Translational and of Medicine at Molecular Imaging Institute

Radiogenomics of prostate cancer:

Correlation between multiparametric MRI features and genomics markers of aggressiveness

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INTRODUCTION

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- Prostate cancer (PCa) diagnosis is generally based on transrectal ultrasound-guided biopsy. However, biopsies are invasive and prone to sampling error and carry a risk of infection. Therefore there is a significant need for more accurate and noninvasive techniques for determination of PCa aggressiveness.
- Radiomics analysis enables extraction of a large quantity of parameters that can be correlated to underlying tumor biology in several cancers, including PCa.
- **Objectives:**
 - (1) To assess the association of 1st and 2nd order radiomics features based on multiparametric magnetic resonance imaging (mpMRI) with histopathologic Gleason score, gene signatures and gene expression levels in PCa (2) To build machine learning models based on radiomics eatures to predict adverse histopathologic score and the Decipher genomics metastasis risk score¹.

RESULTS

Patient demographic, clinical and genomic characteristics

Parameter	Classification	Value
Age: mean (range)	Mean (range)	64 (41 – 76) y
Serum PSA	Mean ± SD (range)	8.0 ± 6.1 (2.5 – 29.7) ng/ml
Tumor location	PZ/TZ	54 (84%)/10 (16%)
Gleason score of index lesions on prostatectomy specimen	6/7/8/9	4 (6%)/46 (72%)/3 (5%)/11 (17%)
Pathologic stage	T2/T3	41 (64%)/23 (36%)
PI-RADS	3/4/5	3 (5%)/29 (45%)/32 (50%)
Lesion size	Mean ± SD (range)	1.5 ± 0.7 (0.4 – 3.7) cm
Decipher score	<0.6 (low-to-intermediate risk) / ≥ 0.6 (high risk of metastasis)	41 (64%)/23 (36%)

METHODS

Patients

86 patients that had an MRI exam at 3.0T Siemens Skyra before undergoing prostatectomy

Excluded (n=22)

- No lesion identified on MRI (n=6)
- Lesion location did not match between MRI and pathology (n=6)
- Previous treatment (n=4)
- No genomics testing (n=3)
- Different DWI parameters (n=2)
- > 6 months between MRI and prostatectomy (n=1)

Final population: 64 patients with 64 index prostate cancer lesions

Reference standard

- One abdominal radiologist identified the location of the index lesion with reference of MRI and prostatectomy pathology report
- Lesions in PZ and TZ included
- Assessment of PI-RADS and lesion score

mpMRI analysis workflow

Correlation of radiomics features with Gleason score

14 radiomics features showed significant correlation with Gleason score. Strongest correlation observed for mean kurtosis parameter K (r=0.39, FDR-adjusted P=0.001).

Correlation of radiomics features with gene expression levels

- A total of 311 significant correlations of 40 DWI features and 132 genes were found (**Fig 1**).
- Hierarchical clustering divided genes in 6 different clusters. Functional enrichment analysis showed that the genes were involved in the following biological processes: Cluster 1, immune response activation; Cluster 2, binding functions; Cluster 3, cell cycle processes; Cluster 4, single gene MYO1B (motor protein); Cluster 5, DNA repair, Cluster 6, hormone secretion.





- Retrieval of T2W and DWI images (b50, 1000, 1600, 2000)

- Calculation of DWI maps: ME ADC_{ME}, ADC from DKI ADC_{DKI} and kurtosis parameter K



ROI delineation

of index lesion



T2W GLCM Sum Average 16 bins Total number of extracted features/ lesion= 224

Genomics analysis

- On sample of index lesion of prostatectomy specimen
- Expression levels of 698 PCa-related genes and 40 gene expression signatures, including Decipher, retrieved from the Genomics Resource Information Database (GRID, Clinical Trials Identifier NCT02609269)

Statistical analysis

- Correlation analysis (Pearson or Spearman) to assess the association of 226 mpMRI features (histogram features, texture features, lesion size and PI-RADS) with Gleason score, gene signature scores and gene expression levels. P-values were adjusted for multiple testing using False Discovery Rate (FDR) correction.
- Significant associations between genes/gene signatures and radiomics features were



Correlation of radiomics features with gene expression signatures

- 50 significant correlations observed involving 31 mpMRI radiomics features and 19 signatures.
- For Decipher, the strongest association was observed with GLCM texture feature sum average on TWI with 64 bins (r=0.40, FDR-adjusted P=0.030)
- Most significant correlations were observed with gene signature PORTOS, an emerging genomics classifier for prediction of response to salvage radiotherapy² (25 radiomics features, stronger r=-0.481, FDR-adjusted P=0.002).

Machine learning prediction models (Fig. 2)

- Highest diagnostic performance for prediction of Gleason scores reached when using radiomics features of T2WI only (crossvalidated AUC=0.72)
- For Decipher, highest diagnostic performance reached when combining images of all assessed MRI methods (T2WI+ADC_{ME}+DKI, cross-validated AUC=0.84)

CONCLUSIONS

MRI radiomics features are promising for noninvasive assessment of PCa aggressiveness on the



Fig. 2. ROC curves of the cross-validated multiparametric MR imaging radiomics prediction models for prediction of Gleason score (left) and Decipher score (right).

clustered using an unsupervised hierarchical clustering methods. Clusters of genes were subjected to functional enrichment analysis using ToppGene. Machine learning models for prediction of Gleason \geq 8 and Decipher \geq 0.6 Lasso-regularized logistic regression analysis • Nested cross validation strategy • 5-fold inner cross validation to optimize regularization parameter • Outer cross validation using leave-one-out strategy • Model performance assessed using ROC analysis

histopathologic and genomics level. Our findings need to be validated in a prospective study.

ACKNOWLEDGEMENT

This research was supported by the 2017 Judy and Ronald Baron Prostate Cancer Foundation Young Investigator Award (awarded to Stefanie Hectors).

¹ Erho N et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One. 2013;8(6):e66855.² Zhao SG et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol. 2016;17(11):1612-20.