Editorial

Is it time to retire sentinel lymph node biopsy and use multi-omics prediction models?

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The approach to the axillary lymph nodes (ALN) in breast cancer surgery has shifted from the ALN dissection (ALND) in all patients to intraoperative sentinel lymph node biopsies (SLNB) and full dissection is rarely considered. Whilst the more conservative approach causes less morbidity in comparison to ALND, the incidence of complications is still significant, including pain, sensory or motor disorders and lymphoedema, affecting upper limb function in up to 22% of patients (1). This is particularly relevant to patients with small tumours and a lower risk of metastasis to ALN, such as a subset of the triple-negative breast cancer (TNBC).

Models for lymph node metastasis (LNM) prediction tool are reported amongst breast cancer, but majority are non-specific to TNBC and do not include genomic variables (2-7). Therefore, predictors of LNM are required but models with sufficient predictive value are still lacking for TNBC.

The study by Li *et al.* (8) worked on samples from a pre-established cohort of 445 patients with TNBC who underwent surgery at the Fudan University Shanghai Cancer Center. The primary aim of the study was to employ a multi-omics approach to determine any predictors of LNM in TNBC; 38.0% of the cohort had LNM, genomics data was available via WES in 59.6% and via OncoScan in 86.5%; and transcriptomics data available was available in 77.8% via RNA-seq. Following the collection of this data, the group was divided into a training set used to develop the model (n=305) and a validation set (n=140). The division was based on whether patients had surgery before an arbitrary date and the two sets had no significant differences in their baseline characteristics. Models based on key markers of five different approaches [clinical, genomics, somatic copy number alterations (SCNA), transcriptomics and molecular subtypes] were then constructed with the aim of achieving good predictive value in the validation set. The results from these were then used to construct a multi-omics model consisting of five markers (tumour size, SCNAs of *ZBTB6* and *MTHFD1*, mRNA levels of *GLP1R* and *NPY5R*). The molecules selected as yet have not been mechanistically linked to lymph node spread.

Distinctive signatures were observed between lymph node positive and negative cases. SCNA analysis revealed that deletion and amplification were less commonly seen in samples with LNM but had poor predictive value in the validation set. The analysis of the mutational profiles found statistically significant differences in the frequency of mutations in various genes (*WDR63*, *COL5A1*, *ATG2B*, *C17orf104*, *DDX41*, *F5* and *LOXHD1*) but the mutational profile was not predictive of LNM status. These genes may be of passenger status. Interestingly, LNM-positive samples had a slightly higher mutational burden but this was not statistically significant,

possibly in line with previous findings (9). Out of the single-omics models, the best predictive performance [area under receiver operating characteristic (ROC) curve =0.656] in the validation set and the most significant difference between patients with and without LNMs was shown by the transcriptomic model, which indicated changes in the regulation of 3,420 proteins associated with LNM. The multi-omics model achieved a good predictive performance (area under ROC curve =0.807) in the validation set, which was markedly better than any result with single-omics models. Despite the limited sample size of this study, the low end of the 95% confidence interval for this statistic is 0.709, still amounting to good predictive value.

Clinical and pathological data has proven to be strong factors to predict LNM. In a large cohort of 28,966 TNBC, age, race, primary tumour location, histological type and tumoral T stage provided were included on the model which achieved an area under the curve (AUC) of 0.684 and 0.689 respectively on the training and validation cohort (7). The reported AUC from other studies which used clinical, radiological and histological factors showed comparable results to Li *et al.* and might be more feasible for wider application (3-7). In general, these nomograms have had a reliable predictive value of axillary lymph node positivity, but none of them have been tested under a clinical trial nor included in clinical practice for the decision of axillary surgical conduct in patients with early breast cancer, especially TNBC that have different subtypes with different molecular characteristics and therapeutic responses. Luo *et al.* (6) in 2022 constructed and validated a risk model to estimate the probability of ALNM, using data from 11 differentially expressed genes associated with staging of primary tumour size where 81/326 tumours were TNBC and the prediction ALNM specificity was above 80%, false positive below 20% and accuracy approximately 80%. Despite being retrospective, the authors demonstrated the need to use clinical/pathological and genomic data to build more accurate models for predicting LNM. One might argue that available genomic data before surgery might contribute to a precision medicine approach in TNBC, but to date only the presence of specific germline variants, might drive considerations on surgical approach or systemic treatment, specially BRCA (10-12).

With this study, Li *et al.* have convincingly demonstrated the superiority of a multi-omics approach in predicting LNM in TNBC to single-omics approaches, and have constructed a promising model that could prevent significant morbidity (8). Even with a conservative threshold, the model may be integrated within an algorithm whereby SLNB could be carried out only in borderline cases. However, this model looks promising and can be a basis for further investigations, we believe it is not ready for application outside research. Since axillary lymph node status is the most important predictor of prognosis in early TNBC, it is important that any model that replaces SLNB will require a comparable sensitivity and specificity. The sensitivity of SLNB is reported in the literature as being around 50–70% and with a specificity of 99% (13). Therefore, any proposed model should be able to offer comparable rates alongside a low false negative rate once it might wrongly impact on de-escalation of treatment. Other barriers to overcome include the cost and timeliness of genomic sequencing; and batch effects that arise from using different sequencing platforms. Their work has suggested previously unidentified markers of LNM in TNBC and have built upon previous work investigating mutational burden in LNM this population. Linking these markers to the biology of LNM is another important area of future research. All of these lines of research would benefit from prospective studies with higher power and more diverse populations in case of genetic differences between ethnic groups. Finally, since genomic data has been useful to predict survival outcomes and to tailor adjuvant treatment in hormonal receptor positive breast cancer, future research should focus on models incorporating clinical data to allow us to personalize curative treatment in TNBC (14).

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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