# *Correlating imaging parameters with molecular data: a novel approach to improve the management of oncological patients*

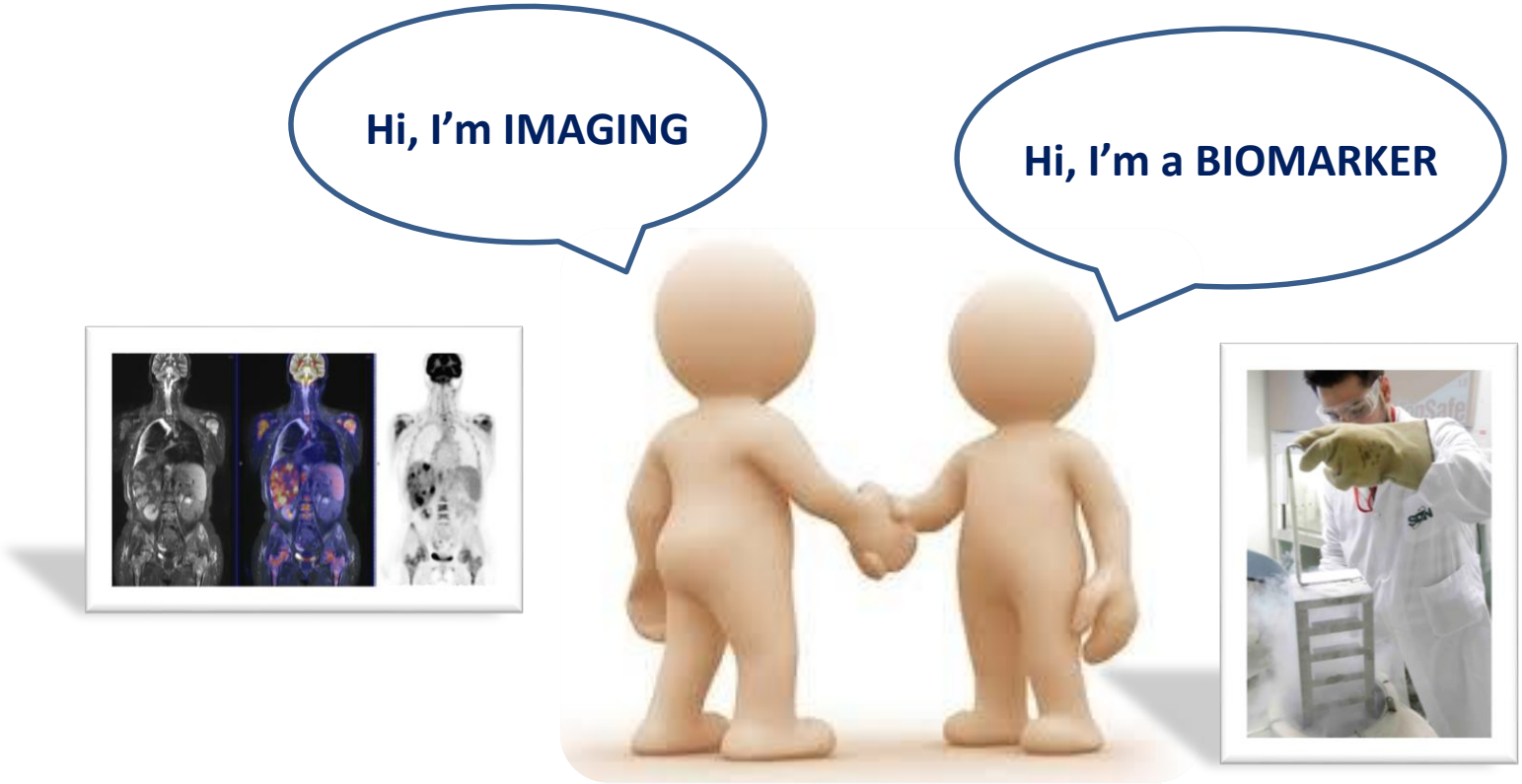
**Biomarcatori e Tecniche di Diagnostica per Immagini nella Valutazione dell'Infiammazione in Oncologia**

*Roma, 22 Febbraio 2019*

*Mariarosaria Incoronato*

# IRCCS SDN MISSION

**INTEGRATING** the imaging results with molecular biology results in order to improve the management and the "clinical decision making" of the BC patient.




BIOMARKERS DISCOVERY

International Journal of
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# Radiogenomic Analysis of Oncological Data: A Technical Survey

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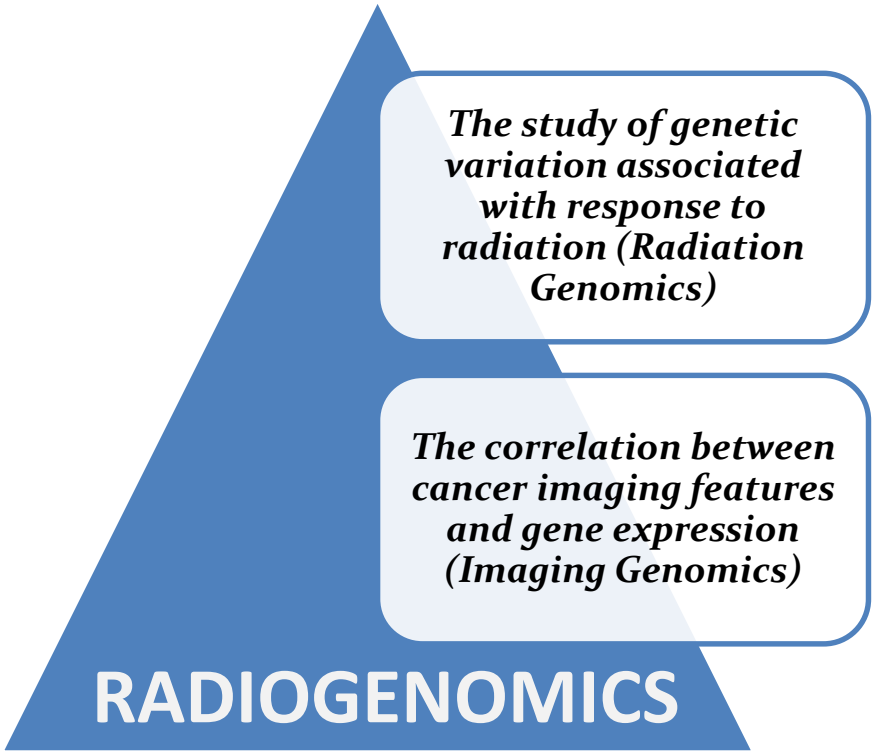
***Could the integration of imaging parameters and biological markers improve the management of oncological patients?***

## *Radiation genomics*

***Genetic variation, such as single nucleotide polymorphisms, is studied in relation to a cancer patient's risk of developing toxicity following radiation therapy. It is also used in the context of studying the genomics of tumor response to radiation therapy***

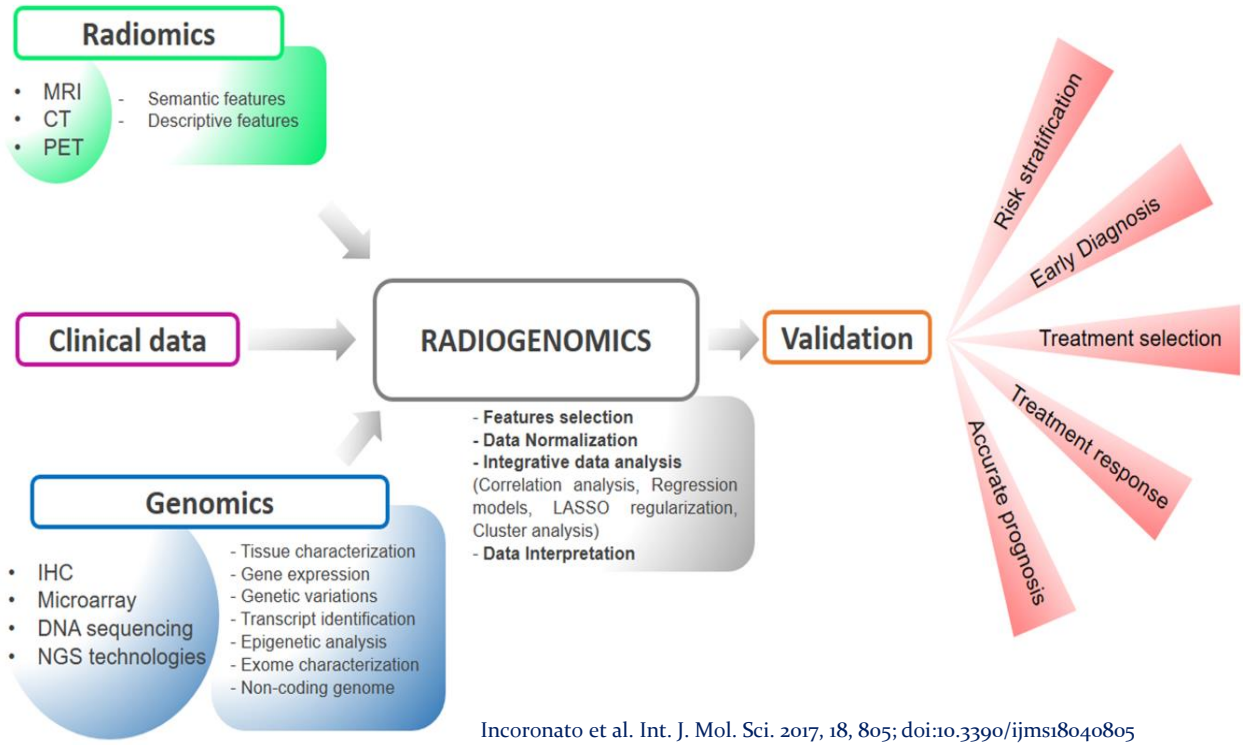
## *Imaging genomics*

***In imaging genomics, radiogenomics can be used to create imaging biomarkers that can identify the genomics of a disease, especially cancer without the use of a biopsy.***



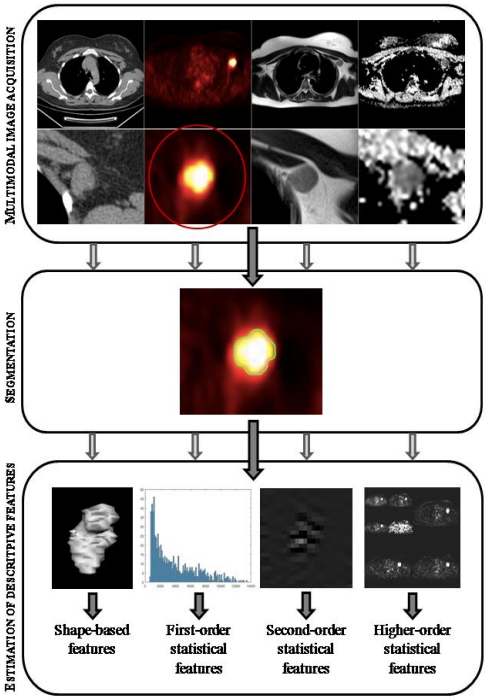
# Radiogenomics

Technological improvements in the field of imaging and molecular biology have led to the "Radiogenomics" or "Imaging Genomics". Literally, Radiogenomics refers to the **analytical processes aimed to correlate cancer imaging features (Radiomics) with Genomic data.**




Incoronato et al. Int. J. Mol. Sci. 2017, 18, 805; doi:10.3390/ijms18040805

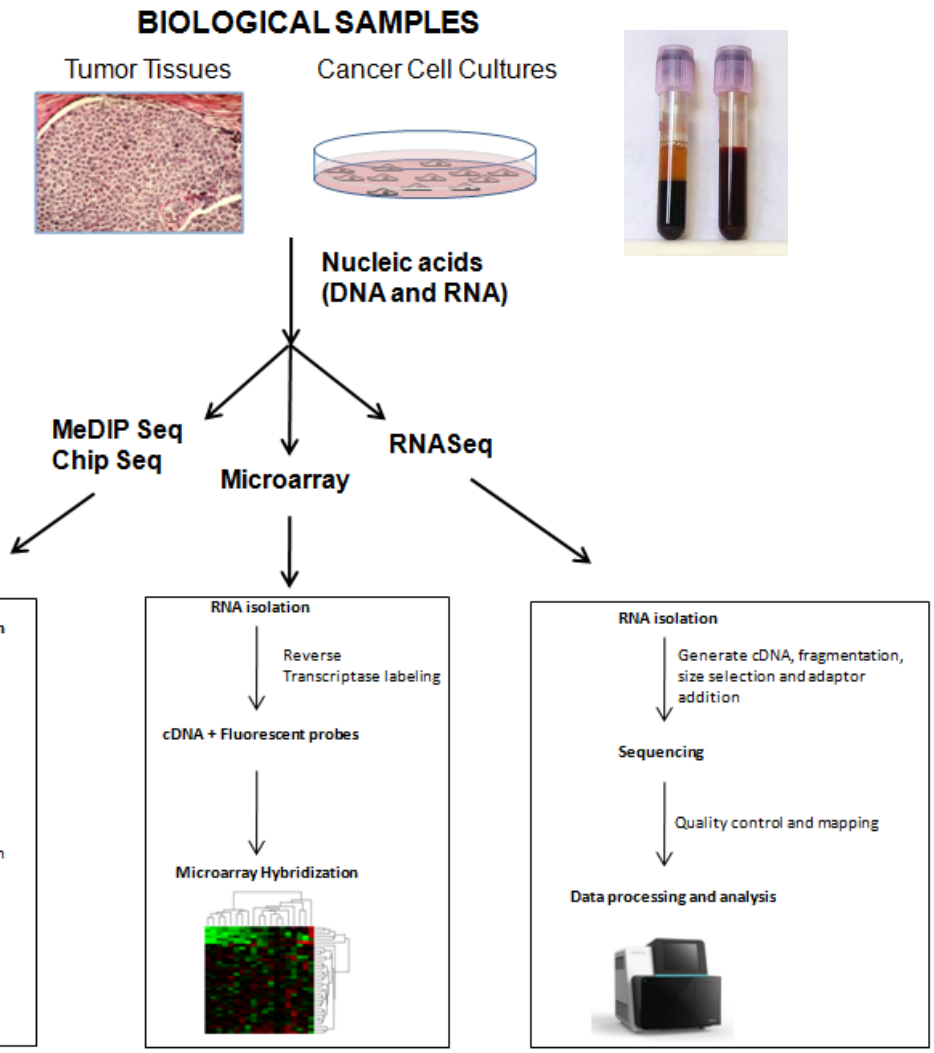
**Radiomics** refers to the comprehensive quantification of tumor phenotypes by the extraction of a large amount of quantitative features from medical images. This high-throughput extraction of quantitative imaging features is the result of a workflow composed of three main steps



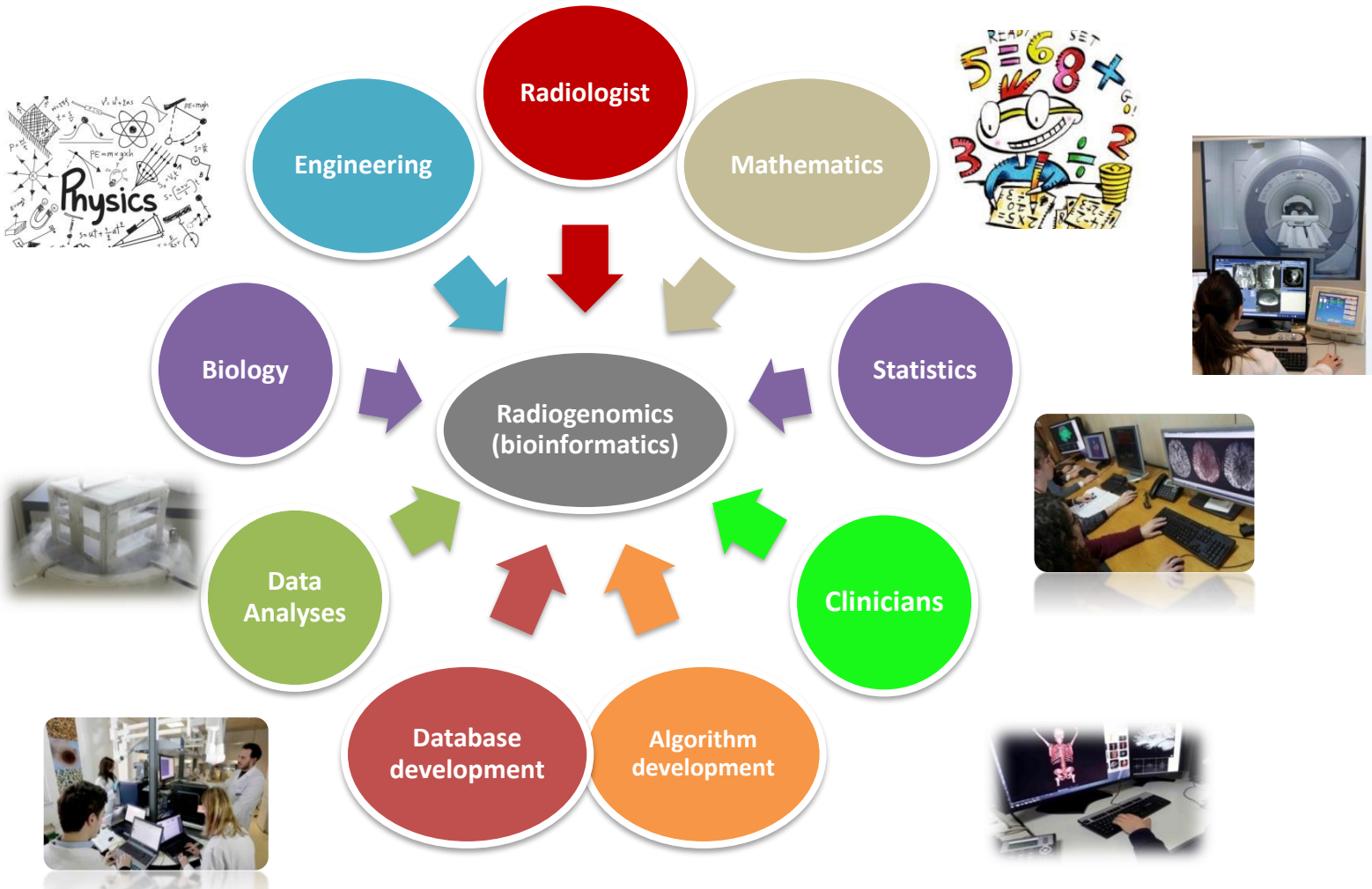

- Acquiring the images
- Segmenting the regions of interest (ROIs)
- Estimating descriptive features

**A great advantage of radiomic analyses is their feasibility with conventional clinical images (PET, CT, MRI). The first step of radiomic pipeline, in fact, involves the acquisition of images that are typically part of diagnostic or treatment planning protocols for oncological patients**

**Genomics** is the study of the entirety of an organism's genes actually performed by the combination of high-throughput molecular biology technologies with complex computing and math techniques (bioinformatic analysis). Generally, two technologies are critical for genomics analysis: 1) microarray; and 2) next generation sequencing (NGS)



**Once both radiomic and genomic features are extracted, radiogenomic analysis will be performed.** **Radiogenomic** approaches are extensively based on numerical calculus and computer science methods, allowing the management and analysis of a huge number of variables for each sample and modality.



*Relationship between functional imaging and immunohistochemical markers and prediction of breast cancer subtype: a PET/MRI study*

**Mariarosaria Incoronato, Anna Maria Grimaldi, Carlo Cavaliere, Marianna Inglese, Peppino Mirabelli, Serena Monti, Umberto Ferbo, et al.**

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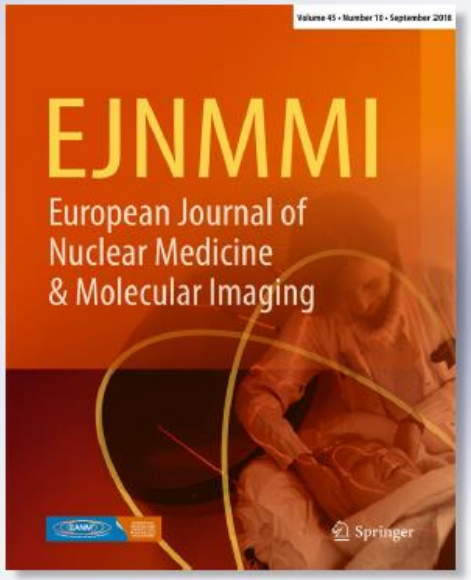


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**PURPOSE: The aim of this study was to determine if functional parameters extracted from the hybrid system positron emission tomography/magnetic resonance imaging (PET/MRI) correlated with the immunohistochemical markers of breast cancer (BC) lesions, to assess their ability to predict BC subtypes.**

| N° patients | 50 |
|---|---|
| **Age** | **52.5 (35-80)** |
| **Receptor status** | **Number** |
| ER+ | **42** |
| ER- | **8** |
| PR+ | **43** |
| PR- | **7** |
| HER+ | **19** |
| HER- | **31** |
| **Proliferation index** | |
| Ki-67 <20% | **12** |
| Ki-67 ≥20% | **38** |
| **Grade** | |
| G1 | **1** |
| G2 | **27** |
| G3 | **22** |

**Table 1.** Clinical features of tumour lesions.

| **Subtype** | **Luminal A** | **Luminal B** | **HER2 enriched** | **Basal like** |
|---|---|---|---|---|
| **Number** | 13 | 29 | 4 | 3 |
| **Lesion size (cm)** | 3.8 (0.7-5.0)* | 4.1 (2.3-7.8)* | 4.2 (2.9-6.6)* | 4.2 (2.6-7.1)* |

**Table 2.** Molecular subtype and relative lesion size.
*Mean and size range in parenthesis.

| | |
|---|---|
| Luminal A | ER+, PR≥20%, Her2-, Ki67<20% |
| Luminal B | - ER+, Her2-, PR<20% or Ki67 ≥20%;<br>- ER+, Her2+, Ki67 and PR any value |
| Basal-like | ER-, PR-, Her2- |
| Her2-like | ER-, PR- and Her2+ |

## CORRELATION ANALYSIS

**Perfusion, diffusion and metabolic imaging parameters**

- **Ktrans: forward volume transfer constant**
- **Ve: extravascular extracellular space volume**
- **Kep: reverse efflux volume transfer constant**
- **SUV: metabolic standardized uptake value**
- **SUL: lean body mass**
- **ADC: apparent diffusion coefficient**
- **Lesion size**

**Mann–Whitney U test**

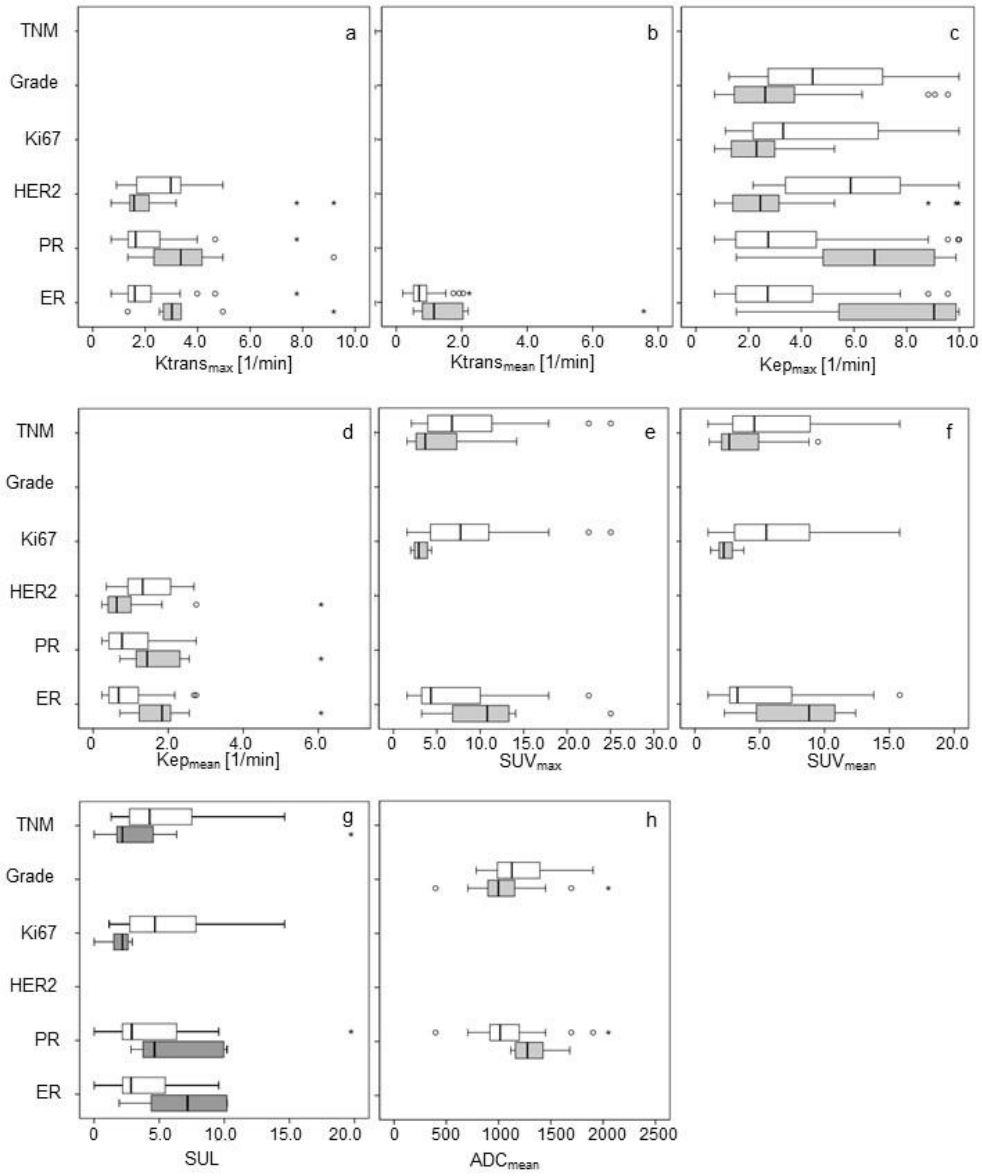



**Fig. 3** Association study among IHC markers versus perfusions and diffusion imaging parameters. White colour refers to positive receptors status (ER, PR and HER2), high Ki67, Grade 3, and T3-4 staging; grey colour refers to negative receptors status (ER, PR and HER2), low Ki67, Grade 2, and T1-2 staging. Standard box plot, in which the vertical line represents the median, the thick line the interquartile range, and the thin line the maximum and minimum values. The circular and star dots represent the outliers.

## ABILITY OF PET/MRI PARAMETERS TO DISCRIMINATE BETWEEN BC MOLECULAR SUBTYPES

| | |
|---|---|
| Luminal A | ER+, PR≥20%, Her2-, Ki67<20% |
| Luminal B | - ER+, Her2-, PR<20% or Ki67 ≥20%;<br>- ER+, Her2+, Ki67 and PR any value |
| Basal-like | ER-, PR-, Her2- |
| Her2-like | ER-, PR- and Her2+ |

**Kruskal–Wallis test and pairwise comparisons**

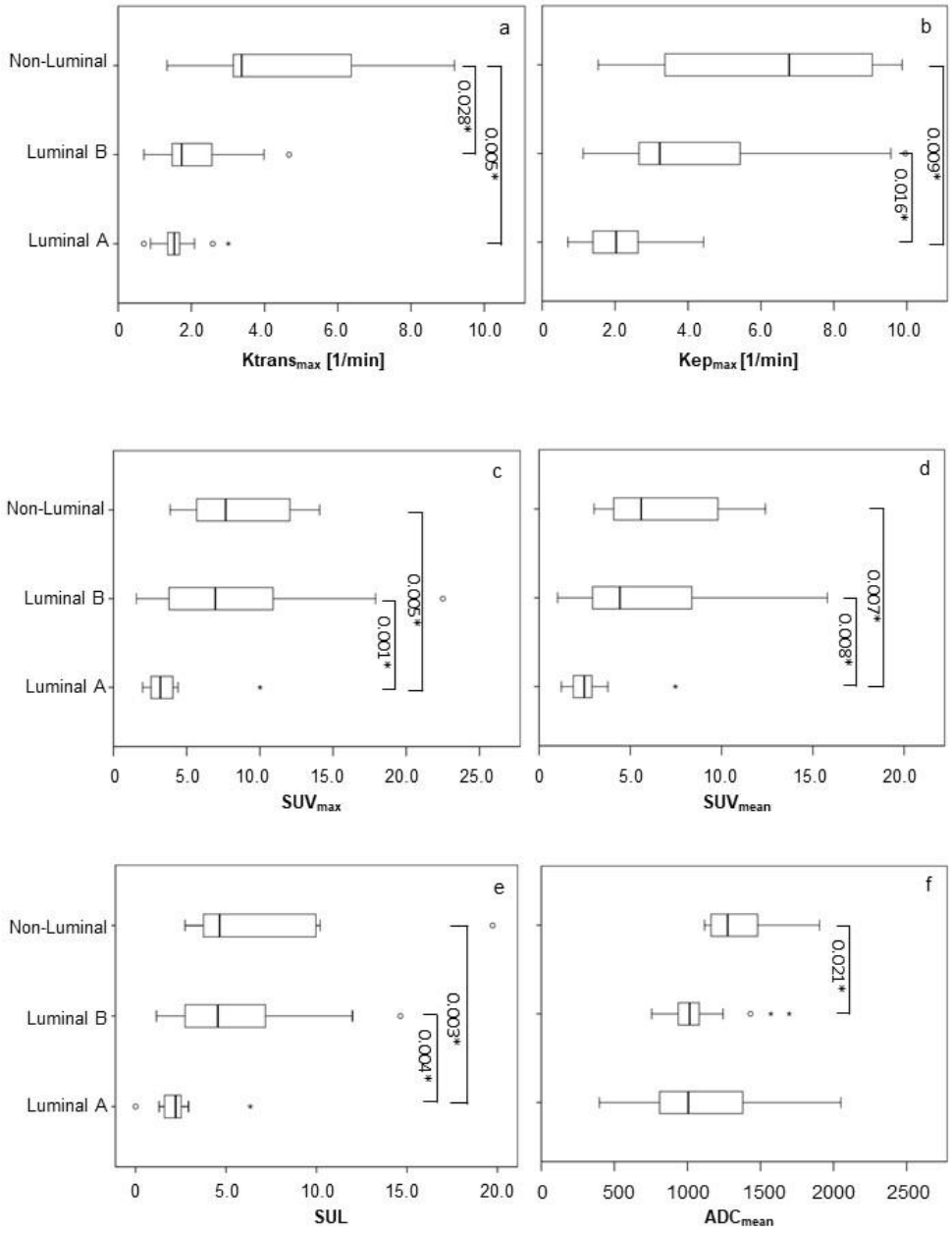
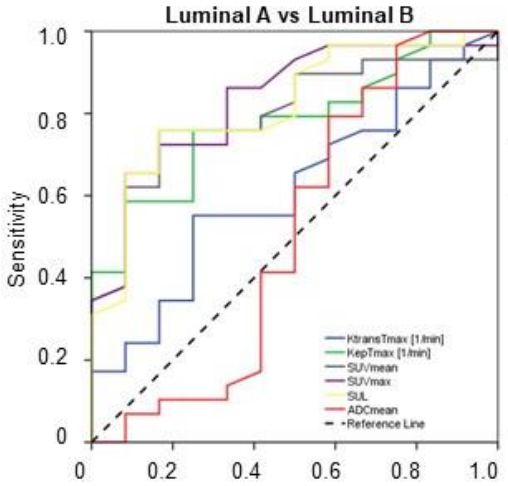



**Fig. 4** Distribution of imaging parameters versus tumour subtypes. Standard box plot, in which the vertical line represents the median, the thick line represents the interquartile range, and the thin line represents the maximum and minimum values. The circular and star dots represent the outliers. *Indicates statistical significance achieved after correction for pairwise multiple comparisons.

# DIAGNOSTIC ACCURACY OF IMAGING PARAMETERS

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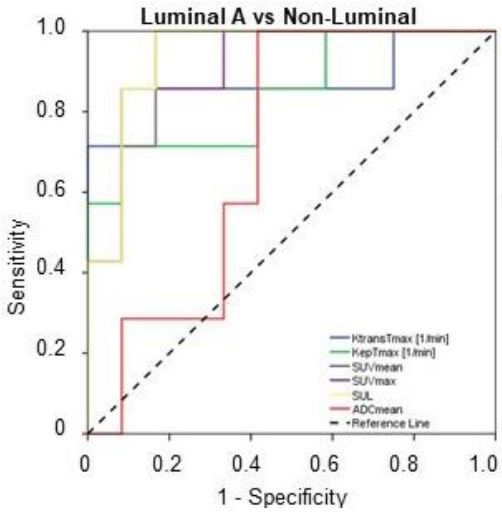
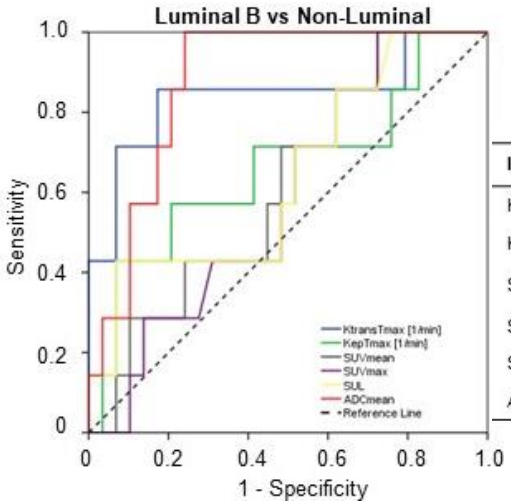
| Imaging parameters | AUC | Std. Error | p-value | Cut-off |
|---|---|---|---|---|
| $Ktrans_{max}$ [1/min] | 0.614 | 0.09 | 0.258 | 1.69 |
| $Kep_{max}$ [1/min] | 0.779 | 0.07 | 0.005* | 2.64 |
| $SUV_{mean}$ | 0.799 | 0.07 | 0.003* | 2.93 |
| $SUV_{max}$ | 0.833 | 0.07 | <0.001* | 4.43 |
| SUL | 0.813 | 0.07 | 0.001* | 2.72 |
| $ADC_{mean}$ | 0.509 | 0.12 | 0.931 | 770.50 |




| Imaging parameters | AUC | Std. Error | p-value | Cut-off |
|---|---|---|---|---|
| $Ktrans_{max}$ [1/min] | 0.881 | 0.10 | 0.007* | 2.76 |
| $Kep_{max}$ [1/min] | 0.845 | 0.10 | 0.014* | 3.70 |
| $SUV_{mean}$ | 0.929 | 0.06 | 0.002* | 2.97 |
| $SUV_{max}$ | 0.917 | 0.07 | 0.003* | 4.48 |
| SUL | 0.945 | 0.50 | 0.001* | 2.72 |
| $ADC_{mean}$ | 0.702 | 0.12 | 0.151 | 1076.00 |




| Imaging parameters | AUC | Std. Error | p-value | Cut-off |
|---|---|---|---|---|
| $Ktrans_{max}$ [1/min] | 0.842 | 0.10 | 0.005* | 2.90 |
| $Kep_{max}$ [1/min] | 0.660 | 0.13 | 0.194 | 6.54 |
| $SUV_{mean}$ | 0.616 | 0.11 | 0.349 | 2.97 |
| $SUV_{max}$ | 0.589 | 0.11 | 0.472 | 3.83 |
| SUL | 0.643 | 0.12 | 0.246 | 9.648 |
| $ADC_{mean}$ | 0.877 | 0.06 | 0.002* | 1098.50 |

**Fig. 5** ROC curve analyses. Diagnostic accuracy of imaging parameters were evaluated among breast cancer subtypes, as indicated: luminal A vs luminal B subtypes (panel a), luminal A vs Non-luminal subtypes (panel b) and luminal B vs Non-luminal subtypes (panel c), tables on the right summarize AUC, p-value and cut-off values of imaging parameters taken in account for ROC curve analyses (* indicates p-value statistically significant).

## MULTIVARIATE ANALYSES FOR PREDICTION STUDIES

**True: correctly predicted cases; False: not correctly predicted cases.**

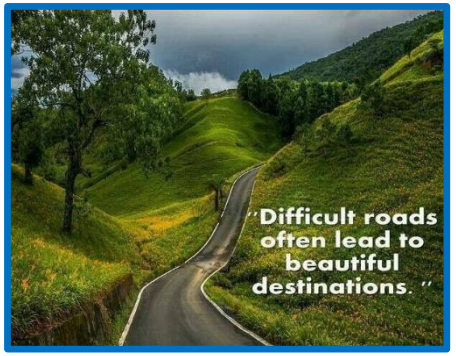
### Logistic regression for predictive model

| | Estimate | Std. Error | Wald | df | Sig. | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| Ktransmax | 1.169 | 0.368 | 10.073 | 1.00 | 0.002 | 0.447 | 1.890 |
| SUVmax | 0.234 | 0.081 | 8.283 | 1.00 | 0.004 | 0.075 | 0.394 |

| | Number of predicted subtype (%) | | |
|---|---|---|---|
| Subtypes defined by IHC (n°) | **Luminal A** | **Luminal B** | **Non-luminal** |
| **Luminal A (13)** | True 9 (69.2%) | False 4 (30.8%) | False 0 (0%) |
| **Luminal B (29)** | False 3 (10.3%) | True 25 (86.2%) | False 1 (3.5%) |
| **Non-luminal (7)** | False 0 (0%) | False 3 (42.9%) | True 4 (57.1%) |

**CONCLUSIONS: Using multivariate analyses of both PET and MR parameters, a prognostic model including $Ktrans_{max}$ and $SUV_{max}$ was able to predict 38/49 tumor subtypes (77.6%, $p<0.001$), with higher accuracy for the luminal B subtype (86.2%).**

***Could the integration of imaging parameters and biological markers improve the management of oncological patients?***



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谢谢
dakujem vám
merci
ありがとう
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baie dankie
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धन्यवाद
molte grazie
gracias
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