Editorial Commentary | Data Sciences

A machine learning-based algorithm to eliminate breast and axillary surgery in patients with breast cancer and pathological complete response after neoadjuvant chemotherapy

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Comment on: Pfob A, Sidey-Gibbons C, Rauch G, *et al.* Intelligent Vacuum-Assisted Biopsy to Identify Breast Cancer Patients With Pathologic Complete Response (ypT0 and ypN0) After Neoadjuvant Systemic Treatment for Omission of Breast and Axillary Surgery. J Clin Oncol 2022;40:1903-15.

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Efforts have continually been made over the two past decades to de-escalate loco-regional and systemic treatments in patients with breast cancer (BC). Regarding loco-regional therapies, several trials demonstrated equivalent survival in de-escalating routine therapies such as omission of axillary dissection or radiotherapy in selected patients (1,2). Consistently, the modern approach to neoadjuvant chemotherapy (NACT), more and more used during the last decades, allows for downstaging of cancer and less mutilating breast and axillary surgery. Its efficacy in triple-negative (TN) and human epidermal growth factor receptor 2 (HER2)-positive BC continues to improve with incremental gains in the rate of pathological complete response (pCR), which reaches today 60% and, in several cases, leads to improvements in event-free survival. In this context, a natural next question is whether surgery can be omitted in selected patients thus allowing avoidance of complications from surgery and anaesthesia, improved cosmesis, increased patient satisfaction, and reduced cost and resource use. As oncologists, we often discuss with our BC patients the potential for pCR following NACT, and their first reaction is often to ask if this would allow them to avoid surgery. So far, our answer has always been "only surgery is able to confirm pCR", but it might change in a close future. Indeed, in a recent article titled "Intelligent Vacuum-Assisted Biopsy to Identify Breast Cancer Patients With Pathologic Complete Response (ypT0 and ypN0) After Neoadjuvant Systemic Treatment for Omission of Breast and Axillary Surgery", reported in the *Journal of Clinical Oncology*, Pfob *et al.* described a model that identifies BC patients with pCR response (ypT0 and ypN0) to NACT who may be able to avoid breast and axilla surgery (3). They retrospectively analyzed individual data from patients enrolled in two US prospective trials that evaluated the use of a minimally invasive vacuum-assisted biopsy (VAB) to reliably exclude residual cancer in the breast after NACT between 2016 and 2020. Their model is a machine

learning algorithm-based VAB model combining both patient, imaging, tumor, and VAB variables. It was defined in a multicentric discovery set including 318 patients with a cT1–3N0–1M0, HER2-positive, TN, or highly proliferative luminal B-like BC who had VAB performed before surgery. The robustness of this intelligent VAB model was then tested in an independent unicentric validation set of 45 patients, and its ability to predict residual cancer was compared against the actual results of the pathological evaluation of breast and axillary surgery. In the validation set, this intelligent model showed a false-negative rate (FNR) of 0% [95% confidence interval (CI): 0–13.7%] for detecting residual cancer, a specificity of 40% (95% CI: 19.1–63.9%) and AUC of 0.91 (95% CI: 0.82–0.97). Importantly, it performed better than imaging after NACT alone, VAB alone, or combinations of both using narrow patient selection criteria. Therefore, the authors concluded that this intelligent VAB model can reliably exclude the presence of residual cancer after NACT and before surgery, thus paving the way for omission of breast and axillary surgery for these exceptional responders in future trials.

Until now studies evaluating the prediction of pCR were based on breast imaging (4), minimal tumor biopsy (5), and tumor biology (6). Although promising, none of these predictive models proved to be as robust as the model developed by Pfob *et al*. with a 0% FNR. In fact, the algorithm used in their study accumulated all these parameters, and the five most important ones were tumor cells in VAB, accompanying *in situ* disease, lesion diameter on imaging before and after NACT, and VAB needle size. Although the rate of 0% of missed cancer in an external validation set is very promising, further prospective confirmatory evidence needs to be obtained with the primary objective to prospectively demonstrate that pCR prediction allows to omit surgery safely, ie without loco-regional relapse (LRR) during the follow-up. Initial efforts to omit surgery and instead to deliver radiation alone after achievement of complete clinical response failed because of unacceptably high LRR rates, probably due to the absence of precise imaging or VAB approaches to predict pCR (7,8). However, prospective studies are underway to determine whether a subgroup of patients may forego surgery in the setting of clinical complete response after NACT. The MD Anderson-promoted multicenter trial for eliminating breast surgery for invasive BC in exceptional responders to NACT based on image-guided VAB evidence of a pCR was recently reported in the *Lancet Oncology* (9). Women aged 40 years or older, not pregnant, with unicentric cT1-2N0–1M0 TNBC or HER2-positive BC and a residual breast lesion less than 2 cm on imaging after standard NACT were eligible for inclusion. A minimum of twelve 9G image-guided VAB were required. If no invasive or *in-situ* disease was identified, breast surgery was omitted and patients received standard radiation therapy alone (whole-breast radiotherapy plus a boost). Of 50 enrolled patients (42% with TNBC and 58% with HER2-positive BC), VAB identified a pCR in 31 patients (62%, 95% CI: 47.2–75.4%). Very promisingly, after a median follow-up of 26.4 months [interquartile range (IQR), 15.2–39.6], no ipsilateral breast tumor recurrence occurred in these 31 patients, and no serious biopsy-related adverse event or treatment-related death occurred. One may suppose that such results might be further improved using the intelligent VAB model developed by Pfob *et al*. who showed better FNR than other models based on imaging after NACT alone, VAB alone, or combinations of both using narrow patient selection criteria.

Altogether, these data suggest that surgery may be avoided for exceptional responder patients, provided that these latter are properly identified. Intelligent VAB provides the perspective to overcome this main limitation of pCR prediction accuracy. The study's strength is its 0% FNR. Indeed, on one hand, de-escalation by eliminating surgery may help reduce the treatment burden for patients and improve their quality of life (10,11), which is a principal concern in curative strategy. On the other hand, it is critical to avoid loco-regional or metastatic recurrence that would result from an inappropriate de-escalation strategy in patients whose tumor has not been entirely eradicated by chemotherapy. Like others (12), we reported a strong negative survival impact of residual nodal tumor burden (ypN1), and completion of axillary lymph node dissection is recommended for sentinel lymph node biopsy micro- and macro-metastases after NACT (13). Moreover, for cN1 patients, the highest axillary pCR rate was reported for ER-negative/HER2-positive tumor subtype, but without major differences in axillary pCR rates per tumor subtype (14). The use of radiological imaging is limited to predict small residual nodal disease (i.e., micrometastasis), as illustrated in the GANEA study with 8.1% of the 123 cN0 patients that were staged as ypN1mi after surgery (15). The rate of ypN1 in cN0 patients after NACT is estimated between 1 and 2.1% according to molecular subtype of the tumor (16). Moving forward, given that invasive BC currently displays a 50% or more chance of having a pCR in the breast and nodes following NACT

(17-21), another challenge would be to identify all patients with pCR eligible for a de-escalation strategy. In the Pfob *et al*. study, the specificity of intelligent VAB model was only 40% and will need to be improved. But the potential for improvement exists, likely though more experience in performing and evaluating minimally invasive biopsies after NST, since 53.3% of VAB in the validation set were deemed to be unrepresentative by the biopsying physician and 24.4% by the pathologist.

Besides the needed validation of every new predictive model in prospective clinical trials, many other factors might prevent the applicability of this study's results to clinical practice. The effective implementation of digital health tool remains influenced by various stakeholders, social expectations, and environmental contexts. Many promising technological innovations in health and social care are characterized by non-adoption or abandonment by individuals or by failed attempts to scale up locally (22). By examining de-escalation processes, introduction, testing, and implementation of recommendation to limit surgery have often taken several decades (23). On the patients point of view, it is controversial whether the stress and apprehension brought on by more imaging, additional biopsies, and the potential for increased rates of local recurrence is justified in foregoing a low-morbidity outpatient procedure (24). Indeed the 7.1% complication rate of VAB is clinically meaningful (25) with regards of the 1.9% morbidity estimated at 30-day for lumpectomy with sentinel node biopsy after a radiographical complete response (26). All these questions, including cost-effectiveness issues, will need to be clarified in future clinical trials. However, this study, *via* the development of a machine learning algorithm–based innovative tool, is a new step forward in the growing body of data identifying potential low-value breast cancer surgery to de-implement. A first prudent step could be to consider sentinel lymph node biopsy in patients identified as in-breast pCR, in order to avoid ignoring an absence of in-node pCR with a risk of undertreatment, while waiting for higher performances of radiological imaging to predict small residual nodal disease.

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Footnote

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