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Triple negative breast cancer under neoadjuvant treatment: the role of assessment ultrasound.

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Abstract

Triple-negative breast cancer is a separate entity that comprises several molecular subtypes driven by specific genetic alterations that might potentially be targeted. However, currently most patients continue to receive standard chemotherapy regimens.

Neoadjuvant treatment is accepted for larger tumours and locally advanced disease as it might offer surgical and oncological advantages; among them, it allows a live assessment of tumour sensitivity to treatment, leading to a prompt discontinuation of ineffective therapies to avoid unnecessary toxicities.

It is well known that TNBC is very responsive to chemotherapy, with high rates of pathologic complete responses that can also be quite rapid.Â

In this scenario, an accurate assessment of residual tumour size and extension becomes crucial for an adequate surgical planification and a prognostic prediction.Â

Patients should be assessed before, half-way through neoadjuvant chemotherapy and at the end of this treatment. It seems that MRI is the most accurate technique to assess this, but ultrasound and mammogram are the most widely used.Â

In this context of uncertain diagnosis, we decided to evaluate our results in an audit of TNBC patients receiving neoadjuvant treatment. Our aim was to know the role of ultrasound alone in assessing the pathological response in our patients.Â

Background

Triple-negative breast cancer (TNBC) is a heterogeneous subgroup of breast cancer (BC) defined by the lack of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This entity comprises several histological and molecular subtypes driven by specific genetic alterations. These could potentially be targeted, however, most of these patients continue nowadays to receive standard chemotherapy regimens.

Neoadjuvant treatment is considered standard for patients with larger tumours (> 2.0 cm) and locally advanced disease [1] as this might offer surgical and oncological advantages, such as reduction in tumour size which might allow surgical resections in those initially ineligible [1] or switching from mastectomy to breast conservative treatment [1] [2].

In addition to these, it allows as well anÂ *in vivo* Â assessment of tumour sensitivity to treatment, [1] leading to a prompt discontinuation of ineffective therapies to avoid unnecessary toxicities [1].

It is well known that TNBC is very responsive to chemotherapy, with high rates of pathologic complete responses (pCR] [3,4] that can also be quite rapid. In fact, Huober, et al. [5] have reported responses after only two cycles of treatment.

This has a significant clinical impact as it has been demonstrated a survival advantage for patients who show pCR over those with residual disease after neoadjuvant treatment. [6,7].

In this scenario, an accurate assessment of residual tumour size and extension becomes crucial for an adequate surgical planification and a prognostic prediction. Nowadays, surgery is still unavoidable even in the context of pCR, but there are trials underway which could give us further answers.Â

Patients should be assessed before, half-way through neoadjuvant chemotherapy and at the end of this treatment [8]. But in this context, the question arising is: Â can any imaging technique allow an early prediction of pCR in these patients?

Old studies such as the published by Atkins *et al* in 2012, have reported that breast ultrasound and MRI were more accurate than mammogram in predicting residual tumour size following neoadjuvant chemotherapy in TNBC patients, showing, however, that none of these modalities was predictive of a pCR [9].

Other studies have shown that breast ultrasound is clearly more accurate than mammogram in predicting the size of residual disease (91.3% compared to only 51.9% respectively).Â However, once again, there was no difference in their ability to predict a pCR [10].

MRI has an excellent ability for assessing both residual disease extent and early treatment response [11,12] and also a better correlation with pathological

findings.

However, despite these benefits, it is not performed routinely in all centres, whereas mammogram and ultrasound continue to be the preferred radiological evaluations. Both modalities are performed together rather than separately and predict the amount of residual disease and complete pathological response before any surgical planning.

With all these inconsistent findings, we decided to assess our results in an audit of our TNBC patients. Our aim was to evaluate the role of ultrasound alone in assessing the pathological response in TNBC patients receiving neoadjuvant chemotherapy.

Audit results

We evaluated the data of 33 patients treated within the previous 12 months. All were women, with a mean age 50 years old (27-70). All received neoadjuvant chemotherapy. Different regimens were used, either Carboplatin and Paclitaxel +/- Olaparib within the Partner trial or the standard FEC/Docetaxel or FEC/Paclitaxel.

Patients were assessed initially, half-way through the chemotherapy and at the end with an US of the breast and axilla. All of them performed a mammogram as well but this was not taken into consideration for our audit purpose. Â

Our results showed that the US helped classify correctly 62.5% of the patients, with a tendency to maximise real pathological benefits as shown in the table 1 and 2.

Table 1:Â

Response	Radiological	Pathological	Wrong US classification/ real pathological response
CR	12	7	5 / PR
Â	Â	Â	Â
PR	18	12	6 / 1 SD and 5 CR
Â	Â	Â	Â
SD	1	0	1 / 1 PD
Â	Â	Â	Â
PD	1	1	0

CR â€“ complete response, PR â€“ partial response, SD â€“ stable disease, PR â€“ progressive disease

Table 2:Â

US classification	Â	Diminishing real response	Maximising real response
Correct	20 (62.5%)	Â	Â
Wrong	12 (37.5%)	6 (50%)	6 (50%)

However, if we consider only response, regardless of complete or partial, and add SD as well to this group, the US is able to classify correctly 96.8% of patients (Table 3).Â

Table 3:Â

US response (CR + PR + SD)	Â
Correct	31 (96.8%)
Wrong	1 (3.2%)

When we assessed only the ability of predicting pathological CR (pCR), our audit showed 12 pCR but only 5 were correctly diagnosed by the US (41.6%).

Brief discussion

Our results have clearly evidenced that the US, as radiological evaluation of tumour response in TNBC patients receiving neoadjuvant chemotherapy, is far away from ideal in terms of correct classification of pCR. However, it is able to guess correctly if a patient is responding to chemotherapy in most cases. We only found that it clearly failed when showing radiologically SD as the pathological finding showed clear PD.

Another interesting data from our audit is the fact that the US could underestimate the real benefit but it can also overestimate it in a similar proportion of cases.Â

There are several studies in the published literature showing that although there are different radiological techniques used to assess tumour response in this group of patients, MRI has been found the most accurate of all in patients receiving NACT [13,14].

The definitions of radiological CR are different among imaging techniques even if the procedures use the WHO [15] or the EORTC/ RECIST [16] criteria.

As examples, the study by Schott *et al* determined the sensitivity of mammogram, US, and MRI for detecting pathological CR (pCR) in this context as 50%, 25%, and 25%, respectively [17].

Shin *et al* published an accuracy of pCR prediction of 38% for mammography, 13% for US, and 75% for MRI [18]. Our study shows that US is able to predict pCR in >40% of cases.

In our population of patients we seem to have obtained better figures for the role of US in the assessment of response. However, our study is very small and carried out in a single centre, focused only on a specific entity of breast cancer, factors that will diminish the possibility of extrapolation but not the value of these findings to our patients.Â

Conclusion

Despite our better results, the assessment US continues to give diagnostic uncertainty. Our findings, give us a clear idea of how to interpret US assessments and how to explain adequately to our patients, taking into account the pitfalls of this technique. In this way, patients could be prepared for the potential change in pathological results after

surgery when comparing to radiological findings, and also understand clearly why at this point in time, surgery is unavoidable.Â Â

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