Original Article

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Comparing the Efficiency of Imaging Modalities in Detection of Recurrent Breast Cancer

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ABSTRACT

Objective: To investigate the effectiveness of the different imaging modalities in detecting recurrence in breast cancer follow-up.

Materials and Methods: Sixty-four women with recurrent breast cancer were examined between January 2020 and July 2022. Recurrency was divided into four categories: local; regional; second primary; and distant metastasis. The detectability of recurrent lesions with mammography (MG), ultrasound (US) and magnetic resonance imaging (MRI), was evaluated. In addition, recurrences that firstly appeared by positron emission tomography (PET) scan were recorded.

Results: Twenty-seven (42.2%) recurrences were local, 10 (15.6%) were regional and 27 (42.2%) were second primary. Forty-six (71.9%) of them were determined to have invasive carcinoma, 8 (12.5%) were ductal carcinoma *in situ*, and 10 (15.6%) were axillary metastases. Eight (12.5%) of them were first diagnosed by PET-computed tomography/MRI. Among the available images performed, 78.7% could be detected pathologically by MG, 95.2% by US, and 100% by MRI. Distant metastasis associated with other types of recurrence was detected in 6 (9.4%) cases.

Conclusion: MRI is the most powerful imaging modality in detecting recurrent breast cancer. With the addition of US to routine MG follow-up, a higher rate and early detection of recurrent cancers can be achieved.

Keywords: Breast cancer; magnetic resonance imaging; mammography; recurrence; ultrasound

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Key Points

- Mammography and ultrasound (US) are complementary modalities in breast cancer follow-up.
- US and magnetic resonance imaging (MRI) are the most potent imaging modalities in detecting breast cancer recurrence.
- Axillary US increases the accuracy of radiological imaging for regional recurrence in experienced hands.
- MRI and positron emission tomography imaging added to the algorithm in selected cases can significantly contribute to the detection of recurrence.

Introduction

The incidence of breast cancer is increasing with the effective use of screening programs and technological developments. According to Globocan 2020 data, breast cancer is the most frequently detected cancer in the female population in Turkey, with more than 24 thousand new cases reported annually (1). Thus, management and outcome have gained increasing importance in patients with breast cancer. Cancer screening and post-treatment follow-up aim to reduce morbidity and mortality rates with early diagnosis. Personal breast cancer history is a significant risk factor for being diagnosed with cancer for the second time (2-4). It has been reported that local recurrence is an independent factor predicting survival, and patients with recurrence have a higher risk for distant metastasis or death compared to non-recurrence patients (5). Each subtype of breast cancer or different gene expression shows different behavioural patterns (6). Particularly, luminal subtypes are expected to show recurrence at a lower rate over many years, while non-luminal subtypes show in the first years after initial treatment (7, 8). Therefore, it is crucial to understand the natural history of different tumors to detect the presence of residual or recurrence early for intervention.

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There is variability between guidelines for post-surgical follow-up in different disciplines. While some of the considerations in these guidelines are evidence-based, some are at the recommendation level. While some guidelines recommend starting imaging in the sixth month after radiotherapy, many recommend not starting until one year (9). Imaging frequency is recommended to be annual in most of the guidelines (9). However, according to the guidelines, mammography (MG) is the only evidence-based imaging method for detecting recurrence at follow-up (2, 3, 10, 11). However, in many centres, ultrasound (US), magnetic resonance imaging (MRI) and even positron emission tomography (PET) are used in addition to MG. In this process, there is a need for a multidisciplinary approach that includes physicians from different specialities, such as surgeons, radiologists and oncologists.

The aim of this study was to investigate the effectiveness of different imaging modalities in detecting recurrence in post-treatment follow-up in breast cancer to inform physicians.

Materials and Methods

The ethics committee of the University approved this retrospective study (approval number 449166, date: 05.08.2022). Among the cases treated for breast cancer, those who attended for screening or diagnostic purposes between September 2019 and September 2022 were incuded and retrospectively assessed. Cases categorized as Breast Imaging and Reporting Data System (BI-RADS) 4 or 5 according to the imaging findings were included in the study. The exclusion criteria of the study were: i) cases without any suspicious radiological findings for recurrency in follow-up; ii) radiologically suspicious but histopathologically benign lesions; iii) category BI-RADS 4 or 5 lesions with unavailable histopathological diagnosis; and iv) cases with histopathologically proven recurrence but missing imaging findings.

MG, US, and MRI images obtained radiologically were evaluated. The presence of mass, microcalcification, asymmetry, or distortion in MG and a vascularized mass or non-mass area on US and abnormal contrast enhancement on MRI was considered pathological. In addition, lesions that arose with abnormal fluorodeoxyglucose uptake with PET-CT/MRI for the first time were recorded.

Detection of tumoral tissue on follow-up images within three months after surgical treatment was considered residual disease. A new tumoral focus developing after this period was considered a recurrence. Recurrent lesions were divided into four groups (Figure 1):

1. Local recurrence - the new tumoral focus at the same site as the first primary after breast-conserving surgery (BCS) or in the chest wall after mastectomy;

2. Regional recurrence - ipsilateral axillary or supraclavicular lymphadenopathy;

3. Second primary - tumoral tissue of different localization or morphology from the primary lesion;

4. Distant metastasis.

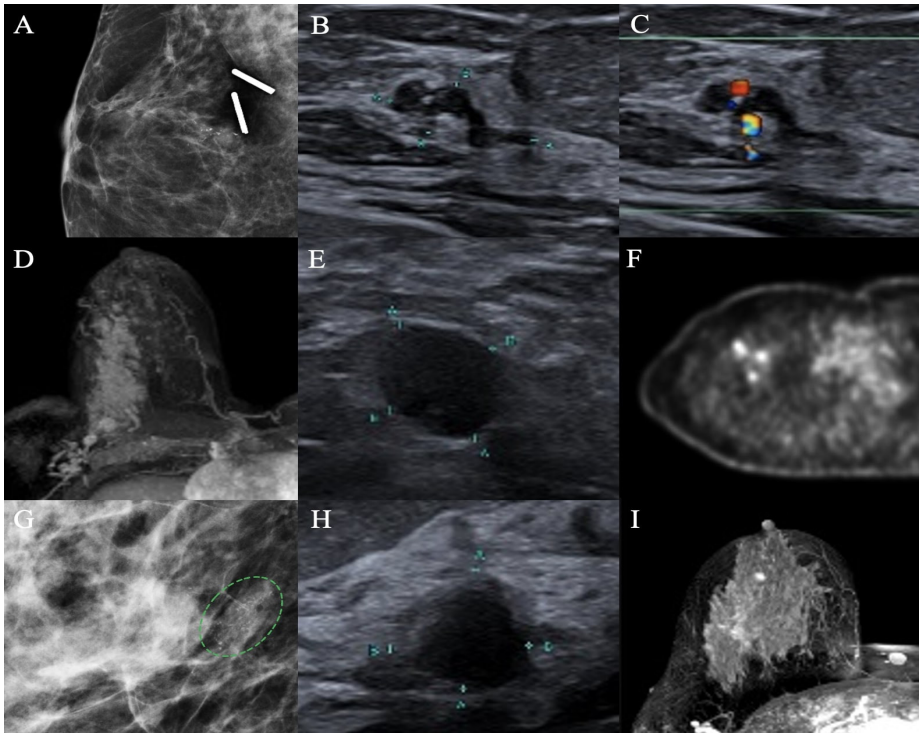

Figure 1. Types of recurrence **(A-C)** Local recurrence in a 55-year-old woman with a history of IDC. Indistinct density and accompanying microcalcifications in the operation site on the right MLO view and a non-mass hypoechoic area associated microcalcifications on US diagnosed as IDC **(D-F)** Regional recurrence in a 53-year-old woman with a history of grade 3 DCIS with microinvasive carcinoma. Preoperative MRI demonstrating extensive non-mass enhancement of DCIS, US shows ALN metastasis with the absence of hilar echogenicity **(G-I)** Secondary primary in a 50-year-old with a history of grade 2 IDC. MG shows a cluster of pleomorphic microcalcifications, while US and MRI demonstrate a mass appearance at the retro areolar area diagnosed as IDC

IDC: invasive ductal carcinoma; US: ultrasound; MRI: magnetic resonance imaging, MG: mammography; DCIS: ductal carcinoma in situ; MLO: mediolateral oblique

Age, family history, physical examination findings, side, BI-RADS categorization, histopathological diagnosis and timing of the primary and recurrent breast carcinoma, histologic grade, molecular subtype, and axillary status were recorded. Recurrence-free survival time for each case was calculated in months and recorded. In addition, the treatment method of the primary tumor and axillary approach and, if applicable, the treatment protocol of the current tumoral focus were documented.

Recurrent tumors were divided into two groups, with primary pathology being ductal carcinoma *in situ* (DCIS) or invasive carcinoma.

In the descriptive analysis, the frequency of all variables was recorded.

Results

A total of 64 recurrent lesions were identified in the data extraction process. Local recurrence was detected in 27 (42.2%) cases, regional recurrence in 10 (15.6%) and second primary in 27 (42.2%) (Figure 2). Initial and final histopathological results of the recurrences arising during follow-up are detailed in Figure 3. There was no recurrence presenting as distant metastasis, while it was accompanied by the other types of recurrence in six (9.4%) cases. The primary pathology of 11 (17.2%) cases was DCIS with a recurrence-free survival time of 12471.83 months, and 53 (82.8%) were invasive carcinoma with a recurrence-free survival time of 122.576.45 months. Of the invasive carcinomas, 71.9% (n = 46) were luminal, 6.3% (n = 4) were human epidermal growth factor receptor 2-enriched, and 4.7% (n = 3) were in the triple-negative breast cancer subgroup. Family history was positive in only 23.4% of the cases. Demographic data are summarized in Table 1.

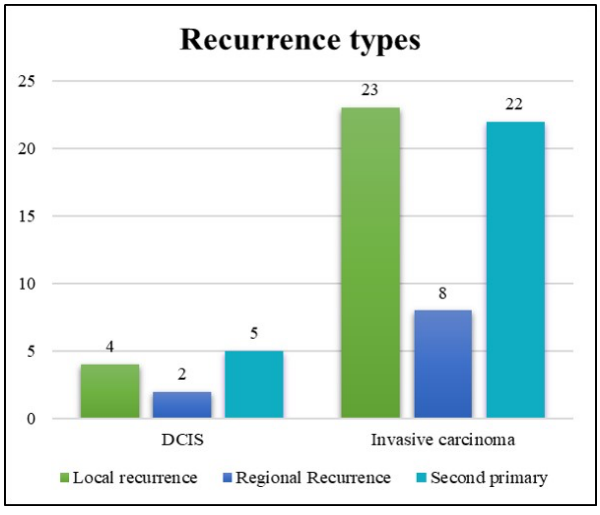

Figure 2. Distribution of the types of recurrence

Table 1. Demographic data

	n = 64
Age, mean ± SD (min–max)	57.96 11.25 (28–89)
Recurrence-free survival time, mean ± SD (min–max) (months)	122.81 75.1 (6–312)
Family history, n (%)	
Yes	15 (23.4)
No	49 (76.6)
Initial tumor side, n (%)	
Left	36 (56.3)
Right	28 (43.7)
Initial diagnosis, n (%)	
DCIS	11 (17.2)
Invasive carcinoma	
Luminal	46 (71.9)
HER2-enriched	4 (6.3)
TNBC	3 (4.7)
Initial axillary operation, n (%)	
None	10 (15.6)
SLNB	22 (34.4)
Dissection	32 (50)
Initial axillary involvement, n (%)	
No	32 (50)
Yes	32 (50)

DCIS: ductal carcinoma *in situ*; HER2: human epidermal growth factor receptor 2; SD: standard deviation; SLNB: sentinal lymph node biopsy; TNBC: tripple negative breast cancer

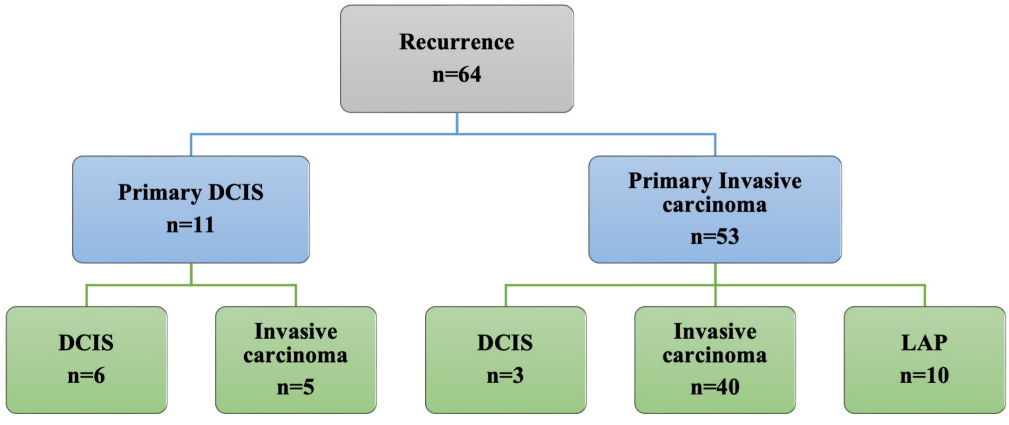

Figure. 3. Initial and final histopathologies of cases with recurrence

In 26.5% (n = 17), MG could not be obtained due to mastectomy or other reasons. Breast density was type A in 1.6% (n = 1), type B in 31.2% (n = 20), type C in 39.1% (n = 25) and type D in 1.6% (n = 1). In cases with type B, US could detect regional (axillary) recurrences that MG could not detect in three cases and local recurrence in one case, while MG was superior in detecting the second primary in one case. Among type C cases, US could detect regional (axillary) recurrence in two cases, local recurrence in one case and the second primary in one case, which MG could not detect. Both US and MG detected the pathology in cases with type A (n = 1) and type D (n = 1) density.

Among the available images examined, 78.7% of recurrences could be detected pathologically by MG, 95.2% by US, and 100% by MRI. Eight (12.5%) recurrences were first diagnosed by PET-CT/MRI. Of these, six were local, and two were regional recurrences (Figure 4). US was positive in all of these cases while 2 of 3 cases with MG were positive. Physical examination was positive in only two cases. These cases were not scanned by MRI.

Forty-six (71.9%) of recurrent lesions were reported to have invasive carcinoma, 8 (12.5%) were DCIS, and 10 (15.6%) were axillary lymph node metastases. The histologic grades of primary pathology and the type of recurrence are summarized in Table 2.

Initial surgical, local and/or systemic therapies and other relevant demographic data are summarized in Table 3, as the cases were divided into two groups according to the final pathology.

While locoregional recurrence was observed in 71.9% of the cases whose initial operation was BCS, this rate was 43.7% in cases with mastectomy.

The physical examination findings were negative in 80% (n = 8/10) of the cases recurrent with lymphadenopathy (LAP). Among all recurrences, sentinal lymph node biopsy (SLNB) was performed in 22 cases, dissection in 32 cases, and there was no intervention performed in the axilla in 10 cases at the time of initial diagnosis. In 60% of regional recurrences occurring with LAP, no surgical intervention was applied or SLNB was performed, while 40% underwent axillary dissection.

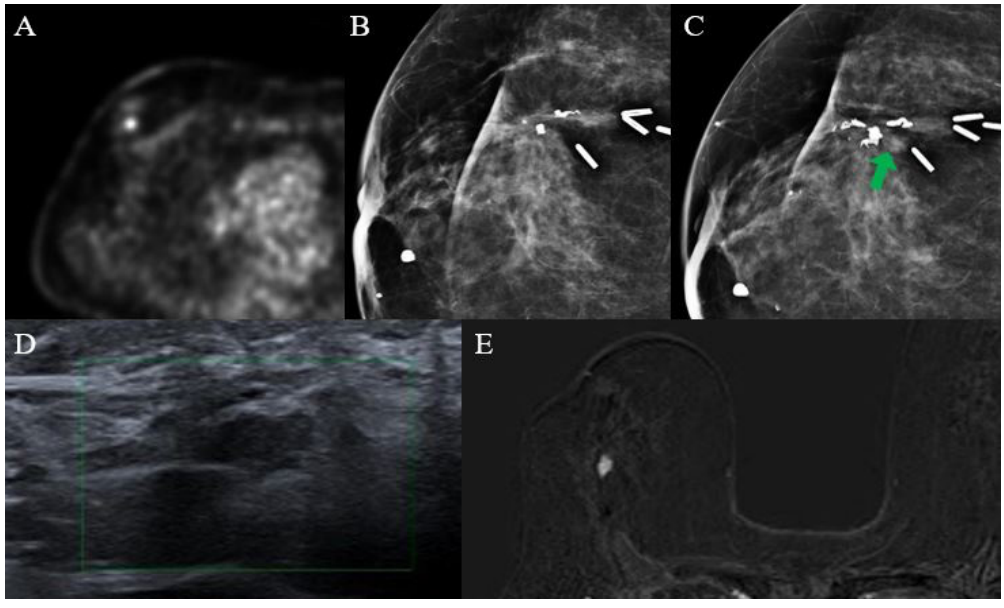

Figure 4. A local recurrence in a 58-year-old woman with a history of mucinous carcinoma **(A)** Abnormal FDG-uptake at the operation site on PET scan **(B)** Postoperative changes on the right CC view that examined in 2018 and followed by consecutive PET scans **(C-E)** But also visible on MG, US and MRI

PET: positron emission tomography; US: ultrasound; MRI: magnetic resonance imaging, MG: mammography; FDG: fludeoxyglucose; CC: craniocaudal

Table 2. The types of primary and recurrent tumors

Recurrent tumor		**Primary tumor**		
		DCIS	**Invasive carcinoma**	**ALN metastasis**
DCIS (n = 11)	n (%)	5 (45.4)	6 (55.6)	-
Invasive carcinoma (n = 53)				
Grade 1 (n = 2)	n (%)	-	1 (50)	1 (50)
Grade 2 (n = 38)	n (%)	3 (7.5)	28 (70)	7 (17.5)
Grade 3 (n = 13)	n (%)	-	11 (84.6)	2 (15.4)

ALN: axillary lymph node; DCIS: ductal carcinoma *in situ*

Table 3. Initial and final status of the disease

		DCIS	Invasive carcinoma
Initial surgery			
Mastectomy	n (%)	6 (54.5)	26 (49)
Breast-conserving surgery	n (%)	5 (45.5)	27 (51)
Hormonal/Chemotherapy			
Yes	n (%)	1 (9)	51 (96.2)
No	n (%)	10 (91)	2 (3.8)
Radiotherapy			
Yes	n (%)	3 (27.2)	30 (56.6)
No	n (%)	8 (72.3)	23 (43.4)
Axillary surgery			
None	n (%)	4 (36.4)	6 (11.3)
SLNB	n (%)	7 (63.6)	15 (28.3)
Dissection	n (%)	-	32 (60.4)
Recurrence-free survival time, mean SD (min–max), months		12471.83 (6-206)	12376.45 (8-312)
Recurrence type			
Local	n (%)	6 (54.5)	22 (41.5)
Regional	n (%)	-	10 (18.9)
Second primary	n (%)	5 (45.5)	21 (39.6)
Distant metastasis	n (%)	-	6 (11.3)
Final imaging purpose			
Screening	n (%)	7 (63.6)	31 (58.5)
Diagnostic	n (%)	4 (36.4)	22 (41.5)
Final physical examination			
Normal	n (%)	7 (63.6)	31 (58.5)
Pathologic	n (%)	4 (36.4)	22 (41.5)
Final BI-RADS			
IV	n (%)	7 (63.6)	25 (47.2)
V	n (%)	4 (36.4)	28 (52.8)

BI-RADS: Breast Imaging and Reporting Data System; DCIS: ductal carcinoma *in situ*; SD: standard deviation; SLNB: sentinal lymph node biopsy

In terms of treatment, 22 patients received systemic treatment, two received only radiotherapy, and 31 received chemoradiotherapy after surgery. Remarkably, there was no treatment given to nine cases.

Of the recurrences, 25 were treated with mastectomy, 15 with BSC, 4 with axillary dissection and 2 with excision. Twelve cases were referred to the medical oncology department for systemic treatment before surgery. While four cases were planned for surgery, the outcome of two cases could not be learned.

Discussion and Conclusion

In the present study, US and MRI were found to be the most effective imaging modalities for detecting the recurrence of breast cancer, with rates of 95.1% and 100%, respectively. Although this rate was recorded as 78.7% for MG, it was remarkable that clinicians' tendency to request MG was lower. Physical examination was positive in only 59.3% of the cases. Therefore, it appears that supporting the algorithm with US and, if necessary, MRI, in addition to physical examination and MG in the post-treatment follow-up will increase the diagnostic efficiency.

Postoperative follow-up in breast cancer aims to prevent treatment-related side effects or complications and to detect possible local/systemic recurrence or a second primary focus as early as possible, ideally while still asymptomatic. Thus, high mortality rates may be prevented because recurrent breast cancer can be successfully treated if detected earlier. In the study of Pawloski et al. (12), patients with mastectomy were found to be at higher risk for recurrence, as index tumors are more aggressive and diagnosed at a more advanced stage. However, it has been reported that the recurrence rate is higher in DCIS patients who underwent BCS compared to mastectomy (12). In the same study, a higher rate of invasive carcinoma was found in recurrences after mastectomy and an equal rate of invasive and *in situ* cancers after BCS (12). Therefore, the authors highlighted that, regardless of the primary surgery, an annual check-up should be performed in every case treated for DCIS (12). In our study population, most patients'

primary pathology was invasive carcinoma (82.8%) and the most frequent type of recurrence was invasive carcinoma (75%).

It has been reported that the frequency of recurrence after mastectomy varies between 2-15% according to the tumor type and stage. The recurrence most frequently occurs in the skin and subcutaneous soft tissue adjacent to the pectoral muscle (13). Physical examination is one of the most critical steps in follow-up. However, physical examination alone is not reliable. It has been stated that MRI can be advantageous in the presence of suspicious physical examination findings, and some clinicians primarily advocate MRI for follow-up for implant integrity (13). In the present study, there was no significant physical examination finding in any of the cases smaller than 1 cm and any of the regional recurrences with LAP. Physical examination was negative in 59.4% of the cases. Most of them were regional recurrence to the axilla or second primary. These results reinforce the importance of radiological imaging.

MG, on the other hand, is the primary imaging method for the breast, used for both screening and diagnostic purposes. It is also used in the follow-up of successfully treated breast cancer. Annual screening MG after BSC is recommended by many authors (9, 14). Henderson et al. (15) indicated that in the early postoperative period, imaging was performed more frequently than recommended in the guidelines with different modalities, while the tendency to use imaging over time decreased after surgery. It has also been stated that MG can detect lesions with a better prognosis in the early period compared to the other techniques, and the survival rate is higher in MG-detected lesions (16). However, the sensitivity and specificity of MG in women treated for breast cancer are lower than in women without cancer (17-19). Furthermore, on MG imaging findings suggestive of recurrence the similar to findings in malignancy (20).

US may complement MG and is also a highly effective imaging modality for chest wall and axillary evaluation where MG is insufficient (21). For this reason, US is used in follow-up to investigate locoregional recurrence in patients with mastectomy. In addition, US provides additional information in distinguishing between postoperative changes and local recurrence. US imaging is recommended at regular intervals in the postoperative period (22, 23). In the present study, US did not detect recurrence in only three cases; one was a subpectoral mass, one was DCIS, and the other was LAP.

Breast MRI is more sensitive for detecting cancer than MG and US (21). However, evidence about the post-treatment role of MRI in breast cancer is limited. Especially after the first year of surgery, MRI has been reported to have high sensitivity and specificity in differentiating postoperative changes and recurrent breast cancer (24, 25). However, Park et al. (26), after reviewing over one thousand MRI examinations, reported that MRI was more effective after the third year of surgery. In addition, some authors have highlighted that women with personal breast cancer, especially after BCS, benefited greatly from MRI scanning (26). Thus, this use of MRI for follow-up is still controversial due to the lack of conclusive evidence. In the present study, 48.4% of the cases were scanned with MRI, and all recurrences were successfully detected.

The sensitivity of PET imaging in detecting breast cancer recurrence has been reported to range from 89–100% (27). However, in addition to containing radiation exposure, the lack of anatomical and morphological details reduces its specificity (28). In our case series, all PET-detected recurrences were demonstrated by conventional imaging prior to undergoing PET. When evaluated with other imaging methods, all but one axillary LAP, which could not be detected on US, could be seen. This finding shows that US is a valuable method for the follow-up and has high accuracy in experienced hands.

There are some limitations of this study. First, this is not a cancer outcome study. We only included the cases detected for recurrence in a limited period of time. Second, most cases were still having NAC regimens or were on the treatment list. So, it is not possible to report the final outcome for all patients. Third, factors affecting recurrence were not investigated, which were beyond the scope and design of the study. Last, due to the limited number of cases, it was not possible to draw robust conclusions about the ability of the various modalities to detect recurrence in terms of breast density.

MG and US, the primary imaging methods for the breast, are complementary modalities in follow-up. Although not adequately supported in the guidelines, in experienced hands, US can be used effectively to assess regional lymph nodes in addition to the breast. Systematic reviews of clinical trials are needed to support the adoption of US in guidelines. In addition, MRI and PET imaging, added to the algorithm in selected cases, may significantly contribute to the detection of recurrence.

Ethics Committee Approval: This study was approved by Istanbul University-Cerrahpasa, Non-Interventional Clinical Research Ethics Committee on 05.08.2022 with the decision number 449166.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.K., P.K., Y.K., T.O.; Concept: S.A.K., A.B.; Design: S.A.K.; Data Collection and/or Processing: S.A.K., P.K., Y.K., T.O.; Analysis and/ or Interpretation: S.A.K., P.K.; Literature Searching: S.A.K., A.B.; Writing: S.A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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