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PROJECT

Supervisor: ___Fiorino Claudio__

Title: Advanced computational methods to assess and validate Imaging biomarkers to predict toxicities after Radiotherapy of breast cancer

Curriculum: _____ Clinical and Experimental Medicine

Link to the personal page of the University or relevant hospital site website: <https://it.linkedin.com/company/mp-dream-group>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Radiotherapy is a cornerstone of breast cancer cure but is associated with acute and late toxicities. Traditional prediction models rely mainly on clinical and dosimetry variables, often failing to capture patient-specific tissue susceptibility. Recent research within the group of the supervisor has shown that breast densitometry and imaging-derived features correlate with outcomes [1] while models combining dosimetry and clinical features were also developed for selected toxicities [2-5]. The need of integrating multi-layer information, including dosimetry, clinical and imaging features, into robust and validated prediction models is of paramount importance.

Rationale and hypothesis

We hypothesize that integrating advanced breast densitometry and radiomic descriptors will improve prediction of radiotherapy-related toxicity. Furthermore, translating these models into clinically usable tools could allow radiation oncologists to personalize treatment planning. In addition, the interplay between age and presence of cardiac calcifications, both found highly predictive of cardio-vascular late toxicity [5], needs to be better investigated; the available datasets offer the opportunity to model temporal evolution of cardiac damage using synthetic imaging approaches.

Objectives and specific aims

The three-year PhD project will be based on an in-house cohort of 1350 breast cancer patients treated and monitored since 2009 [6,7] and an external validation cohort (REQUITE [8,9]). The project, linked to the ongoing AIRC-funded project (IG 2025 ID 32254), will focus on:

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Model validation and methodological refinement

To improve densitometric modeling by better analyzing adipose–glandular distribution patterns. Exploring radiomic features of larger/most important fat and glandular compartments.

Validate models onto an external cohort.

Development of imaging-based predictive tools

To finalize automated pipelines to process breast imaging data, to highlight tissue regions mostly associated to high-risk radiation-induced toxicities (acute toxicity, 6-month edema, late FATP—fibrosis, atrophy, telangiectasia, pain).

Modeling cardiac toxicity progression

Validating cardiovascular models based on the combination of clinical/dosimetry and cardiac calcification scores features. Physics-Informed Neural Networks (PINNs) will be explored to model the temporal and spatial evolution of coronary calcification clusters.

Expected outcomes

This project will externally validate and extend predictive models linking clinical, dosimetry, breast tissue composition, radiomics features with radiotherapy outcomes. In addition, synthetic imaging models may enable early prediction of cardiac calcification evolution and their meaning in predicting cardiovascular events. Together, these results will contribute to a precision-radiotherapy framework aimed at reducing treatment toxicity.

Skills that the student should acquire (max. 600 characters including spaces):

The PhD candidate will acquire advanced skills in medical imaging analysis, including breast densitometry modeling, radiomics extraction, and spatial pattern–response analysis. Training will include development and validation of predictive models using large clinical datasets, implementation of machine learning methods, and generation of spatial risk maps and AI-generative synthetic imaging. The candidate will also develop competencies in translational research, integrating imaging, clinical, and dosimetry data into clinically usable decision-support tools for personalized radiotherapy.

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References (max. 15)

- [1] Mori M, Belardo A, Vincenzi MM, Fodor A, Mangili P, Palazzo G, Gabellini MU, Tummineri R, Torrisi M, Vecchio AD, Muzio ND, Fiorino C. Breast density histogram analysis: the role of fat in outcome prediction after Whole Breast Radiotherapy. *Pract Radiat Oncol.* 2025 Dec 13:S1879-8500(25)00319-4. doi: 10.1016/j.prro.2025.12.004.
- [2] Ubeira-Gabellini MG, Mori M, Palazzo G, Cicchetti A, Mangili P, Pavarini M, Rancati T, Fodor A, Del Vecchio A, Di Muzio NG, Fiorino C. Comparing Performances of Predictive Models of Toxicity after Radiotherapy for Breast Cancer Using Different Machine Learning Approaches. *Cancers (Basel).* 2024 Feb 25;16(5):934. doi: 10.3390/cancers16050934.
- [3] Cicchetti A, Mangili P, Fodor A, Gabellini MG, Chiara A, Deantoni C, Mori M, Pasetti M, Palazzo G, Rancati T, Del Vecchio A, Gisella Di Muzio N, Fiorino C. Skin dose-volume predictors of moderate-severe late side effects after whole breast radiotherapy. *Radiother Oncol.* 2024 May;194:110183. doi: 10.1016/j.radonc.2024.110183.
- [4] Vincenzi MM, Cicchetti A, Castriconi R, Mangili P, Ubeira-Gabellini MG, Chiara A, Deantoni C, Mori M, Pasetti M, Palazzo G, Tummineri R, Rancati T, Di Muzio NG, Vecchio AD, Fodor A, Fiorino C. Training and temporally validating an NTCP model of acute toxicity after whole breast radiotherapy, including the impact of advanced delivery techniques. *Radiother Oncol.* 2025 Mar;204:110700. doi: 10.1016/j.radonc.2024.110700.
- [5] Belardo A, Dimayuga KB, Perna L, Fodor A, Giannini L, Mangili P, Palazzo G, Pasetti M, Torrisi M, Tummineri R, Vecchio AD, Di Muzio NG, Fiorino C. Density and volume of cardiac calcifications detected on planning CT predicts cardiotoxicity after hypo-fractionated whole breast Radiotherapy. *Radiother Oncol.* 2025 Oct;211:111098. doi: 10.1016/j.radonc.2025.111098.
- [6] Fodor A, Brombin C, Mangili P, Borroni F, Pasetti M, Tummineri R, Zerbetto F, Longobardi B, Perna L, Dell'Oca I, Deantoni CL, Deli AM, Chiara A, Broggi S, Castriconi R, Esposito PG, Slim N, Passoni P, Baroni S, Villa SL, Rancoita PMV, Fiorino C, Del Vecchio A, Bianchini G, Gentilini OD, Di Serio MS, Di Muzio NG. Impact of molecular subtype on 1325 early-stage breast cancer patients homogeneously treated with hypofractionated radiotherapy without boost: Should the



indications for radiotherapy be more personalized? *Breast*. 2021 Feb;55:45-54. doi: 10.1016/j.breast.2020.12.004.

[7] Fodor A, Brombin C, Mangili P, Tummineri R, Pasetti M, Zerbetto F, Longobardi B, Galvan AS, Deantoni CL, Dell'Oca I, Castriconi R, Esposito PG, Deli AM, Rancoita PMV, Fiorino C, Vecchio AD, Di Serio MS, Di Muzio NG. Toxicity of Hypofractionated Whole Breast Radiotherapy Without Boost and Timescale of Late Skin Responses in a Large Cohort of Early-Stage Breast Cancer Patients. *Clin Breast Cancer*. 2022 Jun;22(4):e480-e487. doi: 10.1016/j.clbc.2021.11.008.

[8] Seibold P, Webb A, Aguado-Barrera ME, Azria D, Bourgier C, Brengues M, Briers E, Bultijnck R, Calvo-Crespo P, Carballo A, Choudhury A, Cicchetti A, Claßen J, Delmastro E, Dunning AM, Elliott RM, Fachal L, Farcy-Jacquet MP, Gabriele P, Garibaldi E, Gómez-Caamaño A, Gutiérrez-Enríquez S, Higginson DS, Johnson K, Lobato-Busto R, Mollà M, Müller A, Payne D, Peleteiro P, Post G, Rancati T, Rattay T, Reyes V, Rosenstein BS, De Ruyscher D, De Santis MC, Schäfer J, Schnabel T, Sperk E, Symonds RP, Stobart H, Taboada-Valladares B, Talbot CJ, Valdagni R, Vega A, Veldeman L, Ward T, Weißenberger C, West CML, Chang-Claude J; REQUITE consortium. REQUITE: A prospective multicentre cohort study of patients undergoing radiotherapy for breast, lung or prostate cancer. *Radiother Oncol*. 2019 Sep;138:59-67. doi: 10.1016/j.radonc.2019.04.034.

[9] Rattay T, Seibold P, Aguado-Barrera ME, Altabas M, Azria D, Barnett GC, Bultijnck R, Chang-Claude J, Choudhury A, Coles CE, Dunning AM, Elliott RM, Farcy Jacquet MP, Gutiérrez-Enríquez S, Johnson K, Müller A, Post G, Rancati T, Reyes V, Rosenstein BS, De Ruyscher D, de Santis MC, Sperk E, Stobart H, Symonds RP, Taboada-Valladares B, Vega A, Veldeman L, Webb AJ, West CM, Valdagni R, Talbot CJ; REQUITE consortium. External Validation of a Predictive Model for Acute Skin Radiation Toxicity in the REQUITE Breast Cohort. *Front Oncol*. 2020 Oct 30;10:575909. doi: 10.3389/fonc.2020.575909.