ORIGINAL ARTICLE

A Retrospective Cohort Study Assessing Ability of Radiological Investigations to Predict Axillary Nodal Status in Breast Cancer

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ABSTRACT

Background: In the past few decades, due to complications of axillary surgery there has been a drive to de-escalate axillary surgery for secondary involvement of axillary lymph nodes with breast cancer.

Objective: This study aims to assess the diagnostic ability of different imaging modalities for accurately predicting axillary lymph node involvement in breast cancer with a particular focus on identifying N2 axillary nodal disease from N1.

Methods: A retrospective cohort of all axillary dissections for breast cancer performed in Basildon University Hospital in the last 3 years (2021-2024) were assessed. Axillary lymph node status on pre-operative imaging was compared with histological lymph node yield. A subgroup of patients without neo-adjuvant chemotherapy was also assessed. The ability of imaging modalities to predict lymph nodes positive for metastasis, especially N2 disease (number of metastatic nodes of more than 3) was assessed using the ROC curve. Sensitivity and specificity were also computed.

Results: There was a total of 133 patients, 131 females (98.5%) and 2 males (1.5%). 36 patients had neoadjuvant chemotherapy (NACT). The false negative rate of identification of any lymph node metastasis was as follows: US (n=40/133, 30.1%), CT (n=48/125, 38.4%), MRI (60/98, 61.2%), and PET CT (n=11/34, 32.3%). The sensitivity for identifying the N2 axillary nodal stage for US, CT, MRI, and PET CT was 36.4%, 48.7%, 17.6%, and 53.3% respectively. The specificity for identifying those without N2 axillary nodal stage for US, CT, MRI, and PET CT was 88.2%, 78.4%, 93.3%, and 60.0% respectively. The area under the curve (AUC) for accuracy in the prediction of N2 nodal disease for US, CT, MRI, and PET CT was 0.62, 0.64, 0.55, and 0.58 respectively.

Conclusion: None of the imaging modalities had high accuracy in the prediction of the N2 axillary nodal stage. CT and PET CT had higher sensitivity in predicting the N2 axillary nodal stage, and MRI scans had the highest specificity in identifying those patients who did not have N2 axillary nodes.

Keywords: *Breast cancer, axillary lymph nodes, CT scan, ultrasound for axillary lymph nodes, imaging versus histology for axillary lymph nodes.*

INTRODUCTION

Breast cancer is one of the most common cancers in females [1], accounting for 15% of cancer-related deaths. Expected 5-year survival is 98% in patients with disease confined to the breast; however, it drops to 85% in those with axillary node involvement [2].

Axillary lymph node (ALN) involvement is the most important factor in predicting survival and risk of recurrence. The nodal status will determine the type of surgery, adjuvant therapy, type of reconstruction, and post-op radiotherapy [1]. Hence ALN status is a key factor for staging breast cancer and for assessing the prognosis and therefore deciding on appropriate treatment [2]. The nodal staging in breast cancer is based on several positive nodes identified in the axilla and abnormal internal mammary nodes. Usually, up to 3 nodes with macro-metastasis in the axilla are regarded as N1 stage and 4 to 9 nodes are considered N2 stage without abnormal nodes in the internal mammary chain, or only the presence of internal mammary nodes in the absence of ALN [2].

Ultrasound has been used as a primary modality to predict nodal status in breast cancer [2, 3]. CT scans and MRIs are advantageous as they are less operator-dependent and can assess axillae with reasonable accuracy irrespective of the patient's body habitus [4].

Axillary lymph node dissection has been traditionally used as a standard procedure to stage and treat axilla in node-positive breast cancer patients [5]. However, axillary lymph node dissection is associated with significant morbidity: lymphoedema, paraesthesia, and functional problems to name a few [6, 7]. De-escalation of axillary surgery has been a primary focus in breast cancer management [1, 3]. Studies have also shown axillary node clearance to have no further survival benefit in patients with low axillary nodal burden [3]. It is mainly used to stage the axilla to dictate the adjuvant therapy [3].

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Advancements in technology have led to an increasing focus on finding nonoperative methods to assess axillary node involvement in cancer, including the use of CT scans and other imaging modalities to predict nodal status in breast cancer [6]. Despite ongoing research in this area, there is still no consensus on the best modality for predicting nodal metastasis in breast cancer. In this study, we compared the diagnostic abilities of ultrasound (US), CT, and MRI with histopathology for accurately predicting axillary lymph node involvement in breast cancer. The study aimed to identify the imaging modality that can be most helpful in identifying patients with N2 axillary nodal disease so that the patients who do not have N2 disease can have de-escalation of oncological therapy and axillary surgery.

METHODS

This is a single-centre retrospective cohort study conducted at Basildon University Hospital, Essex, UK. All patients who underwent axillary lymph node dissection (ALND) for breast cancer from January 1, 2021, to December 31, 2023, were included in this study. Patients who did not undergo ALND were excluded. Data was collected retrospectively from patients' electronic records. We gathered information on the number of axillary lymph nodes (ALN) predicted by various radiological investigations and compared these predictions with the histologically confirmed lymph nodes post-ALND. Additionally, we included various clinical, biological, and histological parameters such as BMI, smoking status, menopause status, histological tumor type, genetic testing results, receptor status, and details of neo-adjuvant and adjuvant therapies, including hormonal therapy, chemotherapy, and radiotherapy.

Pre-operative prediction of the nodal status of the imaging modality was assessed. The number of positive or abnormal nodes estimated by the imaging modality was recorded in all patients who underwent breast cancer surgery. They either had primary axillary node clearance with breast surgery, wide local excision, or mastectomy, or they had sentinel node biopsy followed by completion axillary node clearance. ALND was used as a standard to assess the ability of imaging modalities to predict abnormal nodes. In patients who had neoadjuvant chemotherapy or neoadjuvant hormone manipulation, the treatment response could be evident in the histology of the axillary nodes in the form of fibrosis. In these patients, the total number of positive nodes after the neoadjuvant therapy included all nodes with macro-metastasis, micro-metastasis, and fibrosis. Descriptive statistics were carried out for different clinical parameters of the sample population. John Hopkins Medicine ROC curve calculator was used to calculate the accuracy of each imaging modality along with their false negative rates. Diagnostic acuracy parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were also computed.

RESULTS

The study included a total of 133 patients, comprising 131 females (98.5%) and 2 males (1.5%). The mean age of the study population was 60.3 (SD 14.4) years, and the mean BMI was 29.3 (SD 6.6).

Among the participants, 46 patients (34.7%) were smokers, and 9 patients (6.8%) had a strong family history of breast cancer, with hereditary gene mutations identified in 2 patients (1.5%). There were 101 post-menopausal patients (75.9%). The histological outcomes of the patients in the study are described in Table **1**.

Table 1: Histological characteristics of study population. IDC (invasive Ductal carcinoma), ILC (invasive lobular carcinoma), ER (Estrogen receptor), PR (Progesterone receptor).

Study Population Histopathology	**No. of Patients**	**Percentage**
IDC	116	87.9
ILC	13	9.8
Others	4	3.0
ER receptor score		
Score 5-6	5	3.7
Score 7-8	91	68.4
PR receptor score		
Score 5-6	13	9.8
Score 7-8	58	43.6
HER2 positive status	13	9.8
Triple negative breast cancer	13	9.8
T3/4 tumours	30	22.6

A total of 36 patients received neoadjuvant chemotherapy (NACT), with 20 (55.6%) showing a partial response and 10 (27.8%) showing a complete response. Similarly, 8 patients received neoadjuvant endocrine therapy (NAET), with 4(50%) having a partial response and 4(50%) achieving a complete response. Post-operative radiotherapy to the breast was administered to 88 patients (66.2%).

A subset of 34 patients underwent sentinel node biopsy. The mean positive node yield was 1.14, and the mean total number of nodes excised was 2.51. In those who had a completed axillary node clearance (ANC), additional positive nodes were found in 10 patients (29.4%), and 3 patients (8.8%) had their nodal staging upgraded

Table 2: Ability of different imaging modalities to differentiate between N1 and N2 nodal disease.

Imaging	Sensitivity	Specificity	PPV	NPV	FNR	FPR	AUC Curve
US (n=129)	36.4%	88.2%	76.7%	76.5%	45.4%	11.7%	0.62
CT (n=112)	48.7%	78.4%	58.7%	72.3%	51.3%	21.6%	0.64
MRI (n=49)	17.6%	93.3%	88.2%	53.3%	82.4%	6.7%	0.55
PET CT (n=35)	53.3%	60.0%	46.7%	65.0%	46.7%	40.0%	0.58

Table 3: Subgroup analysis: Ability of different imaging modalities to differentiate between N1 and N2 disease in non NACT group.

Imaging	Sensitivity	Specificity	PPV	NPV	FNR	FPR	AUC Curve
US (n=88)	25%	94.2%	91.7%	50.9%	75%	5.8%	0.59
CT (n=85)	40%	88.9%	83.3%	60.0%	60%	11.1%	0.64
MRI (n=38)	12.5%	100%	100%	17.6%	87.5%	0%	0.56
PET CT (n=22)	38.5%	77.8%	84.6%	11.1%	61.5%	22.2%	0.58

from N1 to N2. The mean number of positive nodes for metastasis in the ANC was 2.9 (SD 3.7), and the mean total number of nodes excised was 12.6 (SD 6.5).

The false negative rate of identification of any lymph node metastasis was as follows: US (n=40/133, 30.1%), CT (n=48/125, 38.4%), MRI (60/98, 61.2%), and PET CT (n=11/34, 32.3%). The false negative rate of identification of any lymph node metastasis in the patients without NACT was as follows: US (n=29/90, 32.2%), CT (n=29/85, 34.12%), MRI (7/38, 18.4%), and PET CT (n=10/22, 45.4%).

The accuracy of different imaging modalities in differentiating between N1 and N2 is provided in Table **2**.

Subgroup analysis was conducted to check the accuracy of different imaging modalities in differentiating between N1 and N2 in patients who did not have NACT. 97 patients did not have NACT. Among this group, 90 patients had US, 77 patients had CT scans, 33 patients had MRI and 22 patients had PET CT. The accuracy of each imaging modality is shown in Table **3**. ROC (Receiver operating characteristic) curves for US, CT, and MRI from our study sample are shown in **Figs. (1-3)** respectively.

DISCUSSION

This study has aimed to assess the predictive ability of different imaging modalities for axillary nodal staging when compared with histologically confirmed lymph node yield after axillary lymph node dissection. The false negative rate of different imaging modalities to detect axillary macro-metastasis in the axilla was more than 30%. The sensitivity to predict the N2 stage was higher for CT and PET/CT scans. On the other hand, MRI was most specific in identifying patients who did not have N2 axillary nodal metastasis. Similarly, in subgroup

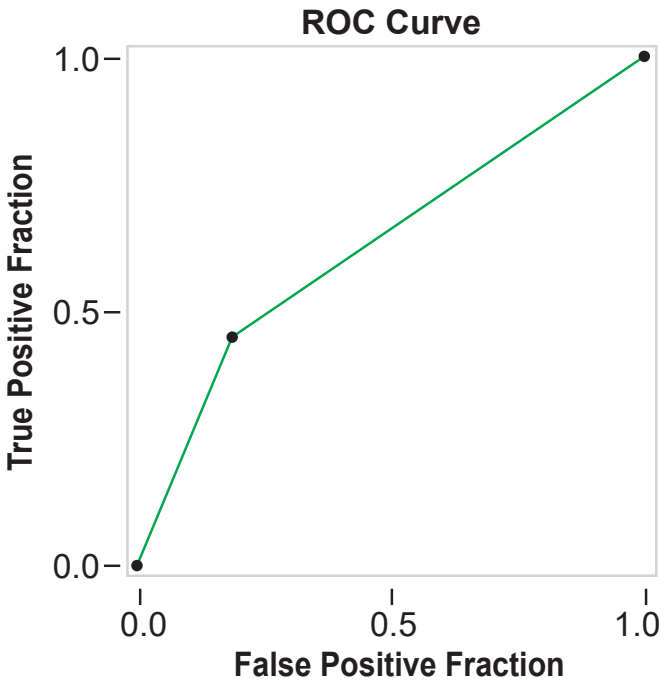

Fig. (1): ROC curve showing accuracy of US scan for detection of metastatic axillary lymph node.

analysis for the patients who did not have NACT, the sensitivity to detect the N2 nodal axillary nodal stage was higher for CT and PET CT. MRI was most specific in detecting those who do not have N2 disease. Overall, the accuracy of most imaging modalities was not higher than 0.70 on the AUC curve.

Few studies have compared radiologically predicted lymph node status with histologically confirmed axillary lymph node (ALN) involvement in breast cancer [8, 9].

A meta-analysis by Morwenn Le Boulc'h *et al*. reported the following sensitivities and specificities: ultrasound (US) had a sensitivity of 55% and a specificity of 99%; MRI had a sensitivity of 83% and a specificity of 85%;

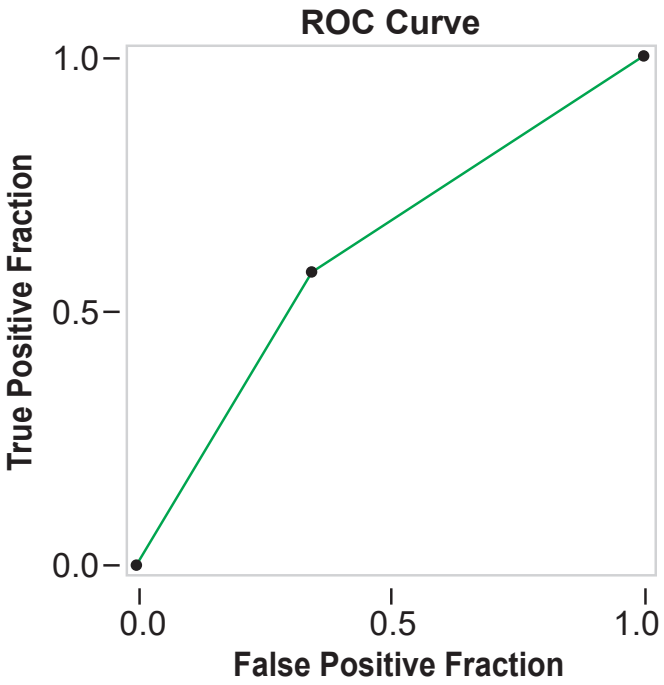

Fig. (2): ROC curve showing accuracy of CT scan for detection of metastatic axillary lymph node.

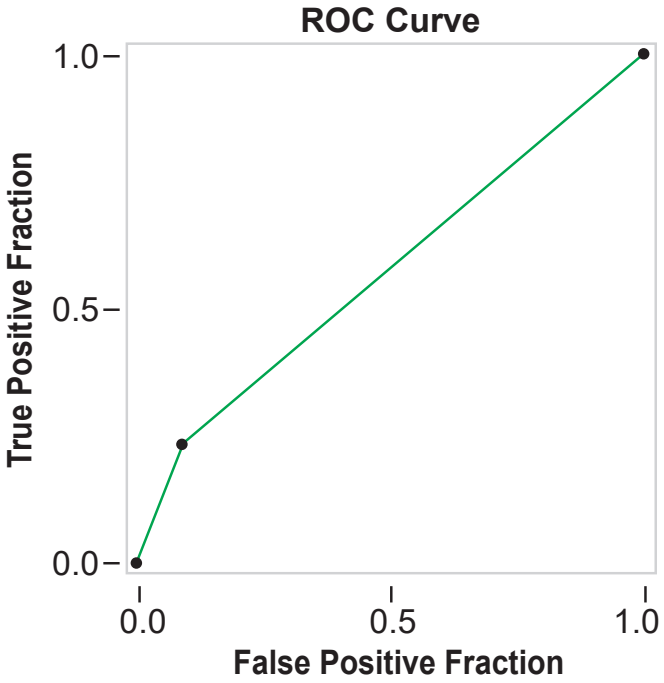

Fig. (3): ROC curve showing accuracy of MRI scan for detection of metastatic axillary lymph nodes.

PET had a sensitivity of 49% and a specificity of 94% [10]. This meta-analysis and systematic review did not include node-positive patients or those who received neoadjuvant chemotherapy in their study. The findings of a study by Sameie *et al.* suggest that none of the imaging modalities are highly accurate in the detection of N2 axillary nodal involvement [11]. MRI scan was highly specific in detecting those patients who did not have N2-3 axillary node metastasis [11]. This can be very important in clinical settings and de-escalated surgical treatment of axilla can only be considered after thorough radiological investigation or wire-guided SLNB [12].

In breast surgery, there have been efforts to avoid axillary node clearance due to its detrimental effects on quality of life (QOL) including chronic pain, numbness of the upper arm, limited mobility of the arm, and other physical, emotional, and sexual aspects, compared to sentinel lymph node biopsy (SLNB) or nonoperative management of the axilla [6, 7]. The ongoing SENOMAC and INSEMA trials provide valuable insights into how axillary surgery affects QOL and support the de-escalation of surgical management of the axilla [13]. Notably, the SENOMAC trial is unique in its inclusion of T3 tumors, whereas other trials primarily focus on early-stage tumors. The oncological outcomes of these trials are still pending [13].

It is important to mention the ACOSOG Z0011 trial, which significantly altered the management of metastatic axillary lymph nodes by demonstrating the non-inferiority of sentinel lymph node biopsy (SLNB) compared to axillary lymph node dissection (ALND) for node-negative T1 and T2 breast cancers in terms of overall survival [8]. The trial showed that patients with 1 or 2 positive sentinel lymph nodes could be effectively treated with breast-conserving surgery (BCS) and systemic adjuvant therapy, rather than undergoing ALND. Before this trial, ALND was considered the gold standard for achieving disease control in cases with positive sentinel lymph nodes [8, 9].

The integration of radiomics or artificial intelligence (AI) with imaging and clinicopathological parameters to predict axillary nodal metastasis appears promising and could transform surgical practice in breast cancer [1, 14]. Radiomics, a recent development leveraging AI, extracts quantitative data from traditional imaging modalities—such as ultrasound [14], MRI [15], CT, or PET/CT [16] and uses this information to create models that objectively quantify lesion heterogeneity, particularly in oncology [14]. Radiomics has been successfully used to preoperatively assess lymph node metastasis in various cancers and shows potential in predicting axillary lymph node involvement in breast cancer, thereby offering insights into prognosis [14, 16].

Neoadjuvant oncological treatment is based on the initial nodal staging predicted by the imaging. If any of the imaging shows N2 disease in the axilla, the patient may be offered aggressive neoadjuvant chemotherapy [17], a higher dose of radiotherapy, or radiotherapy

to the chest wall and regional nodes, which in turn dictates the timing and type of reconstruction offered [18]. Patients with positive axillary nodes post neoadjuvant chemotherapy are treated with ALND or targeted ALND [19]. ATNEC trial is a vital study being conducted in UK. It offers sentinel node biopsy to patients with N1 disease on diagnosis and good response to neoadjuvant chemotherapy. Those with N2 disease are excluded from the study and cannot avoid axillary node clearance.

Our study has several limitations. The study is prone to selection bias as it is a non-randomized cohort study. The effect of neoadjuvant chemotherapy can turn macro-metastasis into fibrosis, however, if there is limited disease or micro-metastasis then this effect may not be conspicuous on histology [20]. It may not be relevant to this study as our study has focused on nodes with macro-metastasis. The number of patients receiving MRI and PET scans was relatively small due to the specialized nature of these investigations, which are typically used after neoadjuvant chemotherapy or for advanced or recurrent cancers. Additionally, this is a retrospective study with a relatively small sample size.

CONCLUSION

None of the imaging modalities were very accurate in predicting N2 nodal staging. The sensitivity to predict the N2 stage was higher for CT and PET/CT scans. On the other hand, MRI was most specific in identifying patients who did not have N2 axillary nodal metastasis.

ETHICS APPROVAL

This study/audit was approved by Audit Department of Mid and South Essex NHS Foundation Trust, registered as GSURG075. All procedures performed in studies involving human participants were following the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

All data is taken from electronic records of patients and is mentioned in the methods.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Nida Bashir: Data collection, manuscript writing, editing, referencing and correspondence.

Ahsan Rao: Data analysis, results formulation, editing, supervision and liaison.

Danny Fraser: Data collection

Fatema Rezai: Data collection

Sanjith Navas: Data collection

REFERENCES

1. Chen MY, Gillanders WE. Staging of the axilla in breast cancer and the evolving role of axillary ultrasound. Breast Cancer (Dove Med Press) 2021; 13: 311-23.
DOI: https://doi.org/10.2147/BCTT.S273039
2. Chang JM, Leung JWT, Moy L, Ha SM, Moon WK. Axillary nodal evaluation in breast cancer: state of the art. Radiology 2020; 295(3): 500-15.
DOI: https://doi.org/10.1148/radiol.2020192534
3. Ngai V, Tai JCJ, Taj S, Khanfar H, Sfakianakis E, Bakalis A, *et al*. Non-invasive predictors of axillary lymph node burden in breast cancer: a single-institution retrospective analysis. Breast Cancer Res Treat 2022; 195(2): 161-9.
DOI: https://doi.org/10.1007/s10549-022-06672-7
4. Lernevall A. Imaging of axillary lymph nodes. Acta Oncol 2000; 39(3): 277-81.
DOI: https://doi.org/10.1080/028418600750013014
5. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, *et al*. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11(10): 927-33.
DOI: https://doi.org/10.1016/S1470-2045(10)70207-2
6. Land SR, Kopec JA, Julian TB, Brown AM, Anderson SJ, Krag DN, *et al*. Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32. J Clin Oncol 2010; 28(25): 3929-36.
DOI: https://doi.org/10.1200/JCO.2010.28.2491
7. Magnoni F, Galimberti V, Corso G, Intra M, Sacchini V, Veronesi P. Axillary surgery in breast cancer: an updated historical perspective. Semin Oncol 2020; 47(6): 341-352.
DOI: https://doi.org/10.1053/j.seminoncol.2020.09.001
8. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, *et al*. Effect of axillary dissection *vs* no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA 2017; 318(10): 918-26.
DOI: https://doi.org/10.1001/jama.2017.11470
9. Man V, Luk WP, Fung LH, Kwong A. The role of pre-operative axillary ultrasound in assessment of axillary tumor burden in breast cancer patients: a systematic review and meta-analysis. Breast Cancer Res Treat 2022; 196(2): 245-54.
DOI: https://doi.org/10.1007/s10549-022-06699-w

10. Le Boulc'h M, Gilhodes J, Steinmeyer Z, Molière S, Mathelin C. Pretherapeutic imaging for axillary staging in breast cancer: a systematic review and meta-analysis of ultrasound, MRI and FDG PET. J Clin Med 2021; 10(7): 1543.
DOI: https://doi.org/10.3390/jcm10071543

11. Samiei S, van Nijnatten TJA, van Beek HC, Polak MPJ, Maaskant-Braat AJG, Heuts EM, *et al*. Diagnostic performance of axillary ultrasound and standard breast MRI for differentiation between limited and advanced axillary nodal disease in clinically node-positive breast cancer patients. Sci Rep 2019; 9(1): 17476.
DOI: https://doi.org/10.1038/s41598-019-54017-0

12. Abel MK, Greenwood H, Kelil T, Guo R, Brabham C, Hylton N, *et al*. Accuracy of breast MRI in evaluating nodal status after neoadjuvant therapy in invasive lobular carcinoma. NPJ Breast Cancer 2021; 7(1): 25.
DOI: https://doi.org/10.1038/s41523-021-00233-9

13. Appelgren M, Sackey H, Wengström Y, Johansson K, Ahlgren J, Andersson Y, *et al*. SENOMAC Trialists' Group. Patient-reported outcomes one year after positive sentinel lymph node biopsy with or without axillary lymph node dissection in the randomized SENOMAC trial. Breast 2022; 63: 16-23.
DOI: https://doi.org/10.1016/j.breast.2022.02.013

14. Tang YL, Wang B, Ou-Yang T, Lv WZ, Tang SC, Wei A, *et al*. Ultrasound radiomics based on axillary lymph nodes images for predicting lymph node metastasis in breast cancer. Front Oncol 2023; 13:1217309.
DOI: https://doi.org/10.3389/fonc.2023.1217309

15. Samiei S, Granzier RWY, Ibrahim A, Primakov S, Lobbes MBI, Beets-Tan RGH, *et al*. Dedicated axillary mri-based radiomics analysis for the prediction of axillary lymph node metastasis in breast cancer. Cancers (Basel) 2021; 13(4): 757.
DOI: https://doi.org/10.3390/cancers13040757

16. Inchingolo R, Maino C, Cannella R, Vernuccio F, Cortese F, Dezio M, *et al*. Radiomics in colorectal cancer patients. World J Gastroenterol 2023; 29(19): 2888-2904.
DOI: https://doi.org/10.3748/wjg.v29.i19.2888

17. Kim R, Osaki A, Tanabe K, Toge T. Neoadjuvant chemotherapy for local advanced breast cancer with stage IIIB. Oncol Rep 2004; 11(6): 1265-72.

18. de Wild SR, Koppert LB, van Nijnatten TJA, Kooreman LFS, Vrancken Peeters MTFD, Smidt ML, *et al*. Systematic review of targeted axillary dissection in node-positive breast cancer treated with neoadjuvant systemic therapy: variation in type of marker and timing of placement. Br J Surg 2024; 111(3): 071.
DOI: https://doi.org/10.1093/bjs/znae071

19. Matuschek C, Jazmati D, Bölke E, Tamaskovics B, Corradini S, Budach W, *et al*. Post-neoadjuvant treatment strategies in breast cancer. Cancers (Basel) 2022; 14(5): 1246.
DOI: https://doi.org/10.3390/cancers14051246

20. Viale G, Fusco N. Pathology after neoadjuvant treatment - How to assess residual disease. Breast 2022; 62(Suppl 1): S25-8.
DOI: https://doi.org/10.1016/j.breast.2021.11.009