TITLE: Prediction of severe early toxicities with pATM blood assay: results from a prospective real-life study in a national center.

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Purpose: We aimed to evaluate the diagnostic performance of the previously reported Ataxia-Telangiectasia Mutated protein (pATM) blood assay on the occurrence of severe early radiotherapy (RT)-induced toxicities in a real-life cohort from the Luxembourgish National Radiotherapy center (APRILUX).

Materials and methods: 200 consecutive patients managed in curative intent for any primary were enrolled (NCT05433974). Total blood was sampled before the initiation of RT and pATM assay was performed by the neighboring independent laboratory - previously trained. We set a pATM concentration cutoff of 57.8 ng/mL to differentiate patients prone to grade <2 vs. grade⩾2 toxicity (ELISA). Patients were assessed in blind weekly during RT and 3 months after completion of RT. The maximal early toxicity endpoint was recorded using the Common Terminology Criteria for Adverse Events (CTCAE v5.0). We also collected clinical and dosimetric parameters with a possible impact on toxicity severity. The correlation was evaluated with univariate analysis and logistic regression. The discrimination power of the pATM assay was evaluated through the Area Under the Receiver Operator Characteristics Curve (AUC-ROC).

Results: The 200 patients were included between October 2023 and May 2024. Among the 198 analyzable patients, 61.1%, 14.1% and 8.6% were treated on breast, prostate and brain, respectively. The mean delivered dose was 51.5 Gy (24.0 – 70.0) with fractionation ranging between 1.80 and 7.25 Gy. 68 out 198 (34,3 %) patients exhibited a grade≥2 toxicity event (any system) - including 29 patients with dermatitis; Specifically, in the breast subpopulation, 29 out of 121 patients (25,6 %) experienced grade≥2 toxicity event including 17 dermatitis.

Grade ≥2 events were associated with RIANS results, phototype, cardiovascular comorbidities and mean dose to heart (p=0.06). On the whole cohort, a combined biological/clinical model including RIANS result (OR=3.2) and phototype (OR=1,57) could predict any grade ≥2 events with an AUC of 0.68. In the breast subpopulation, the AUC reached 0.73 (OR=7.6 and 1.5, respectively). Focusing on grade ≥2 dermatitis in the breast subpopulation, the AUC reached 0.76 with variables including RIANS (OR=3.9), mean dose to heart (OR=1,1) and cardiovascular comorbidities (OR=3,7).

Conclusions: APRILUX is the first real-life prospective study to demonstrate the value of a pre-RT pATM blood assay - performed in a neighboring laboratory - associated with clinical/dosimetric parameters to accurately predict grade ≥2 early toxicity in any system, any primary. The performance increased when focusing on dermatitis and breast cancer patients. Correlation with late toxicity will be reported after a longer follow-up.

SPEAKER BIOSKETCH: Prof Guillaume VOGIN, MD (Centre Francois Baclesse)

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CURRENT AND PAST POSITIONS:
Guillaume Vogin, MD, PhD is professor at Lorraine and Luxemburg Universities, board certified in radiation oncology at the Centre François Baclesse - the national radiotherapy center of Luxembourg. He has specialized in particle radiotherapy, sarcoma, pediatrics and CNS malignancies. He is a renowned expert in the field of radiation toxicity and individual radiosensitivity (IRS). He's clinician scientist (PI) at LIH – TIME group (Tumor Immunotherapy and Microenvironment), focusing on radiomics and bioinformatics applied to radiation toxicity / immune biomarkers discovery

EDUCATION:
Guillaume Vogin obtained his master degree at Harvard Medical School/Brigham & Women's Hospital and his PhD at the Cancer Research Centre of Lyon (UMR Inserm 1052 CNRS 5286 CLB). Collectivelly, he demonstrated that the velocity and efficiency of pATM nuclear activation were correlated with the severity of radiation toxicity. He participates to the developpment of a predictive assay of IRS. GV is actually implementing over 10 regional and national projects in the topic of diagnostic biomarkers of IRS and radiomics applied to radiation toxicity

OTHER RELEVANT PROFESSIONAL ACTIVITIES AND ACCOMPLISHMENTS:
As a teacher, Guillaume Vogin is leading a European program developping innovative multi professional educational initiatives applied to radiation oncology to serve quality of care in the Greater Region and prevent radiation toxicity and accidents (NHL-ChirEx).

Guillaume Vogin is the author of 60+ original peer-reviewed papers and 4 book chapters and monographs as well as two patents. GV is the recipient of several French and European awards (Académie de Stanislas, Fondation des Treilles, Société Française de Pédiatrie, Renaissance Française, Lucien Mallet Medal, Fondation Nuovo-Soldati). He is member of the French Society of Radiation Oncology, the French Society of Pediatric Oncology, the International Society of French-speaking Radiobiologists, the European Society of Therapeutic Radiation Oncology and the International Aerospace Medical Association.