

Exploring Hypoxia in Prostate Cancer With T2-weighted Magnetic Resonance Imaging Radiomics and Pimonidazole Scoring

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Abstract. *Background/Aim:* Radiomics involves high throughput extraction of mineable precise quantitative imaging features that serve as non-invasive prognostic or predictive biomarkers. High levels of hypoxia are associated with a poorer prognosis in prostate cancer and limit radiation therapy efficacy. Most patients with prostate cancer undergo magnetic resonance imaging (MRI) as a part of their diagnostics, and T2 imaging is the most utilised imaging method. The aim of this study was to determine whether hypoxia in prostate tumors could be identified using a radiomics model extracted from T2-weighted MR images. *Materials and Methods:* Eighty eight intermediate or high-risk prostate cancer patients were evaluated. Prior to radical prostatectomy, all patients received pimonidazole (PIMO). PIMO hypoxic scores were assigned in whole-mount sections from prostatectomy specimens by an experienced pathologist who was blinded to MRI. The region of interest used for radiomics analysis included the prostatic index tumor. Radiomics extraction yielded 165 features using a special evaluation version of RadiomiX [RadiomiX Research Toolbox version 20180831 (OncoRadiomics SA, Liège, Belgium)] for non-clinical use. Multivariable logistic regression with Elastic Net regularization was utilised using 10 times repeated 10-fold

cross-validation to select the best model hyperparameters, optimizing for area under the receiver operating characteristic curve (AUC). *Results:* The average (out of sample) performance based on the repeated cross validation using the ONESE model yielded an AUC of 0.60 ± 0.2 . Shape-based features were the most prominent in the model. *Conclusion:* The development of a radiomics hypoxia model using T2 weighted MR images, standard in the staging of prostate cancer, is possible.

Radiomics is a developing field that involves advanced image analysis and high throughput extraction of mineable precise quantitative imaging descriptors or features that serve as non-invasive prognostic or predictive biomarkers (1). The primary function of a predictive biomarker is to accurately determine the outcome of a specified treatment (2). It is based on the hypothesis that tumor characteristics at cellular and genetic levels are captured in the phenotypic patterns seen in medical images (3). These features are often extracted from medical images using advanced mathematical algorithms (4). Currently, imaging features are generally only visually assessed by radiologists or nuclear medicine physicians and described as qualitative biomarkers (3).

High levels of hypoxia are associated with a poorer prognosis in prostate cancer (5). Due to the inefficient oxygenation of tumor vasculature, tumors have been reported to have large regions of hypoxia, relative to the surrounding normal tissue and both acute and chronic hypoxia exist within tumors. Regions of a tumor with a high oxygen concentration are believed to be up to three times more amenable to radiation therapy than hypoxic regions (6). Proteins and gene expression signatures may serve as intrinsic molecular biomarkers in the identification of hypoxia, but to date, none has successfully been implemented in routine clinical practice for the assessment of hypoxia (7). Other methods for identifying hypoxia in tumors

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Table I. Summary of patient characteristics.

Age (years)	Pre-operative PSA (ng/ml)	Gleason score at biopsy	Clinical tumor stages	D'Amico risk stratification	PIMO score
64 (47-75)	12.4 (2.2-145)	7 (6-9)	cT1c (n=37) cT2a (n=8) cT2b (n=8) cT2c (n=4) cT3a (n=7) cT2x (n=14) Not recorded (n=5)	Low risk (n=2) Intermediate risk (n=47) High risk (n=39)	1.9 (0-5)

Values are means with ranges given in parentheses. For clinical T stage and D'Amico risk stratification, absolute numbers of patients are given in parentheses.

include the Eppendorf electrode method and extrinsic markers; such as pimonidazole (PIMO), the latter serving as the method of biological validation in this manuscript. However, the Eppendorf electrode method is an invasive technique and PIMO analysis is not feasible in cases where definitive radiation therapy or chemoradiation therapy are the primary treatments, as no surgical specimen is available.

Medical imaging therefore presents a non-invasive and clinically attractive option for the assessment of hypoxia. Promising imaging techniques such as blood oxygen level dependent and tissue oxygenation level dependent MRI (BOLD-MRI, TOLD-MRI) (8), consumption and supply-based hypoxia MRI (CSH-MRI) (9) or positron emission tomography (PET) using hypoxia-seeking ligands such as fluoro-misonidazole (FMISO), 5 fluoro-azomycin-araboside (FAZA) and [18F]HX4 (10, 11) have all been described. However, these advanced imaging techniques do not have the spatial resolution required to fully sample the tumor microenvironment, and both acute and chronic hypoxia are believed to be micro-regional (12). They are also not routine imaging modalities for the staging and management of prostate cancer unlike multiparametric MRI [T2-weighted, diffusion weighted (DW-MRI) and associated apparent diffusion coefficient (ADC) maps] (13). T2-weighted imaging yields relatively high-resolution images of the prostate and surrounding anatomy, allowing for appreciation of structural differences (14), unlike DW-MRI, where spatial resolution is a known limitation (4).

The development of a non-invasive strategy such as radiomics, using routine T2-weighted MR images to identify hypoxic regions within tumors is of much interest in radiation therapy. Most prostate cancer patients undergo MR imaging as a part of their diagnostics, and T2 imaging is the most utilized imaging method. It is highly stable with minor artefacts compared to other MR imaging sequences such as dynamic contrast enhanced MRI and DW-MRI.

Identification of hypoxia on T2-weighted MRI could easily be implemented in the clinic. It would permit dose escalation to hypoxic regions and could lead to improved

Table II. T2 image scanning parameters.

TR (ms)/TE (ms)	4,144.87/141.76
Flip Angle °	0/90
Acquired matrix (mm)	512×512
Slice thickness (mm)	3
Voxel size (mm ³)	1.5

TR: Time of repetition; TE: Echo time.

treatment outcomes, without the need for additional imaging techniques. To date, the data on such an approach have been limited in prostate cancer (15).

The aim of this study was to determine whether hypoxia in prostate tumors could be identified using a radiomics model extracted from T2-weighted MR images (16).

Materials and Methods

The study used irrevocably anonymised data from 88 intermediate or high-risk prostate cancer patients, as per the D'Amico risk classification, recruited as part of the FUNCTPROST study under a data sharing agreement signed between Trinity College Dublin and Oslo University Hospital, Radiumhospitalet, Oslo, Norway. The clinical features of all 88 analysed patients are summarised in Table I.

The methodological steps of the FUNCTPROST study and procedures were previously published (9). Briefly, all consented patients received the hypoxia marker pimonidazole (PIMO) prior to radical prostatectomy at a dose of 500 mg per m² body surface. MRI scans were acquired adhering to the European Society of Urogenital Radiology (ESUR) 2012 guidelines (17). The imaging parameters of the scan protocol are given in Table II. PIMO hypoxic scores were assigned in whole-mount sections from prostatectomy specimens by an experienced pathologist who was blinded to MRI (Figure 1).

Radiomics region of interest (ROI) definition. The ROI used for radiomics analysis included the prostatic index tumor. The tumor lesion was contoured as part of the FUNCTPROST study on a single axial slice of T2 weighted images by an experienced radiologist. Contouring was aided by the pathological evaluation of hematoxylin and eosin stained whole mount sections.

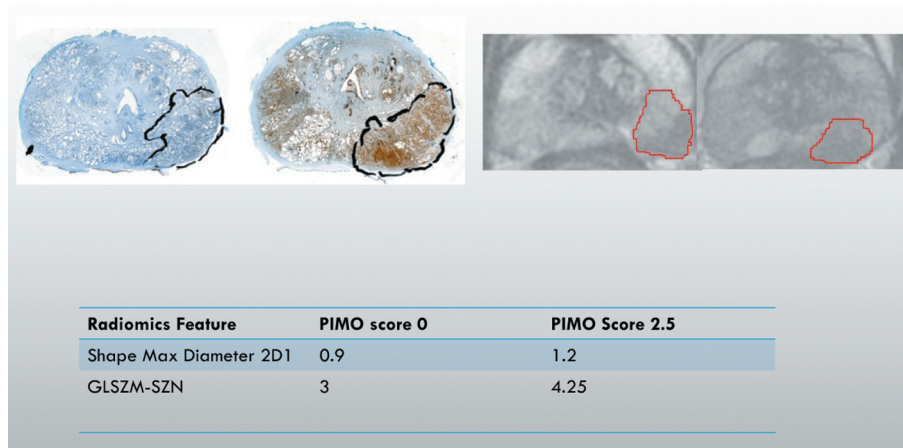


Figure 1. PIMO scored prostatectomy specimens and corresponding regions of interest. Left: Pimonidazole (PIMO)-stained whole-mount section from the prostatectomy specimens of two patients, one with a tumor pimonidazole score of 0 (left) and one with a pimonidazole score of 2.5 (right). Tumor outline is indicated. Right: The corresponding region of interest outlined for both patients on T2-Weighted magnetic resonance imaging. The radiomics feature values for two of the model features are given: Shape Max_Diameter and GLSZM-SZN. Note the higher values for the higher PIMO score.

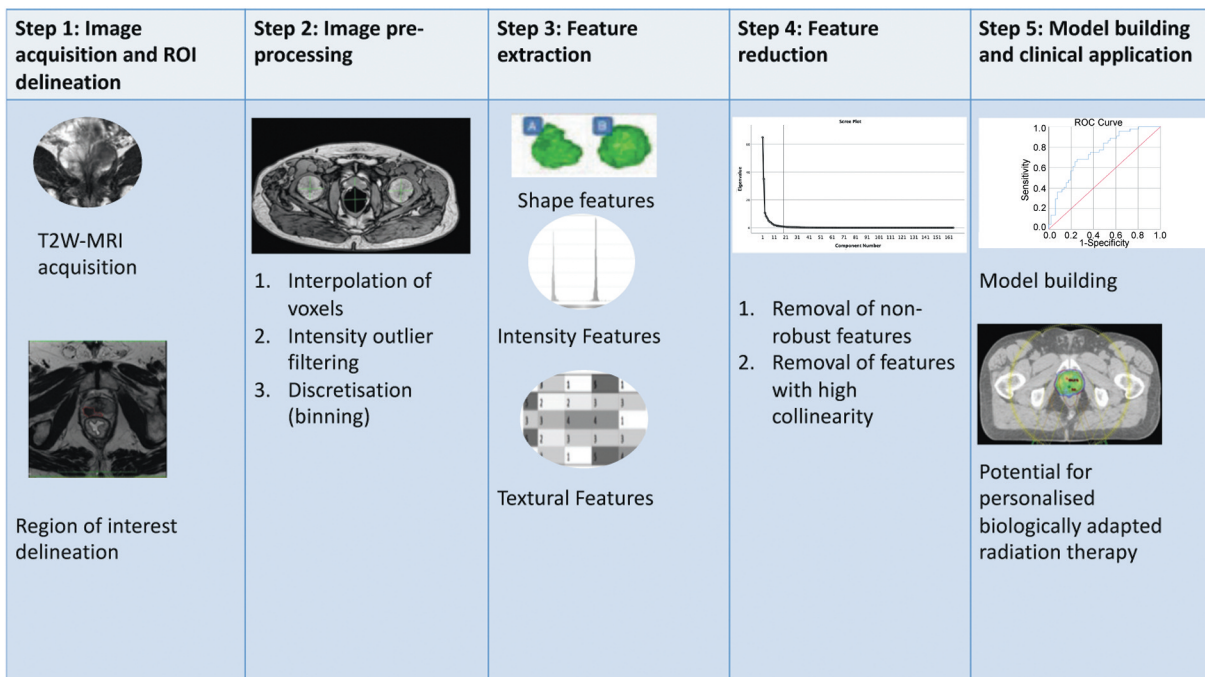


Figure 2. The steps in the radiomics process. Image acquisition and delineation (Step 1) is followed by image pre-processing to compensate for differences in image acquisition protocols (Step 2). Feature extraction (Step 3) can result in hundreds or thousands of features, which need to be reduced (Step 4) in order to produce a model with a reasonable number of variables that are predictive of a given endpoint (Step 5). ROI: Region of interest.

Radiomics features. Feature extraction was performed using a special evaluation version of RadiomiX [RadiomiX Research Toolbox version 20180831 (OncoRadiomics SA, Liège, Belgium)] for non-clinical use. A total of 165 features were extracted, focused on the index lesion. Prior to feature extraction, all images were normalised to zero mean, unit variance, resampling was performed

using 3 mm isotropic voxels, and the bin width utilised was 0.1. The interpolation algorithm utilised was linear. The radiomics pre-processing and feature extraction process is outlined in Figure 2. The features extracted included morphological features, local intensity features, first-order statistics, intensity histogram features, fractal features and the textural feature families of Gray Level Co-

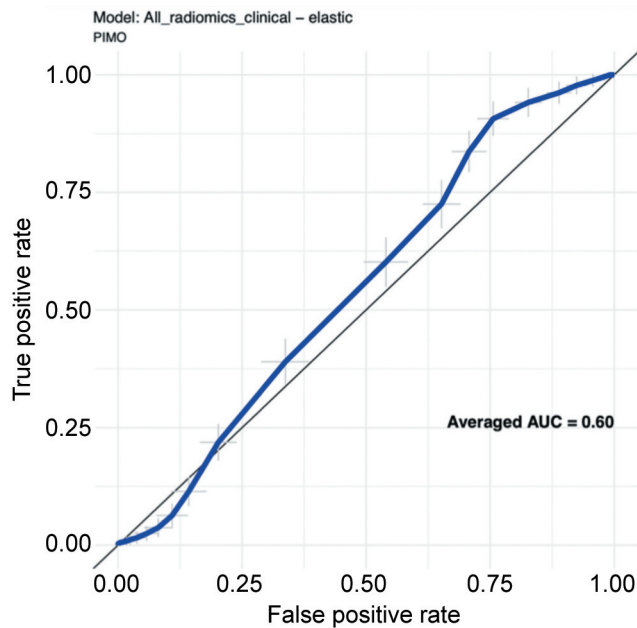


Figure 3. Model results yielded an area under the receiver operating curve (AUC) of 0.60.

occurrence Matrix (GLCM), Gray Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM), Gray Level Distance Zone Matrix (GLDZM), Neighbouring Gray Tone Difference Matrix (NGTDM), and Neighbourhood Gray Level Dependence Matrix (NGLDM).

Statistical analysis. Hypoxia was modelled for statistical analysis using a binary method with PIMO score <3 (not hypoxic) and PIMO score ≥ 3 (hypoxic). Redundant features with high correlation ($\rho > 0.9$), together with features with near zero variance and linear combinations between features were removed from additional analysis.

Multivariable logistic regression with Elastic Net regularization was utilised using 10 times repeated 10-fold cross-validation in order to determine the optimal model hyperparameters, optimizing for area under the receiver operating characteristic curve (AUC). All features were standardized before modelling. The simplest candidate model (*i.e.*, the model with the fewest non-zero coefficients) within one standard error of the best performing model was selected to reduce the chance of overfitting (ONESE).

Results

The average (out of sample) performance based on the repeated cross validation using the ONESE model yielded an AUC of 0.60 ± 0.2 (Figure 3). The most relevant features in the model were Shape-based. Shape_flatness was the most important feature in the model, followed by Shape_spherDisprop and Shape_MaxDiameter2D1. The relative contribution of each to the model is shown in Figure 4 and examples of feature values from PIMO 0 and PIMO 2.5 scores are given in Figure 1.

Discussion

Radiomics-based analysis of hypoxia is in its infancy but has the potential to be of high clinical relevance as conventional measurements of tumor hypoxia using functional imaging, molecular biomarkers or direct probes are expensive, time-consuming and, in some instances, invasive (18). Hypoxia is one of the leading causes of failure of radiation therapy and progression of disease (19) and PIMO staining is an established method for the surrogate assessment of the presence and extent of tumor hypoxia (7).

In this analysis, Shape-based features were the most important in the ONESE model and only one textural feature, GLSZM_SZN was reported in the model. There is a paucity of literature on using radiomics to explore hypoxia in prostate cancer. One pilot study on the association between hypoxia gene profiles and multiparametric MRI in prostate cancer identified 16 T2-weighted textural features, which had significant correlations with three hypoxia gene profiles using both sequencing and immunohistochemical techniques (15). GLCM, GLRLM, GLSZM and local binary patterns extracted from multiparametric MRI and three hypoxia-related gene sets were selected for investigation. These included a 15-gene universal hypoxia gene set (GENE15), a 32-gene prostate specific hypoxia gene set (GENE32), and a 44-gene hypoxia gene set (GENE 44). Although limited to six patients, their results, together with the results of our study with a significantly larger patient cohort, hold promise for future larger scale radiomic analyses.

Considering other cancer sites, Beig *et al.* (20) reported that radiomics textural features were predictive of a hypoxia enrichment score, based on the 21 genes implicated in the hypoxia pathway of glioblastoma multiforme (GBM). Using 180 multiparametric images from GBM patients, three ROIs were defined: oedema, including the non-enhancing tumor; tumor necrosis; and enhancing tumor. On T2-weighted images of the tumor necrosis ROI, the textural feature information measure of correlation 1, which captures co-occurrences and quantifies structural heterogeneity, was identified to be one of the top eight features most associated with hypoxia enrichment score.

By using a methodology similar to that utilised in the current analysis in non-small cell lung cancer (NSCLC), 14 patients who were administered intravenous PIMO within 24 hours of pneumonectomy had their CT images analysed for textural radiomics features (21). Unlike the present study, the ROIs were delineated on the CT images using semi-automation, without reference to the surgical specimens. The textural features that most strongly correlated with PIMO staining were the standard deviation of all pixel values and the mean value of positive pixels.

It is apparent that structural heterogeneity in tumors may identify hypoxia that cannot be determined by traditional

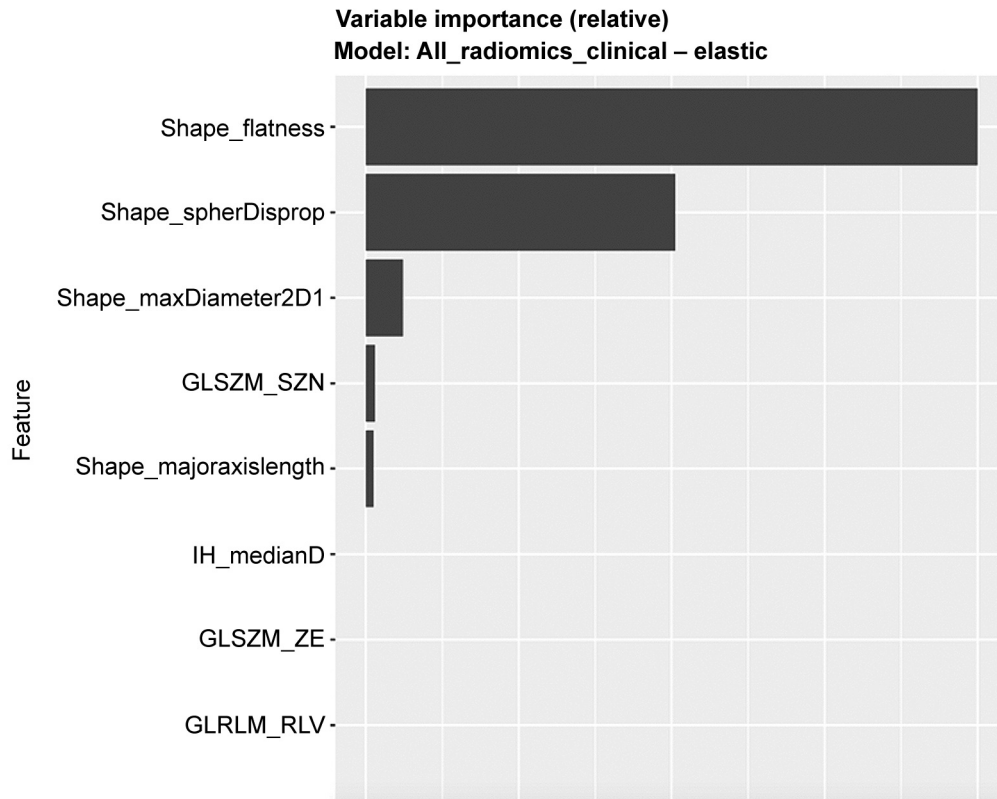


Figure 4. Relative performance of radiomics features in the hypoxia model. Note the prevalence of Shape-based features. *Shape_spherDisprop*: Shape_spherical disproportion; *GLSZM-SZN*: gray-Level size zone matrix-size zone non-uniformity; *IH*: intensity; *Histogram GLSZM_ZE*: gray-level size zone matrix- zone entropy; *GLRLM_RLV*: gray-level run-length matrix-run length variance.

analysis of conventional imaging techniques. Radiomics features extracted from T2-weighted MR images have potential in predicting for PIMO score or hypoxia gene profiles. As textural features quantify the occurrence of various patterns in an image and indicate how the signal response at any given voxel relates to those around it (14), they might have potential as a surrogate for the structural heterogeneity displayed by the hypoxic tumor regions.

In the current radiation therapy workflow, even where adaptive radiation therapy (ART) is routine, a methodology to determine regions of hypoxia and thereby the likely sites of treatment failure is largely absent. Knowledge of the specific radiomics features that can predict for hypoxia, which, from the current analysis and the literature, are likely to be shape and texture-based features, gives the potential for radiomics-based adaptation at the treatment unit, specifically the MRI-linear accelerator. A radiomics based targeted radiotherapy (Rad-TRaP) framework for prostate cancer brachytherapy and external beam treatment planning has been previously proposed (22). However, the radiomic features in this Rad-TRaP study predicted only the location of the prostate cancer lesions, not

the regions of hypoxia within the lesions. Such a framework however, could be extended in future for the purposes of analysing and adapting therapy based on radiomics features predictive of hypoxia. In nasopharyngeal carcinoma, it has been postulated that utilising pre-treatment MR images can predict patients in need of adaptation during therapy. A T2-weighted model had an AUC of 0.750 when predicting eligibility for ART in nasopharyngeal carcinoma, with six selected radiomics features – sphericity, elongation, kurtosis, and three textural features from the GLDM and NGTDM families (23). However, this focused on adaptation based on geometric or dosimetric features only and not on the presence of hypoxia.

The current analysis was performed on T2-weighted MRIs that had been acquired for diagnostic purposes. Therefore, before such a proposal could be deemed feasible, a similar analysis would have to be conducted on the available sequences on the MR-linear accelerator and confirmed in a validation cohort. Adoption of radiomics analysis into cone beam computed tomography (CBCT) workflow is dependent upon the ability to define the ROI on images of limited quality and subjected to noise, making the MR-linear

accelerator a more favourable option. Although it has been determined that some radiomics features are robust to CBCT (24), CBCT radiomics analysis to date has been limited to ascertain prognosis rather than to adapt or intensify treatment, particularly in lung cancer (25).

Limitations. This study has limitations with respect to the radiomics quality score metric (26). No validation was performed in another dataset, data analysed and radiomics package used were not open source, and the study was retrospective in nature.

Conclusion

In this study, we have demonstrated the feasibility of building a radiomics hypoxia model using T2 weighted MR images, standard in the staging of prostate cancer. Our study uniquely trained this model using scores from PIMO-stained whole-mount sections as the biological validation of hypoxia. Revealing the underlying tumor biology from radiomics feature extraction using such standard imaging is an exciting prospect for future study in the era of adaptive radiation therapy and personalised medicine.

Conflicts of Interest

Dr. Ralph T.H. Leijenaar has shares in the company Radiomics (Oncoradiomics SA, Liège, Belgium) and is co-inventor of an issued patent with royalties on radiomics (PCT/NL2014/050728) licensed to the company Radiomics.

Authors' Contributions

ML generated the research idea, performed the radiomics extraction, statistical analysis and led the manuscript writing. RTL conducted advanced statistical analysis. TH and HL contributed data for the analysis and contributed to writing of the manuscript. JG contributed to writing of the manuscript. LM generated the research idea and contributed to manuscript revision.

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