Assessment of Pathological Complete Response Using Vacuum-Assisted Biopsy in Breast Cancer Patients Who Have Clinical and Radiological Complete Response After Neo-Adjuvant Chemotherapy

Breast Cancer: Basic and Clinical Research
Volume 17: 1–7

DOI: 10.1177/11782234231205698

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ABSTRACT

BACKGROUND: Any treatment protocol that leads to complete elimination of surgery may lead to a better patient acceptance of breast cancer treatments.

OBJECTIVES: We conducted this study to assess the feasibility of preoperative vacuum-assisted biopsies in identifying pathological complete response (pCR) and its accuracy in correlation to final histopathology report (HPR), in an Indian setting.

METHODS: This was a prospective study conducted between October 1, 2019, and March 31, 2021. Patients with early breast cancer, estrogen and progesterone receptors negative and either Her2 positive or negative, and who were fit to undergo marker placement at the centre of the tumour and to receive third-generation chemotherapy (4 cycles of 3 weekly doxorubicin and cyclophosphamide followed by 4 cycles of 3 weekly docetaxel) were included in the study. Following the enrolment, a tissue marker was placed at the centre of the tumour and appropriate chemotherapy was started. Patients who achieved clinical complete response were subjected to ultrasound-guided vacuum-assisted biopsy (VAB) from the tumour bed before surgery. Pathology results of the VAB and resected specimen were then compared. Descriptive statistics were used in the study.

RESULTS: Eighteen patients were enrolled in the study, with a mean age of 43.6 ± 9.8 years. However, only 10 were eligible for VAB procedure, and sensitivity and specificity were calculated based on the results of these 10 patients only. Vacuum-assisted biopsy showed sensitivity of 50% and specificity of 100% in identifying pCR. Combination of mammography, ultrasonography, and VAB showed sensitivity of 77.8% and specificity of 66.7% in identifying pCR.

CONCLUSION: Vacuum-assisted biopsy of tumour bed may not be sensitive enough to eliminate surgery even in patients who have had exceptional response to neo-adjuvant chemotherapy.

KEYWORDS: NACT, pCR, exceptional responders, VAB

RECEIVED: March 17, 2023. **ACCEPTED:** September 18, 2023.

TYPE: Original Research Article

FUNDING: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was conducted with the research grant provided by the Indian Council of Medical Research (Project Number 2019-7063).

Grant received from ICMR (a not for profit organization being funded by the government of India).

COMPETING INTERESTS: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Breast cancer ranks as the most common cancer among Indian females with a rate of 25.8 per 100 000 women and mortality of 12.7 per 100 000 women.[1] Even though the breast cancer mortality in the west continues to decline, it is still high in India and other developing countries.[1] For women diagnosed during 2010 to 2014, 5-year survival for breast cancer was 89.5% in Australia and 90.2% in the United States, whereas it was just 66.1% in India.[2]

Advanced stage at the time of presentation due to delay in seeking medical attention is a very important cause for the overall worse outcome of breast cancer in developing countries such as India, and World Health Organization (WHO), in its facts sheet, stresses early detection of breast cancer in developing countries on the lines similar to more high-income nations, where this strategy has been shown to be highly successful.[3]

Fear of diagnosis of cancer and mutilating surgeries is an important cause of delay in presentation in developing countries.[4,5] In India, we routinely come across patients who are worried that their presentation to a doctor would mean an advice of having to undergo an operation. So, with a false hope of self-resolution, patients chose to wait rather than seeking medical help at the earliest. Because of this fact, it can be assumed that any treatment protocol, which leads to complete elimination of surgery, may lead to a better patient acceptance of breast cancer treatments and, in turn, an earlier presentation to the health care providers.

The concept of elimination of surgery after achieving exceptional response to neo-adjuvant chemotherapy (NACT) is not something very new and studies comparing recurrence rates after achieving clinical complete response in patients undergoing radiotherapy alone versus surgery alone were

published as early as 1981.[6-10] However, many of these studies had a non-significant trend towards increased loco regional recurrence and the idea of eliminating surgery could not be incorporated into general clinical practice.

Now, with ever increasing rates of pathological complete response (pCR) due to improvement in neoadjuvant therapies, particularly for triple negative and Her2-positive subtypes, and significant improvements in breast imaging, there has been a resurgence of interest in this area. However, with improved radiologic techniques, there is a problem of over sensitivity. There may be a radiological complete response observed only in 20% of the cases even when the actual pCR rates may be as high as 60% (as seen in TN and Her2-positive subtypes).[11-13]

To overcome this peculiar problem, concept of preoperative biopsies of the tumour bed has come up. There have already been a few published studies that have shown a significant correlation between the preoperative biopsies with postoperative histopathology.[12-16] The investigators, in addition to vacuum-assisted biopsy (VAB), have used thick bore core needle biopsy to assess pCR.[12-16] With the encouraging results observed in these studies, a few groups have also started to further investigate the possibility of avoiding surgery after NACT.[11,17,18]

We conducted this study to assess the feasibility of preoperative VABs in identifying pCR and its accuracy in correlation to final HPR, in Indian setting.

Methodology

Study design and participant selection

This was a prospective study conducted between October 1, 2019, and March 31, 2021, after getting the approval from our institutional ethics committee. The study was conducted in accordance with the Declaration of Helsinki and relevant guidelines were followed for conducting the study. Fisher's formula was used to calculate the sample size. However, because of the COVID-related difficulties, we had to reduce the sample size to 20. We included adult females with early breast cancer. The other inclusion criteria were patients having primary tumour between 1 and 6 cm in size on ultrasound and mammography (MG) and hormone receptor negative tumours, irrespective of the HER2neu status. The patients also had to be fit to undergo marker placement at the centre of the tumour and to receive chemotherapy. Patients with multifocal/multicentric tumours or with extensive ductal carcinoma in situ (DCIS)/microcalcifications and pregnant patients were excluded from the study. Written informed consent was obtained from every patient who agreed to be a part of the study.

Baseline workup

This included an ultrasound of both the breasts and a bilateral MG along with a core biopsy and staging workup which included a chest X-ray, a complete blood count, and liver function tests along with alkaline phosphatase. Staging was done as per AJCC 8th edition anatomical staging for breast cancer.[19]

Marking the centre of the tumour

Following enrolment into the study and before starting NACT, an ultrasound sensitive tissue marker (BARD Ultraclip Dual Trigger Breast Tissue Marker) was placed at the centre of the tumour area using ultrasound.

Administration of NACT

The patients received standard NACT consisting of the following regimen: 4 cycles of 3 weekly doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2 f/b 4 cycles of 3 weekly docetaxel 100 mg/m^2 in patients having triple negative tumours. Patients with Her2neu-positive tumours received 4 cycles of 3 weekly doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2 followed by 1 cycle of docetaxel 100 mg/m^2 and trastuzumab 8 mg/kg loading dose followed by 3 cycles of docetaxel 100 mg/m^2 and trastuzumab 6 mg/kg.

Clinical and radiological assessment of response

Three weeks after the administration of last cycle of NACT, patients were re-evaluated, first clinically followed by MG and ultrasonography (USG). The assessment was done using RECIST criteria v1.1.[20] The response to NACT was divided into complete response (CR), partial response, stable disease, and progressive disease.

Eligibility and procedure of VAB from the tumour bed

Patients who achieved CR, ie, no palpable lump and no residual mass on ultrasound and MG, were subjected to ultrasound-guided VAB from the tumour bed using an 8-G needle using ultrasound-sensitive tissue marker clip as a guide. This was done in the radiology department 1 day prior to surgery. The histopathologists were alerted about the VAB sample that was sent with a special request to note any chemotherapy-related changes and microscopic presence of residual tumour. If the tissue marker clip was removed during the VAB procedure, another one was placed at the same time for easy identification during subsequent wire placement.

Confirmation that VAB was representative of the tumour bed

Direct: If the tissue marker was removed along with the VAB specimen.

Indirect: If chemotherapy-related changes that occur in the tumour bed (like areas of hyalinized vascular stroma with stromal edema and fibroelastosis, foamy histiocytes, aggregates of lymphocytes and hemosiderin pigment, nodules of histiocytes and cholesterol clefts, residual tumour, etc) were seen by the histopathologists.

Surgery

All patients underwent a standard surgery (breast-conserving surgery [BCS] or modified radical mastectomy, as per the clinical situation and patient's preference) 3 weeks after the last cycle of NACT. Breast-conserving surgery could be using palpatory method if the lesion was palpable or using wire and ultrasound-guided localization (WUGL) technique, in cases of non-palpable tumours.[21] The patients who achieved clinical and radiological complete response underwent the surgery after the VAB and those who did not, underwent surgery directly.

Pathology results

Pathology results of the VAB and resected specimen were compared with surgically resected specimen being the gold standard. Pathology results of patients who did not undergo a VAB were also recorded. All the specimens were graded according to residual cancer burden (RCB) classification.[22]

Primary endpoint

The primary endpoint of the study was to assess the sensitivity and specificity of VAB in identifying residual tumour, if any, in patients who achieved clinical CR after NACT.

Secondary endpoints

To assess the sensitivity and specificity of combined MG, ultrasound, and VAB and to assess if there is a learning curve which can improve the sensitivity and specificity of VAB in identifying residual tumour in patients who achieved clinical CR.

Statistical analysis

Descriptive statistics were used in the study. Patient characteristics, tumour characteristics, and response to chemotherapy were expressed in percentages. Sensitivity, specificity, and positive and negative predictive values were calculated using the standard formulae.

Results

Eighteen patients were enrolled in the study, with a mean age of 43.6 ± 9.8 years (range, 27-60). At presentation, 2 patients had anatomical stage IA disease (T1N0M0), 6 had IIA disease (T2N0M0), and 10 patients had stage IIB disease (8 had T2N1M0 and 2 had T3N0M0 disease). None of the patients had pure or concomitant DCIS on core biopsy. Post NACT, 9 patients had clinical and radiological complete response (ycT0N0M0) (Figure 1), 1 had complete response at the primary site but residual lymph nodes (ycT0N1M0), and 8 patients had residual primary tumour but no lymph nodes (5 had ycT1N0M0, 3 had ycT2N0M0). The other pre- and post-NACT tumour characteristics are given in Table 1.

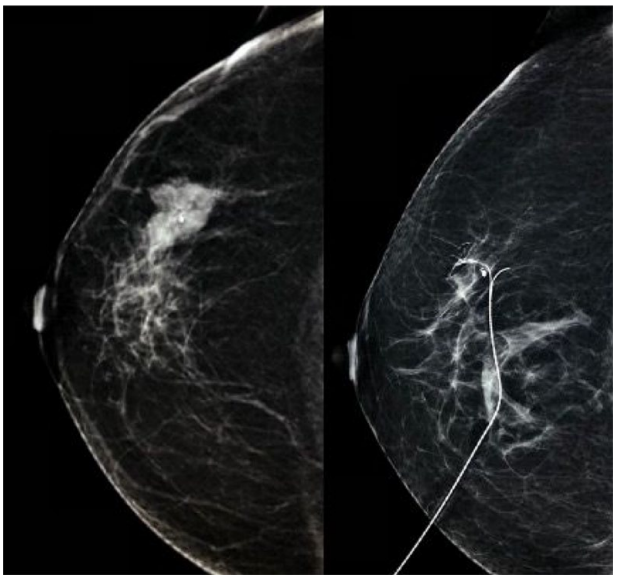

Figure 1. Pre-NACT and immediate preoperative cranio-caudal mammogram images of patient who achieved both radiological and pathological complete response.
NACT indicates neo-adjuvant chemotherapy.

Out of 18, only 10 (55.6%) patients were eligible and underwent VAB (Figure 2). Out of these 10, tissue marker retrieval (direct criteria) could be done only in 1 patient (10%). In this patient, another tissue marker clip was immediately placed at the centre of the tumour bed to allow easy identification at subsequent surgery. There was presence of histopathological evidence (indirect criteria) as well in her VAB specimen. Overall, after using both direct and indirect criteria, VAB specimen was found to be representative of tumour bed in 9 (90%) patients. Residual tumour on VAB specimen was found in 2 (20%) patients.

All the 18 patients underwent surgery. Fifteen (83.4%) underwent BCS, 14 (77.8%) using WUGL, and 1 (5.6%) underwent standard BCS using palpatory method. One of the patients who underwent WUGL had positive lateral margins which necessitated a re-excision. The margins subsequently came out to be negative on re-excision.

Postoperative histopathology showed no residual tumour at primary site in 9 (50%) patients and a median tumour size of 0 mm (interquartile range [IQR], 13; range, 0-50). None of the patients had residual pure of concomitant DCIS on postoperative histopathology. A median of 17 axillary lymph nodes were retrieved (IQR, 10; range, 6-25), out of which a median of 0 LN was positive (IQR, 2; range, 0-6). On doing RCB classification of postoperative specimen, 7 patients (38.9%) fell in RCB class 0, 2 (11.1%) in RCB class 1, 8 (44.4%) in RCB class 2, and 1 (5.6%) fell in RCB class 3. Seven patients (38.9%) were classified as ypT0N0, 3 (16.7%) patients each as ypT1N0 and ypT1N1, and 1 (5.6%) each as ypT0N1, ypT0N2, ypT1miN0, ypT1N2, and ypT2N0.

Out of a total of 8 patients in whom VAB was not planned because of residual lesion in imaging, 3 patients (37.5%) had achieved pCR and rest had residual disease on final histopathology.

Table 1. Tumour characteristics (pre- and post-NACT).

CHARACTERISTICS	PRE-NACT	POST-NACT
No. of patients with clinically palpable lump in breast	18 (100%)	3 (16.7%)
No. of patients with clinically palpable LNs in axilla	8 (44.4%)	2 (11.1%)
Duration of lump in months at the time of presentation (median, IQR, range)	8, 9.25, 0.25-12	
Quadrant		
Upper outer	9 (50%)	
Lower outer	5 (27.8%)	
Upper inner	2 (11.1%)	
Central	2 (11.1%)	
Lower inner	0	
Size (in mm, median, IQR, range)	29, 14, 11-53	0, 15, 0-50
Microcalcifications on mammography	5 (27.8%)	1 (5.6%)
T staging		
0	0	10 (55.6%)
1	2 (11.1%)	5 (27.8 %)
2	14 (77.8%)	3 (16.7%)
3	2 (11.1%)	0
N staging		
0	10 (55.6%)	16 (88.9%)
1	8 (44.4%)	2 (11.1%)
M staging		
0	18 (100%)	18 (100%)
Type of tumour		
Invasive ductal carcinoma	18 (100%)	
Grade of tumour		
1	0	
2	3 (16.7%)	
3	15 (83.3%)	
Endocrine receptors positive	0	
Her 2 neu positive	5 (27.8%)	
Appropriate chemotherapy received (as per study protocol)	18 (100%)	
Clinical response to chemotherapy (at primary tumour site)		
Complete response		10 (55.6%)
Partial response		5 (27.8%)
No response		1 (5.6%)
Progressive disease		2 (11.1%)

Abbreviations: IQR, interquartile range; LN, lymph node; NACT, neo-adjuvant chemotherapy.

On correlating between VAB and surgery in the 10 patients who underwent both VAB and surgery, 6 (60%) had no residual cancer either on VAB or surgery, 2 (20%) had residual cancer both on VAB and surgery, and 2 (20%) had no residual cancer on VAB but had residual cancer on surgery. Out of the 2 patients who had no residual cancer on VAB but had residual cancer on surgery, 1 had VAB which was representative of the tumour bed whereas the other one did not. There was 1 patient who underwent VAB and had no residual tumour in VAB or at primary site but had residual tumour in lymph nodes.

Characteristics of VAB and MG + US + VAB as a test to detect residual cancer in the tumour bed are given in Table 2.

No effect of learning curve was noted on VAB characteristics. First 5 VABs had similar sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) as the last 5 VABs.

Discussion

Axilla has led the way in de-escalation in breast cancer–related surgery. Current guidelines recommend SLNB in clinically node negative patients who are undergoing either upfront surgery or post NACT.[23] Over and above this, in patients undergoing upfront surgery in the form of BCS and have 1 to 2 positive lymph nodes out of 3 to 4 retrieved during sentinel lymph node biopsy, further axillary clearance may be omitted.[23] Guidelines even recommend complete avoidance of axillary sampling in elderly breast cancer patients if the clinical suspicion of axillary lymph nodal metastases is very low.[23]

Focus is henceforth shifting to de-escalation of surgery in the breast.[24] And although this direction is for both non-invasive and invasive cancers, non-operative management of invasive cancers pose greater challenges than that of non-invasive cancers.

Biggest challenge in de-escalation of surgery in invasive cancers is that not intervening in potentially curable tumours, especially in patients who are otherwise fit and willing for treatment and have tumours that are high grade and endocrine receptor negative with a high potential to metastasize within a short span, may not be medically and ethically justifiable. Hence, any potential surgical de-escalation in invasive cancers can only be done after administration of one or other type of systemic therapy.

A major problem in dealing with post systemic therapy is that pCR may not be very reliably predicted by radiology. There is a problem of both over and under sensitivity (Figure 3).[25] Magnetic resonance imaging (MRI) of the breast, the most sensitive of all breast radiology, has an accuracy of only 74% in identifying pCR.[11] Even if the biopsy of tumour bed shows that there is no residual tumour, it may be unacceptable to both the surgeon and the patient, to consider omitting surgery, especially when it has been observed that there may be an inherent false negative associated with the procedure (a finding corroborated in our study as well).[18] This assumes greater importance in current scenario where the oncologist may want to add one of the many post neo-adjuvant and post-surgery therapies in patient who are unable to achieve pCR.[26]

Yet another problem is that of patchy or non-uniform killing of tumour cells by chemotherapy (Figures 4 and 5). Even if we are successfully able to take a representative sample from the tumour bed and it shows no residual tumour cells, there

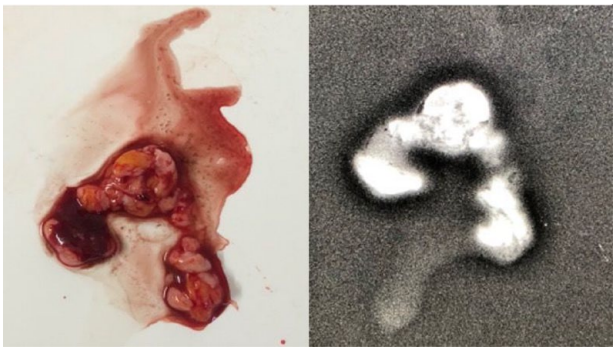

Figure 2. VAB specimen: picture and mammogram image.
VAB indicates vacuum-assisted biopsy.

Table 2. Characteristics of VAB compared with surgery as a gold standard in identifying residual tumour.

	RESIDUAL TUMOUR ON HPR	NO RESIDUAL TUMOUR ON HPR
(a) In all patients who underwent VAB		
Residual tumour on VAB	2	0
No residual tumour on VAB	2	6
Specificity = 100%, Sensitivity = 50%, PPV = 100%, NPV = 75%		
(b) In patients in whom VAB was representative of tumour bed		
Residual tumour on VAB	2	0
No residual tumour on VAB	2	6
Specificity = 100%, Sensitivity = 66.7%, PPV = 100%, NPV = 85.7%		

Abbreviations: HPR, histopathology report; NPV, negative predictive value; PPV, positive predictive value; VAB, vacuum-assisted biopsy.

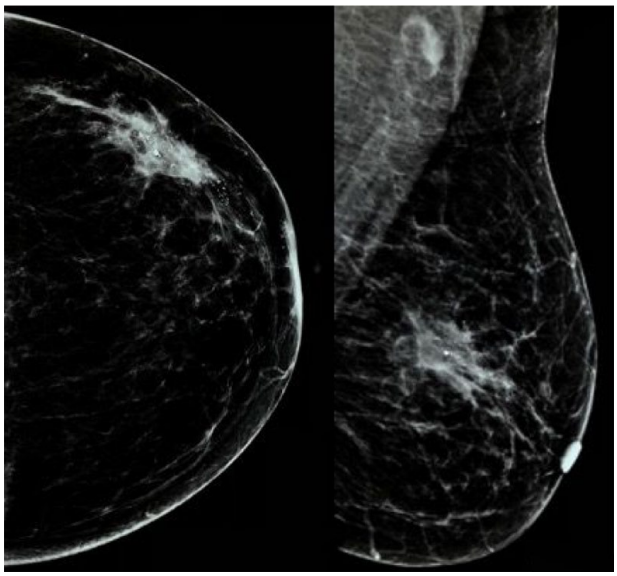

Figure 3. Post-NACT cranio-caudal and mediolateral oblique views of a patient who had residual lesion on mammogram but had pathological complete response on final histopathology.
NACT indicates neo-adjuvant chemotherapy.

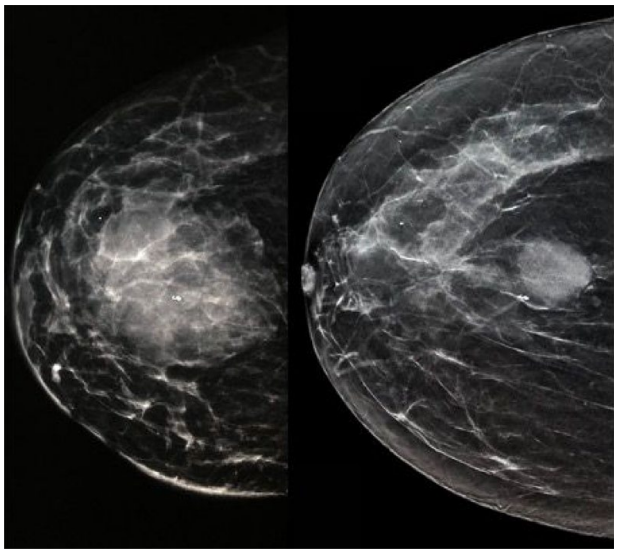

Figure 4. Pre- and post-NACT cranio-caudal mammogram images of a patient with partial clinical response depicting the non-uniform shrinkage of tumour.
NACT indicates neo-adjuvant chemotherapy.

may be a residual patch of viable tumour cells in some other part of the tumour bed which may be missed. The finding in our study that even when there was a direct or indirect evidence of the VAB sample being representative of tumour bed area, there was an associated false-negative rate, and this finding may be due to this very property of chemotherapy-induced tumour cell killing.

Although our study had the advantage of selecting patients with early breast cancer with subtypes that have a high probability of achieving pCR and the use of ultrasound and mammograms, there were some limitations as well. Our target number of patients which was 50 could not be achieved as

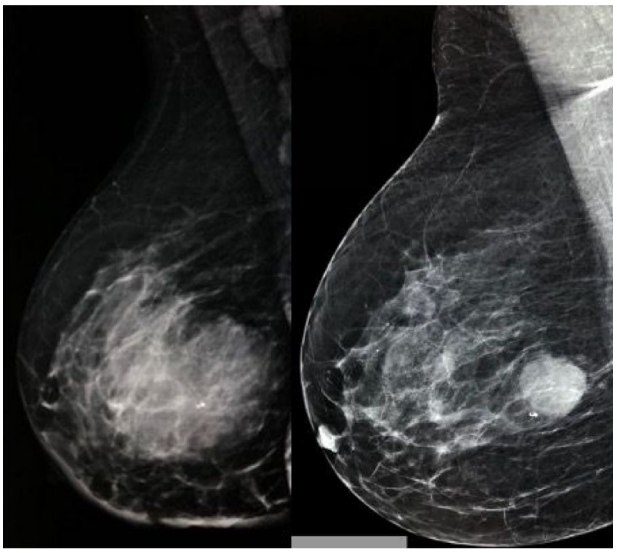

Figure 5. Pre- and post-NACT mediolateral oblique mammogram images of the same patient as in Figure 3.
NACT indicates neo-adjuvant chemotherapy.

there were many patients who withdrew from the study in the wake of COVID pandemic. In addition to this, direct evidence of VAB specimen being from the centre of tumour bed, ie, retrieval of tissue marker, could be achieved in only one patient.

Despite the above-mentioned limitations, there were a few takeaways from our study. Our study re-iterates the fact that preoperative biopsy from the tumour bed has less than ideal sensitivity and even if the specificity may be high, missing a few patients with residual tumour may mean that these patients will be missing on important modifications in their postoperative treatments which may eventually result in poorer overall outcomes. More importantly, can it be used in node positive patients is even a bigger question. Although we all look forward in the direction of de-escalation in breast cancer treatment, it should not come at a cost of potentially increased recurrences and hence poorer outcomes for the patients.

Conclusion

Vacuum-assisted biopsy of tumour bed may not be sensitive enough to eliminate surgery even in patients who have had exceptional response to NACT.

Declarations

Ethics approval and consent to participate

Approval from PGIMER (Post Graduate Institute of Medical Education and Research, Chandigarh) Ethics committee wide approval number IEC-01/2019-1093 dated January 17, 2019. Written informed consent was sought and signed by all the participants before enrolment into the study.

Consent for publication

No data/pictures disclose the identities of the patients. All the patients had given informed written consent before enrolment in the study.

Author contributions

Siddhant Khare: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.
Santhosh Irrinki: Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing.
Ishita Laroiya: Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing.
Tulika Singh: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing.
Amanjit Bal: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing.
Gurpreet Singh: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing.

Acknowledgements

None.

Availability of data and materials

The raw data pertaining to the study will be made available on request to Dr Siddhant Khare (Corresponding Author).

REFERENCES

1. Breast cancer. https://www.who.int/news-room/fact-sheets/detail/breast-cancer. Updated 2022. Accessed 14 April 2022.
2. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391:1023-1075. doi:10.1016/s0140-6736(17)33326-3.
3. Stewart BW, Wild CP. World cancer report 2014. https://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014. Updated 2022. Accessed 14 April 2022.
4. Martei Y, Vanderpuye V, Jones B. Fear of mastectomy associated with delayed breast cancer presentation among Ghanaian women. *Oncologist*. 2018;23:1446-1452. doi:10.1634/theoncologist.2017-0409.
5. Čačala S, Gilart J. Factors relating to late presentation of patients with breast cancer in Area 2 KwaZulu-Natal, South Africa. *J Glob Oncol*. 2017;3:497-501. doi:10.1200/jgo.2016.008060.
6. De Lena M, Varini M, Zucali R, et al. Multimodal treatment for locally advanced breast cancer. Result of chemotherapy-radiotherapy versus chemotherapy-surgery. *Cancer Clin Trials*. 1981;4:229-236.
7. Perloff M, Lesnick GJ, Korzun A, et al. Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. *J Clin Oncol*. 1988;6:261-269. doi:10.1200/JCO.1988.6.2.261.
8. Touboul E, Buffat L, Lefranc JP, et al. Possibility of conservative local treatment after combined chemotherapy and preoperative irradiation for locally advanced noninflammatory breast cancer. *Int J Radiat Oncol Biol Phys*. 1996;34:1019-1028. doi:10.1016/0360-3016(95)02207-4.
9. Ring A, Webb A, Ashley S, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? *J Clin Oncol*. 2003;21:4540-4545. doi:10.1200/JCO.2003.05.208.
10. Daveau C, Savignoni A, Abrous-Anane S, et al. Is radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy? *Int J Radiat Oncol Biol Phys*. 2011;79:1452-1459. doi:10.1016/j.ijrobp.2010.01.003.
11. De Los Santos JF, Cantor A, Amos KD, et al. Magnetic resonance imaging as a predictor of pathologic response in patients treated with neoadjuvant systemic treatment for operable breast cancer. Translational Breast Cancer Research Consortium trial 017. *Cancer*. 2013;119:1776-1783. doi:10.1002/cncr.27995.
12. Tasoulis MK, Lee H, Yang W, et al. Accuracy of post–neoadjuvant chemotherapy image-guided breast biopsy to predict residual cancer. *JAMA Surg*. 2020;155:e204103. doi:10.1001/jamasurg.2020.4103.
13. 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;40:1903-1915. doi:10.1200/JCO.21.02439.
14. Heil J, Schaefgen B, Sinn P, et al. Can a pathological complete response of breast cancer after neoadjuvant chemotherapy be diagnosed by minimal invasive biopsy? *Eur J Cancer*. 2016;69:142-150. doi:10.1016/j.ejca.2016.09.034.
15. Kuerer HM, Rauch GM, Krishnamurthy S, et al. A clinical feasibility trial for identification of exceptional responders in whom breast cancer surgery can be eliminated following neoadjuvant systemic therapy. *Ann Surg*. 2018;267:946-951. doi:10.1097/SLA.0000000000002313.
16. van der Noordaa M, van Duijnhoven FH, Loo CE, et al. Identifying pathologic complete response of the breast after neoadjuvant systemic therapy with ultrasound guided biopsy to eventually omit surgery: study design and feasibility of the MICRA trial (Minimally Invasive Complete Response Assessment). *Breast*. 2018;40:76-81. doi:10.1016/j.breast.2018.04.015.
17. Rea D, Tomlins A, Francis A. Time to stop operating on breast cancer patients with pathological complete response? *Eur J Surg Oncol*. 2013;39:924-930. doi:10.1016/j.ejso.2013.06.005.
18. van Loevezijn AA, van der Noordaa M, van Werkhoven ED, et al. Minimally invasive complete response assessment of the breast after neoadjuvant systemic therapy for early breast cancer (MICRA trial): interim analysis of a multicenter observational cohort study. *Ann Surg Oncol*. 2021;28:3243-3253. doi:10.1245/s10434-020-09273-0.
19. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. *Ann Surg Oncol*. 2018;25:1783-1785. doi:10.1245/s10434-018-6486-6.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247. doi:10.1016/j.ejca.2008.10.026.
21. Khare S, Singh T, Santosh I, Laroiya I, Singh G. Wire- and ultrasound-guided localization: a novel technique for excision of nonpalpable breast tumors. *Breast Cancer*. 2020;14:1178223420938068. doi:10.1177/1178223420938068.
22. *Clinical calculators – examples of gross & microscopic evaluation*. MD Anderson Cancer Center. https://www.mdanderson.org/education-and-research/resources-for-professionals/clinical-tools-and-resources/clinical-calculators/residual-cancer-burden-calculator/clinical-calculators-examples-of-gross-microscopic-evaluation.html. Updated 2022. Accessed 14 April 2022.
23. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35:561-564. doi:10.1200/JCO.2016.71.0947.
24. Shubeck SP, Morrow M, Dossett LA. De-escalation in breast cancer surgery. *NPJ Breast Cancer*. 2022;8:25. doi:10.1038/s41523-022-00383-4.
25. Imaging neoadjuvant therapy response in breast cancer. Radiology. https://pubs.rsna.org/doi/full/10.1148/radiol.2017170180. Updated 2022. Accessed 14 April 2022.
26. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. *J Clin Oncol*. 2021;39:1485-1505. doi:10.1200/JCO.20.03399.