

Analysis of multi-tracer imaging in PROSTATE CANCER

Group 5

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1. INTRODUCTION

The present study aims to compare the efficacy of two different tracers used in **PET/CT Imaging** for the management of prostate cancer. The PET/CT investigation represents a crucial point in the diagnostic-therapeutic path, being fundamental for the visualization and accurate characterization of the tumor.

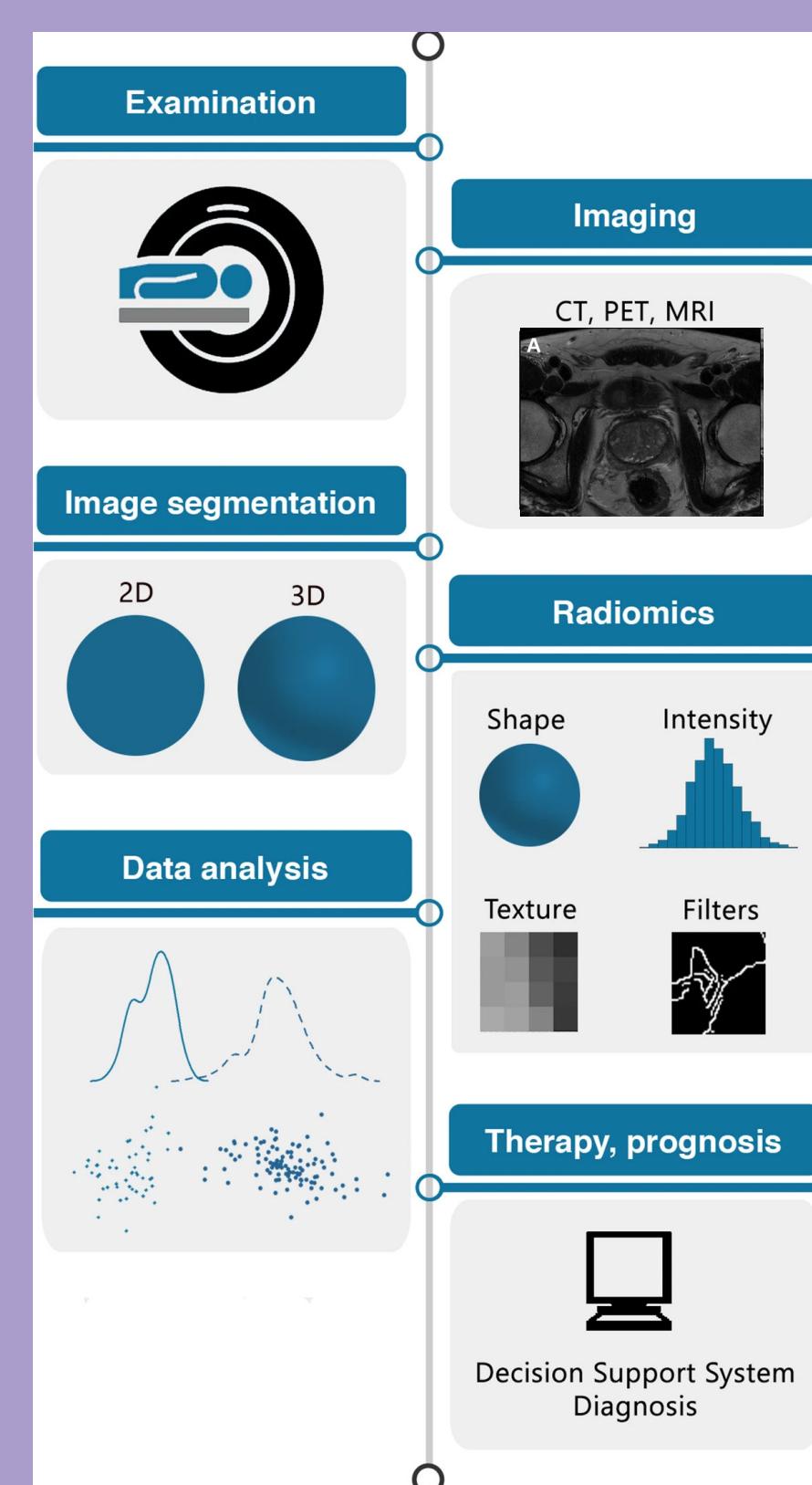
The research is based on a dataset provided by the **Papa Giovanni XXIII hospital** in Bergamo, including sensitive and real data from **93 patients**, for a total of **885 samples** and over **200 variables**.

The methodology is based on an in-depth analysis of numerical and categorical variables, with particular emphasis on data deriving from **radiomics**. The latter, defined as the conversion of images into multidimensional data and their subsequent use for more informed decision-making, is a key component of the study.

The **dataset was stratified** based on the tracer used, allowing a differential analysis of the variables associated with each group. This approach aims to identify **potential differences in the diagnostic and prognostic efficacy of the two tracers**, with the aim of optimizing the clinical management of prostate cancer patients.

3. PCA

The subsequent analysis was conducted separately on these two datasets. The radiomics variables were already categorized into **six groups**:



Morphological: These features describe the shape and size of the lesions.

Intensity based: These features capture the distribution of pixel intensities within the lesion.

GLCM (Gray Level Co-occurrence Matrix): These features measure the texture of the lesion based on the frequency of pixel pairs with specific intensity values.

GLRLM (Gray Level Run Length Matrix): These features assess the texture by evaluating consecutive pixels (runs) with the same intensity.

NGTDM (Neighboring Gray Tone Difference Matrix): These features quantify the difference in intensity between a pixel and its neighbors, reflecting the texture coarseness.

GLSZM (Gray Level Size Zone Matrix): These features characterize the texture by measuring the size of connected regions (zones) with the same gray level.

After an initial variable selection based on correlations equal to or higher than 0.95, we performed PCA (Principal Component Analysis) segmented by categories. We retained the first components that explained more than 90% of the variability for each group.

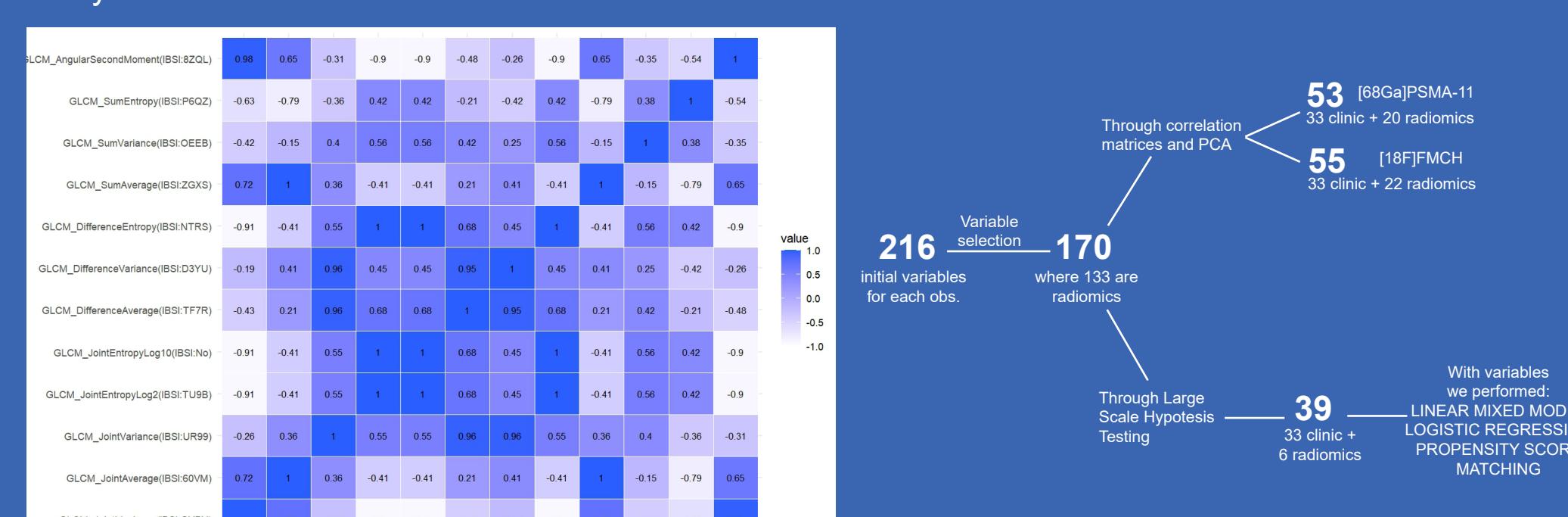
As a result, for intensity-based and GLSZM features, **dataset B needed** one more principal component than dataset A to reach the threshold.

2. DATA ANALYSIS

In the first part of this study, the main considerations regarding patient groups who used the **[¹⁸F]FMCH** (Dataset A), **[⁶⁸Ga]PSMA-11** (Dataset B), or **both tracers** were analyzed.

The distribution of radiomic variables, age differences, treatments received, PSA levels, and the **correlations** between clinical and radiomic variables were examined.

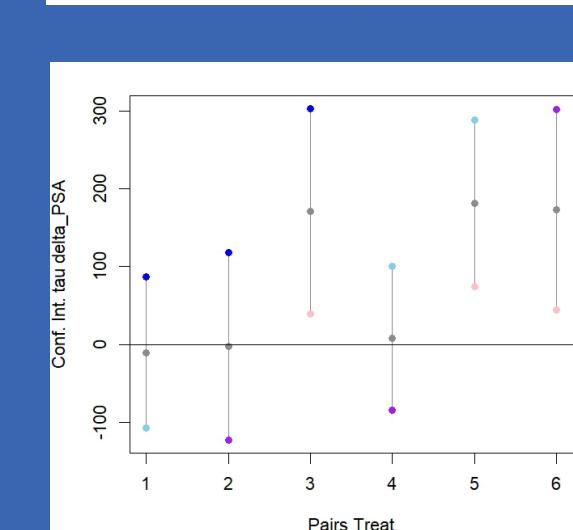
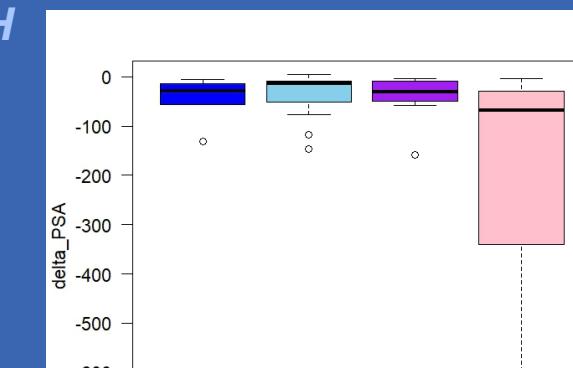
The initial objective was to identify the most significant variables among the 216 available to better understand which factors **most influence** the detection of BRPCA, and then proceed with the data analysis.



Through correlation matrices and PCA, **53** [68Ga]PSMA-11 cases + 22 radiomics and **55** [¹⁸F]FMCH cases + 22 radiomics were selected.

Variable selection for each obs.: **216** initial variables, **170** where 150 are radiomics.

With variables we performed: **LARGE SCALE HYPOTHESIS TESTING**, **LOGISTIC REGRESSION PROPENSITY SCORE MATCHING**.



The graphs present an analysis of variance (**ANOVA**) comparing the effect of different treatments on delta PSA in prostate cancer patients. The treatments analyzed are:

PR: Radical Prostatectomy

EBRT: External Beam Radiation Therapy

BOTH: Combination of Radical Prostatectomy (PR) and External Beam Radiation Therapy (EBRT)

NO: No preliminary treatment

Results:
Primary treatments (BOTH, PR, EBRT) guarantee a lowering of the PSA level, and therefore a decrease in inflammation.

The combination of PR and EBRT does not appear to offer a significant advantage over the individual treatments in terms of PSA control.



4. LINEAR MIXED MODEL

We performed a reduced **Linear Mixed Model** using significant variables to study the effect of the covariates on the results of the therapy, taking into account the grouping effect of the ARM variable. The model revealed that the variability of the random effect is significant, indicating differences in the delta_PSA among the three ARM groups. Moreover, both PSA BR (Biochemical Recurrence) and Gleason score higher than 8 have a **significant negative influence on the outcome**. This means that the therapy was particularly impactful for critical patients with high Gleason scores and those with high PSA BR levels.

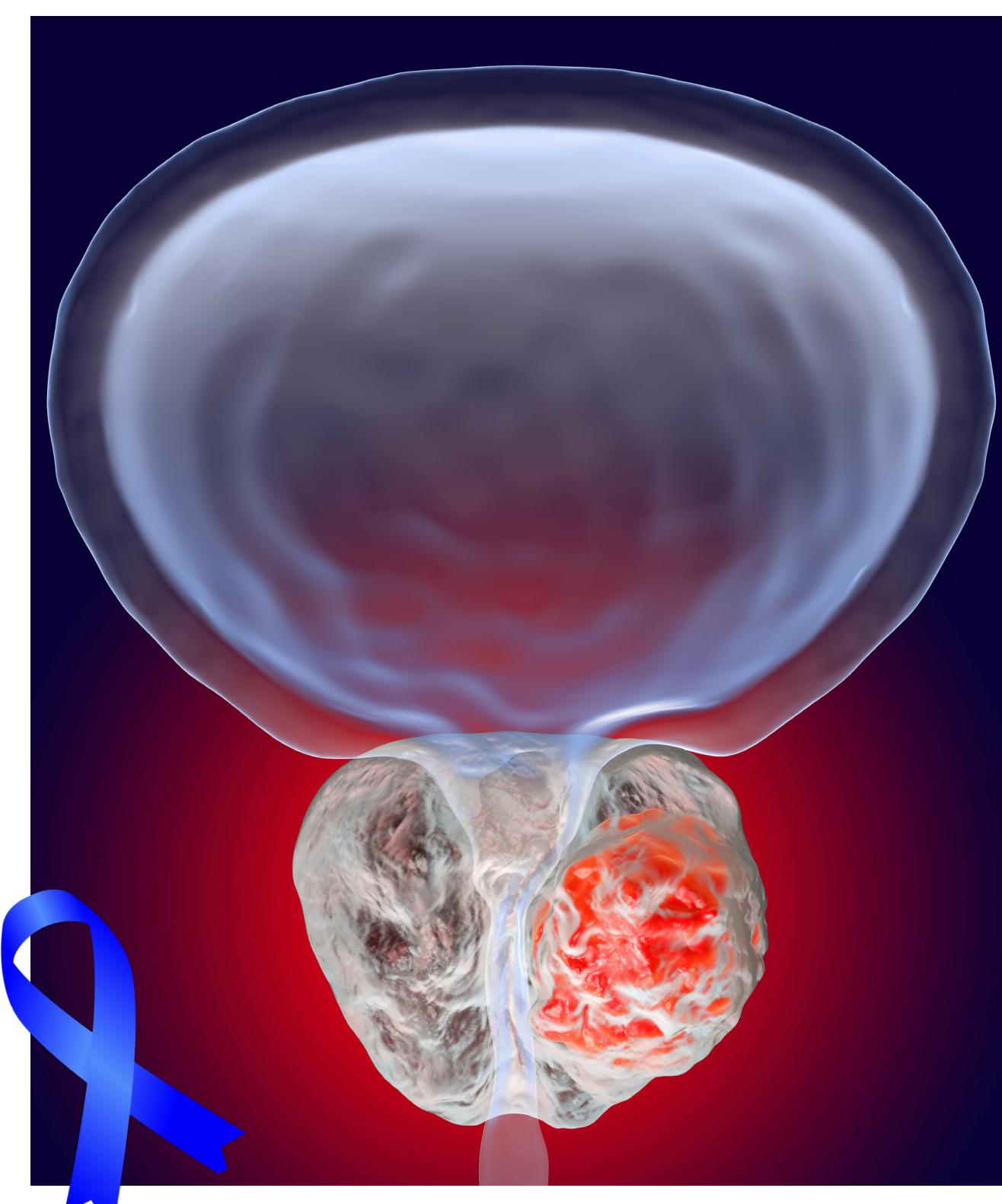
Furthermore, if the number of lesions is higher, the therapy decreases its delta_PSA score, making it less successful.

The equation for the model is as follows:

$$\delta\text{PSA} = n \text{ lesions} + GS + PSA\ BR + (1|ARM)$$

When the number of lesions **increases**, and both GS and PSA BR decrease, the delta_PSA tends towards zero.

Conversely, if the number of lesions **decreases** while GS and PSA BR increase, the delta_PSA decreases significantly.



5. COMPARISON OF DETECTION RATE

An innovative aspect of this research is the **comparative analysis of the detection rate**, in terms of number of lesions identified, between **FMCH** and **PSMA** tracers. The main methodological challenge arises from the fact that patients used one of the two tracers, creating two **independent populations**.

To overcome this limitation and enable a statistically robust comparison, we employed **Propensity Score Matching (PSM)**. This advanced statistical technique allowed observations to be matched based on three key variables: **age**, **Gleason Score** and **pre-therapy PSA level**. PSM allowed us to create comparable datasets for each tracer, where each row represents **paired observations** with similar characteristics. The implementation of the algorithm in R generated two parallel datasets, one for each tracer, containing the number of lesions identified in statistically comparable observations.

The subsequent statistical test on the matched difference revealed, with a highly significant p-value (*p*-value = **0.715**), that the **PSMA tracer identifies on average a significantly greater number of lesions** than the FMCH. This result is in line with expectations, considering that PSMA is the most recent and innovative radiopharmaceutical. However, the analysis also revealed important differences in the performance of tracers in relation to **PSA levels**. For the **FMCH** tracer, detection rates vary significantly: they are **high (67-100%)** when the PSA value is above 5 ng/mL, but **decrease dramatically (5-24%)** for PSA values below 1 ng/mL. In this context, PSMA is emerging as superior to FMCH, demonstrating greater sensitivity and efficacy. These results underline the importance of the choice of tracer depending not only on patient characteristics, but also on PSA levels, offering new perspectives for the **optimization of diagnostic strategies** in recurrent prostate cancer.

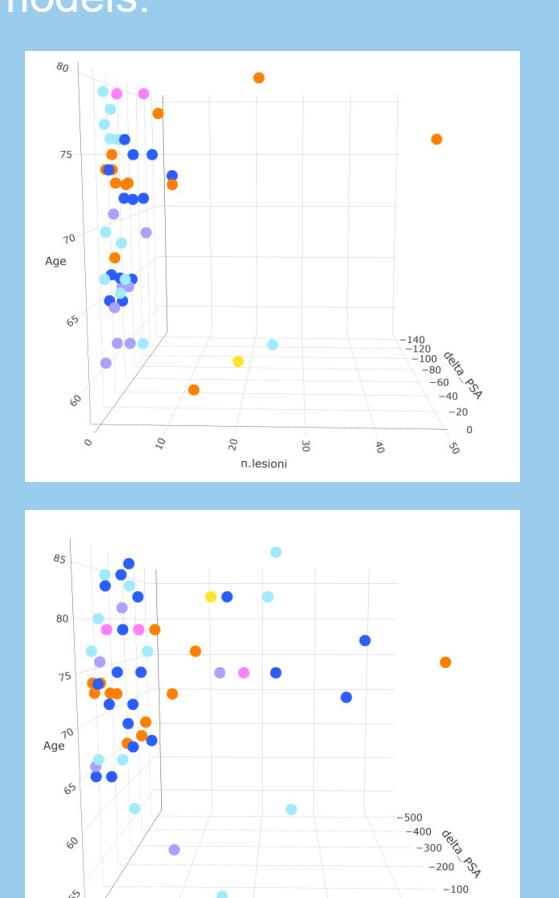
6. LOGISTIC REGRESSION

We performed a **multivariate logistic regression** on two datasets to understand the relationship between Gleason scores and the most significant variables. This type of regression is used to predict a categorical variable with more than two groups. We created two 3-D plots to visualize the results.

Initially, we developed a **general model**, then refined it by focusing only on the variables with the **highest absolute values of t-values**. In both datasets, we found that **delta_PSA**, the number of lesions, and the patients' **age** were **significant predictors**.

To compare the two models, we performed **cross-validation**, using multiple subsets of our datasets to test the models.

The evaluation metrics, including log loss, accuracy, F1-score, and AUC-ROC, indicated that the **model using tracer B performed better than the other model**.



| Accuracy: | Model A | 0.300 |
|-----------|---------|-------|
| F1-score: | Model A | 0.360 |
| Log Loss: | Model A | 4.781 |
| AUC-ROC: | Model B | 2.000 |

AUC-ROC: Both models show **similar AUC-ROC values** across different classes.

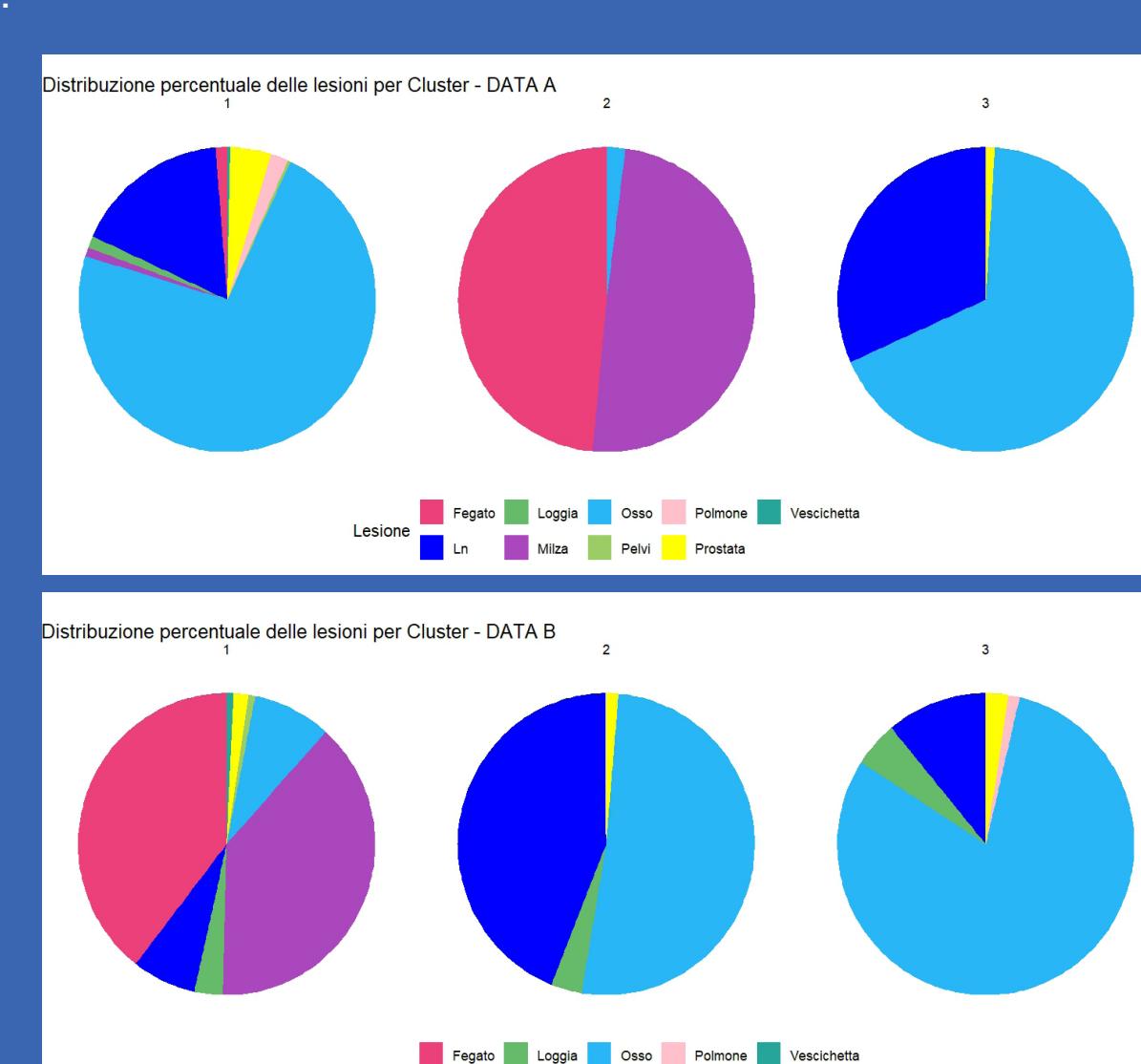
7. HIERARCHICAL CLUSTERING

For hierarchical clustering, we used **Euclidean distance** and **WARD linkage** for dataset A, and **Canberra distance** and **Average linkage** for dataset B. The best combinations, considering the cophenetic coefficient and silhouette score, achieved a 35-40% score in both datasets, which is a good result given the data's complexity.

Following each PCA, we conducted clustering on the radiomic features to identify meaningful clusters. We performed a **PERMANOVA** test (since it is more robust and relaxes the uniform variance and normality assumptions). We obtained a p-value of 1×10^{-3} , allowing us to conclude that cluster membership was significant for both A and B at the 1% and 5% levels.

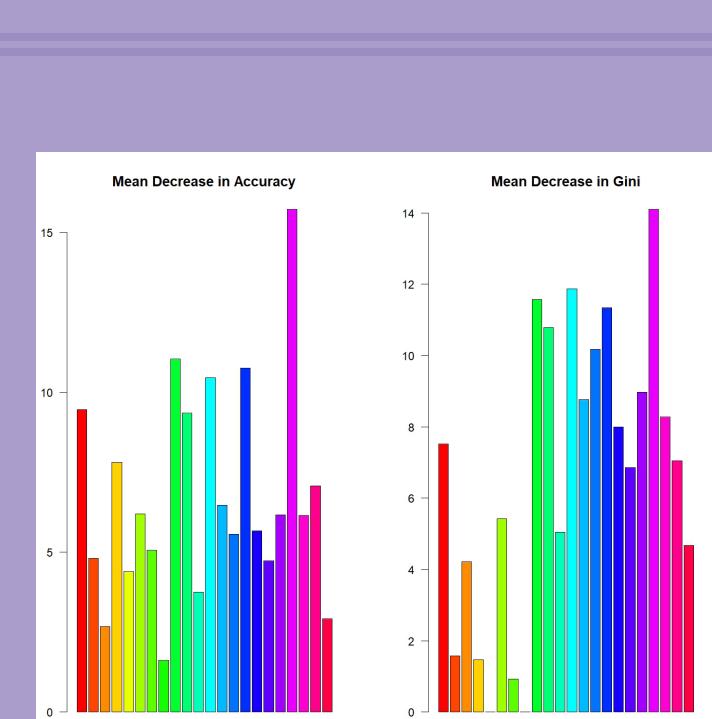
We then aimed to **align the clusters** by testing the lesions they identified. The second cluster from the first dataset and the first cluster from the second dataset aligned well, effectively identifying and grouping liver and spleen lesions among patients. Other alignments, such as the third clusters from both datasets and the first cluster of dataset A with the second cluster of dataset B, were not valid.

However, this confirmed that our clustering was **efficient in distinguishing spleen and liver lesions**.



8. RANDOM FOREST

Random Forest is an algorithm that **iteratively removes each of our radiomic variables** from the clustering process. At each step, it calculates the **mean accuracy** and mean **Gini** values, highlighting the most important variables, which are the ones that produce a higher decrease in these parameters.



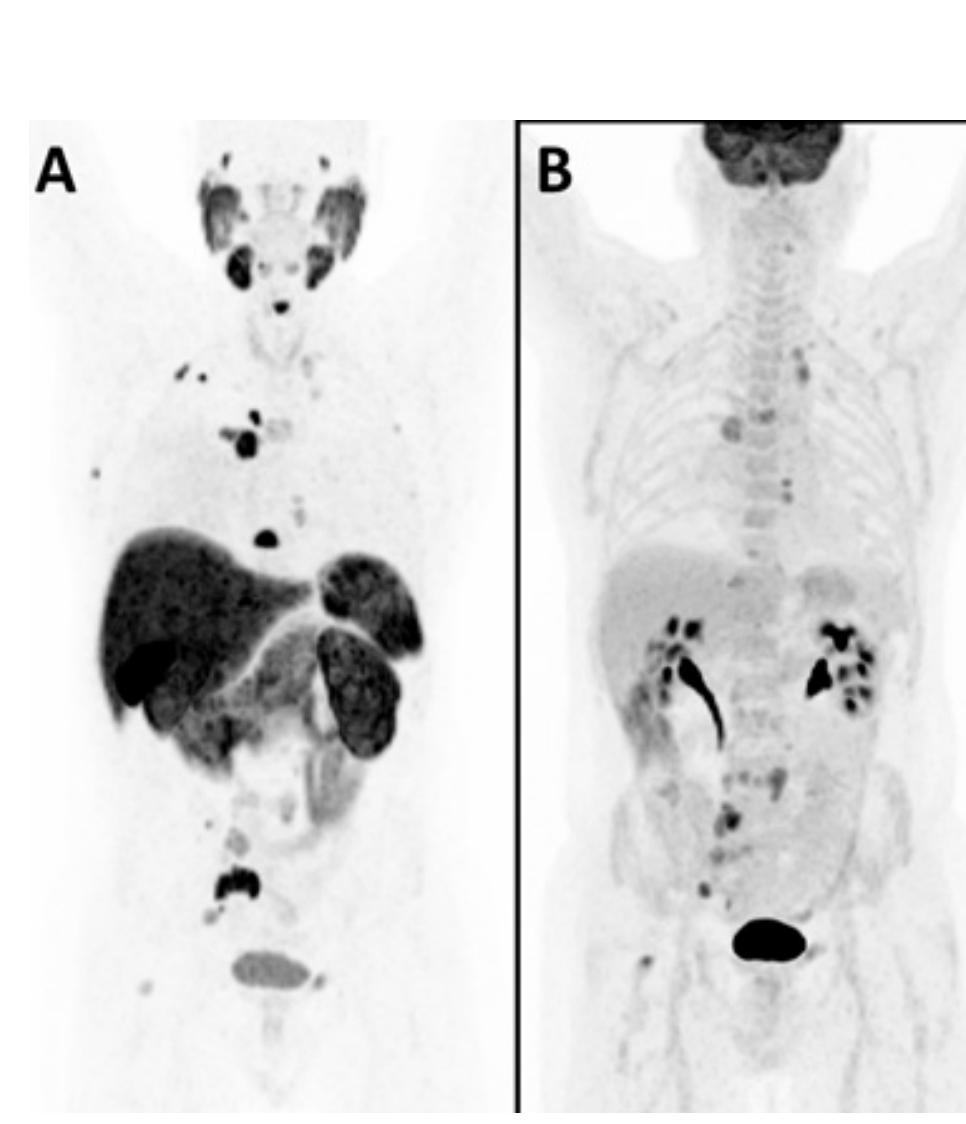
We found that there were 4 variables that mainly influenced our clustering in both groups (although in a different order). The key variables are: second PC **GLSZM**, first PC **GLRLM**, first PC **NGTDM**, and first PC **GLCM**, thereby reducing the radiomic groups from 6 to 4.

9. CONCLUSIONS

This study on multi-tracer imaging in prostate cancer has produced significant results:

1. The **[⁶⁸Ga]PSMA-11 tracer demonstrated greater efficacy in identifying lesions** compared to **[¹⁸F]FMCH**, especially with low PSA levels.
2. **Therapy was most effective in patients with high Gleason scores and high PSA BR levels**, while a higher number of lesions is associated with reduced treatment efficacy.
3. Primary treatments (radical prostatectomy and external beam radiation therapy) effectively reduce PSA levels, with **no significant advantages in their combination**.
4. Radiomic analysis identified key features (derived from GLSZM, GLRLM, NGTDM, and GLCM) that **significantly influence lesion classification**.
5. Logistic regression models, particularly the one using the **[⁶⁸Ga]PSMA-11 tracer**, showed improved performance in **predicting Gleason scores**.

These findings have clinical implications for prostate cancer management, suggesting the **preferential use of PSMA for early diagnosis and monitoring**, and paving the way for more personalized treatment strategies.



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[⁶⁸Ga]PSMA-11 PET/CT vs [¹⁸F]FMCH PET/CT: radiomic analysis of the PROvING - Oligometastatic and Oligorecurrent Prostate cancer: enhancing patients' selection by new Imaging biomarkers - study. Tesi di specializzazione, Dott.ssa Costanza Bachì

