Development of an explainable AI prediction model for arm lymphoedema following breast cancer surgery and radiotherapy

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Background

PRE-ACT (Prediction of Radiotherapy side Effects using explainable AI for patient Communication and Treatment modification) is an ongoing multi-disciplinary European collaborative study with the goal of using Explainable Artificial Intelligence (XAI) to predict long-term side-effects (toxicity) from radiotherapy in breast cancer patients. Some of the factors that increase the risk for clinically significant toxicity are already known, but current approaches to risk prediction mainly use low-dimensional statistical approaches and do not use complex genomics or imaging data. AI and machine learning are already used in some aspects of radiotherapy delivery.

The aim of **PRE-ACT** is to leverage its huge potential towards individual toxicity prediction, and at the same time provide an easily understood explanation to patients and physicians in order to support shared treatment decision-making (Fig. 1).

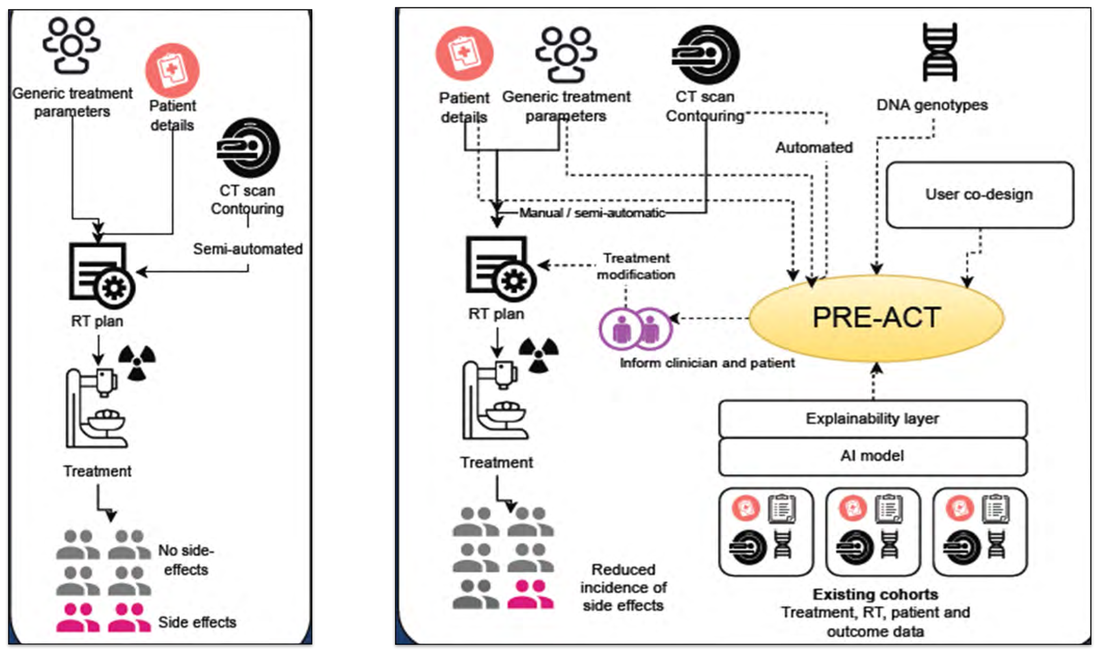

Figure 1. Current radiotherapy workflow is shown on the left-hand slide with the use of semi-automated contouring. PRE-ACT seeks to leverage the potential of AI by learning from existing patient cohorts to build prediction models with built-in explanations for treatment side-effects for use in a clinical support tool, which is being developed in co-design with patients and physicians. The aim is to reduce side-effects for all patients.

Methods

Lymphoedema can be a long-term side effect of surgery and radiotherapy for breast cancer, which can considerably affect quality-of-life (Fig. 2a+b). We developed discretized interpretable multi-layer perceptron (DIMLP) neural network, random forest and gradient boosted tree models for arm lymphoedema following surgery and radiotherapy +/- chemotherapy in three breast cancer patient datasets from European and French multi-centre breast cancer cohorts (REQUITE, Hypo-G, CANTO, total n=6,361).

Using patient demographic and treatment-related features (m=32), we trained the models with 10-fold cross-validation in a 90:10 random-split data set to predict arm lymphoedema (defined as ≥10% increase in arm circumference 15 cm proximal and/or 10 cm distal to the ipsilateral olecranon relative to baseline) up to three years from the start of radiotherapy.

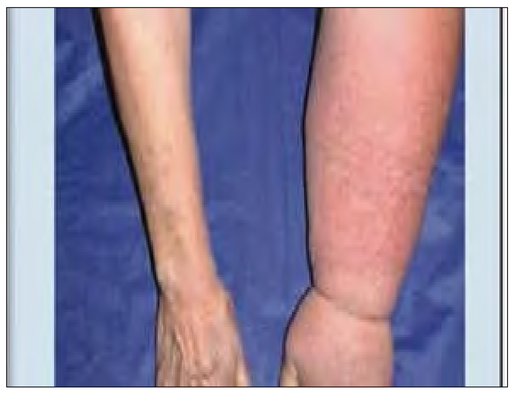

Figure 2a (above): Severe case of left arm lymphoedema after surgery and radiotherapy for breast cancer.

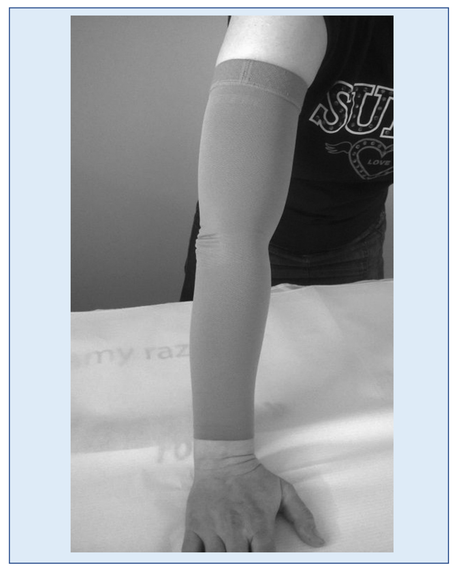

Figure 2b (right): Class II arm compression sleeve for the prevention as well as treatment of lymphoedema of the upper extremities.
https://doi.org/10.1016/j.jpainsymman.2017.04.014

Results

The incidence of arm lymphoedema was 6% across three datasets. Our best-performing model was based on **gradient-boosted decision trees** retaining all 32 patient- and treatment-related features with an average AUC of 0.84 (±0.003) (Fig. 3). Average sensitivity and specificity were 81.6% and 72.9%, respectively. We extracted propositional rules from gradient-boosted decision trees to explain their output to patients and physicians, for example:

- If Nodes_involved ≥2, Type_of_IMRT not Unknown, Type_surgery is Mastectomy, and PR_Status not Negative, Ki-67 <22.5, height <167.5 cm, and weight ≥69.5 kg, then arm lymphoedema;
- If no Intensity_modulated_radiotherapy, no Adjuvant_chemo, type_surgery is LUMPECTOMY, PR_status is POSITIVE, and no Diabetes, then NO arm lymphoedema.

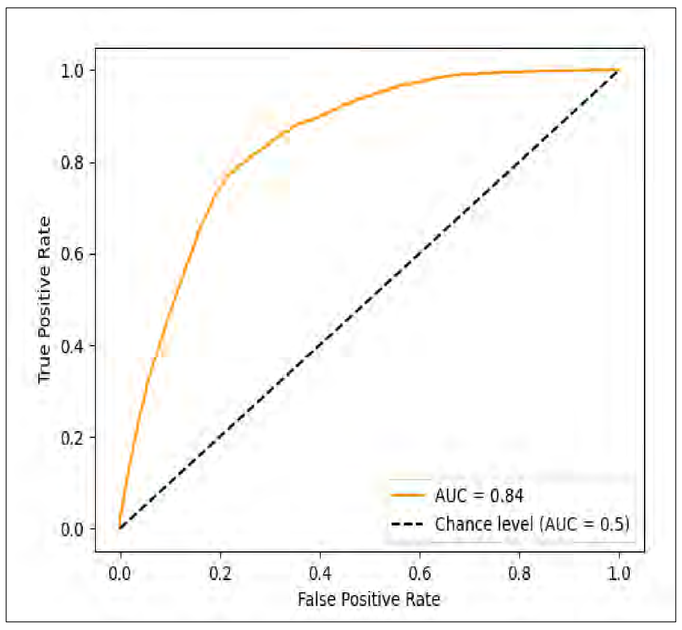

Figure 3: Receiver-Operating Characteristics (ROC) curve for model based on gradient-boosted decision trees involving all patient- and treatment-related features (m=32).

Conclusion

We generated explainable predictions for arm lymphoedema by applying ML algorithms to patient demographic and treatment features. Further inclusion of genomic and radiomic markers are likely to improve accuracy. The final AI model will be incorporated into a **web interface** for providing provide personalised risk predictions for patients and identify those at increased risk of toxicity who may benefit from supportive intervention or a change in treatment plan.

As part of the PRE-ACT study, end-users are involved in the development early on through a process of iterative **co-design** and constant feedback on the AI system. **Bias** inherent in the datasets and incurred by the AI algorithms will be identified and re-solved to ensure that the predictions are robust and fair to ethnicity, healthcare system, and social status. The final AI model will be tested in a **clinical trial** (Fig. 4), which will start recruiting at centres in France, NL and UK in Q4-2024.

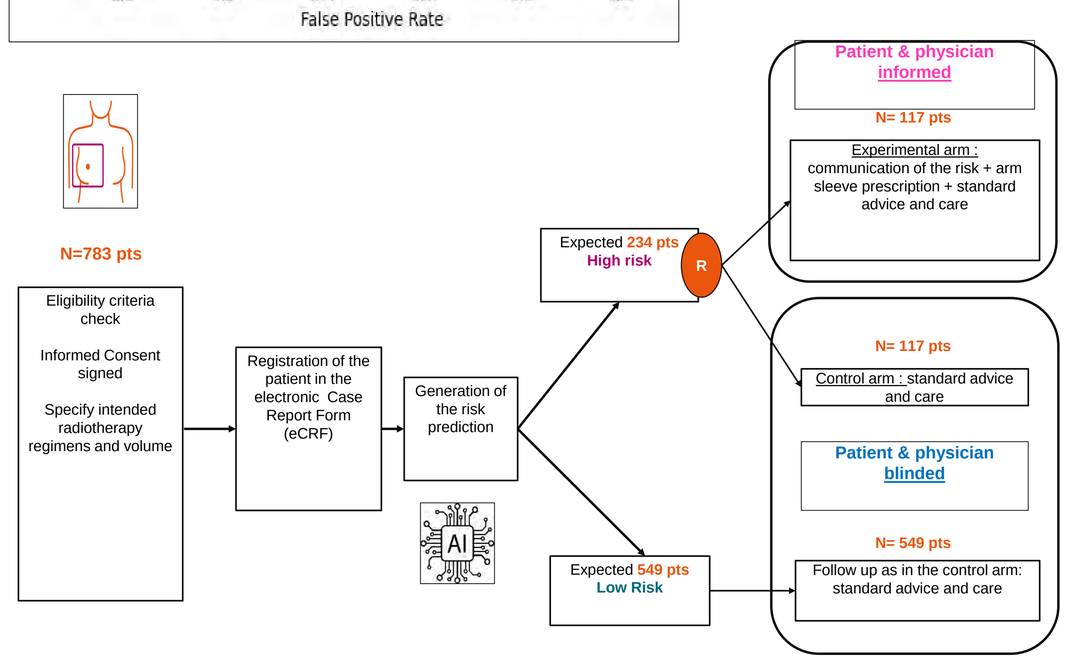

Figure 4: As part of PRE-ACT, the AI tool will be tested in a clinical trial. Patients deemed to be at high risk of developing arm lymphoedema will be randomised into treatment and non-treatment groups. Treatment groups will be offered advice via a web- based app and the use of a compression sleeve, to be worn for 8 hours a day for three months. Primary endpoint will be incidence of arm lymphoedema at 2 years. Due to the discomfort of wearing a compression sleeve, prescribing the arm sleeve according to the risk of lymphoedema is thought to represent a significant improvement for patient care (R = randomization).

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