PRECISION MEDICINE ONLINE

AI Tool for Predicting Breast Cancer Radiotherapy Side Effects Advances Toward Validation Trial

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NEW YORK – Researchers from the University of Leicester want to explore a wider range of predictive capabilities for an artificial intelligence model in an upcoming clinical trial after finding that it can identify patients at risk for arm lymphedema following breast cancer radiotherapy.

PRE-ACT, which stands for Prediction of Radiotherapy side Effects using explainable AI for patient Communication and Treatment modification, is a consortium involving multiple European research centers, patient advocacy groups, clinical centers, and the Paris-based medical technology company TheraPanacea. The interdisciplinary members of this consortium aim to develop AI methods that predict the risk of side effects from radiotherapy, including breast atrophy, heart damage, and arm lymphedema — when fluid typically drained through the body's lymphatic system builds up and causes swelling and infection.

These serious treatment-related side effects are of particular concern because breast cancer patients can live for years taking these therapies. According to Tim Rattay, a consultant breast surgeon and associate professor at the University's Leicester Cancer Research Center, the 10-year survival rate for breast cancer in Europe has risen to 80 percent, driven by early detection and improved treatments. "If four out of five of these women live for at least 10 years, then they potentially have to live with side effects of treatment for quite a long time," Rattay said.

But not every patient will develop those side effects. If researchers can develop tools to identify which patients are most likely to experience them, doctors can intervene to minimize their risk. For example, patients at risk for arm lymphedema might receive supportive treatments like arm stockinettes or prophylactic lymphatic massage, Rattay said.

Rattay and his colleagues developed an AI model to predict arm lymphedema following radiotherapy with or without chemotherapy using data from several breast cancer clinical studies conducted in Europe and North America. The trials included the REQUITE prospective cohort study of patients undergoing radiotherapy for breast, lung, or prostate cancer; the HYPOG-01 trial comparing hypofractionated and standard radiotherapy in breast cancer patients; and the CANTO cohort study of treatment-related chronic toxicity in women with localized breast cancer.

The researchers trained the algorithm on data from more than 6,000 patients using 32 demographic and treatment-related features. Those features include data such as the type of axillary or breast surgery, type of tumor, tumor grade, tumor receptor status, hormone receptor status, HER2 receptor

status, and number of nodes retrieved at surgery. It also incorporates comorbidities such as diabetes, smoking status, and whether the patient had chemotherapy or not. The model predicted arm lymphedema with an average area under the curve of 0.84, 81.6 percent sensitivity, and 72.9 percent specificity. The overall accuracy of the model was about 73 percent.

Rattay and colleagues call this an "explainable" AI model and stress the importance of explainability in the utility of the model's output in patient care. The model generates a set of rules for each patient and produces a list of specific patient features that contribute to the risk prediction. For example, a patient may be at high risk for arm lymphedema because of the number of cancer-involved lymph nodes, the type of radiotherapy received, or body weight. The physician and patient then can use the information to make decisions about supportive or preventive care for lymphedema.

The researchers are now translating the model into a software package that can provide evaluations and predictions for doctors and patients. They hope to validate the model in a 780-patient clinical trial slated to begin in the latter part of 2024 in the UK, France, and the Netherlands, and prospectively show that it can identify those at risk of lymphedema.

In the study, researchers will use the AI model to assign patients to three risk groups. Those deemed to be at high risk of arm lymphedema will be randomized to either receive information from the machine-learning model about lymphedema and an arm sleeve or not receive this intervention. The third group of low-risk patients will not receive any intervention. The investigators aim to complete enrollment by early 2026 and follow patients for two years. The trial will be funded by Horizon Europe, a program for funding research innovations in the region.

Although the upcoming validation trial will focus only on arm lymphedema, Rattay and his collaborators plan to use it as an opportunity to develop the model for predictive capabilities for other side effects such as breast shrinkage, scarring, and pain. While the model won't be used to predict these other side effects for patients and make care decisions within the trial, Rattay said that researchers will still be able to collect data on these other parameters.

Another goal within the trial is to increase the number of features used to train the model and include some genomic data. "We have found that [including genomic data] leads to some improvement," Rattay said, but he noted that the most important features for predicting arm lymphedema have proven to be the patient and treatment factors.

Rattay said that PRE-ACT consortium partner and medical technology firm TheraPanacea has been instrumental in preparing and harmonizing the data for the model and will develop and implement the software in the upcoming trial. If the trial is successful in validating the model for predicting arm lyphedema, TheraPanacea will move forward with a predictive model that comprises the additional side effects and develop it as a commercial product, including obtaining necessary regulatory approvals.

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