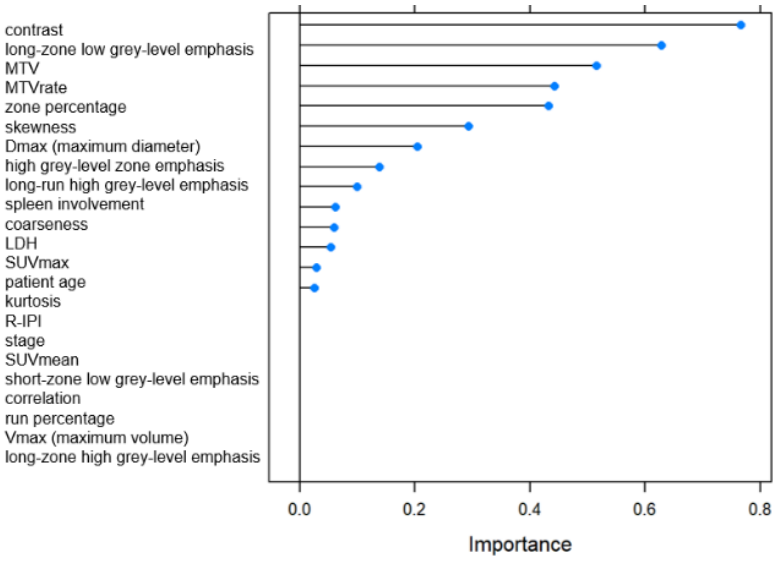

Figure 3. Results of the machine learning-based model for prognostic analysis: relative importance of different parameters within the model.

5. Conclusions

5.1. Prognostic parameters on baseline and interim FDG-PET/CT in DLBCL patients

1. The baseline MTV values and optimal cut-off points obtained by various segmentation methods exhibited significant variation and demonstrated only minor prognostic significance in our multicentric investigation of DLBCL patients. This was the inaugural publication of body weight-adjusted MTV and TLG values and although these values did not demonstrate significantly enhanced prognostic capability over their conventional (non-normalised) counterparts, there were a limited number of instances where body weight-adjusted MTV accurately classified the patient into the appropriate risk group, unlike standard MTV.

2. Interim PET/CT parameters yielded more precise prognostic information compared to baseline volumetric data, with semiquantitative "Deauville-like" metrics (most notably, rPET) demonstrating superior performance in this trial over conventional visual response evaluation (DS). The integration of baseline MTV and ΔSUV_{max} facilitated the differentiation of a patient cohort with notably adverse prognosis.

5.2. Volumetric and textural analysis of PET/CT in patients with DLBCL, introducing the importance of novel MTVrate feature

3. Our retrospective analysis of baseline PET data to assess the prognosis of patients with DLBCL revealed that the individual assessment of various clinical, volumetric, and textural biomarkers provided limited prognostic information, whereas a machine learning-based integrated analysis demonstrated high efficacy.

4. The newly established MTVrate, calculated as the ratio of the largest lesion's volume to total body MTV, had the greatest predictive capability in individual assessments and, when paired with MTV, facilitated the identification of a patient cohort with notably adverse prognosis.

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∑IF: 2.6

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