Original Article

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Is Sentinel Lymph Node Biopsy Necessary in Patients with Ductal Carcinoma in situ of the Breast?

Memenin Duktal Karsinoma İn Situlu Hastalarında Sentinel Lenf Nodu Biyopsisi Gerekli mi?

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ABSTRACT

Objectives: The number of patients diagnosed with ductal carcinoma in situ (DCIS) has increased in the past 20 years with the widespread use of mammography screening. This study aims to investigate which patients with DCIS should undergo sentinel lymph node biopsy (SLNB).

Methods: Between 2008 and 2023, patients diagnosed with DCIS in the General Surgery Clinic were evaluated retrospectively. Age, clinical features, tumor nuclear grade, presence of comedonecrosis, tumor diameter, hormone receptor, presence of microinvasive components, axillary pathology, surgical interventions, locoregional recürrences, overall and disease-free survival information of the patients were evaluated.

Results: Forty-eight patients with a mean age of 52.2+12.4 years (25–76) were included in the study. Mastectomy was performed in 16, breast-conserving surgery in 32, SLNB in 21, axillary dissection in three, and no axillary-directed intervention was performed in 24 patients. Pure DCIS was detected in 44 patients and microinvasive component was detected in four patients (8.3%). No metastasis was detected after axillary sampling. It was statistically significant that a higher proportion of patients who underwent axillary intervention were in the mastectomy group and had diffuse microcalcifications in their mammograms (p<0.001 and p=0.009). Patients were followed up for a mean of 82.5 months, and locoregional recurrence was detected in 3 (6.25%) patients. One of the recurrences was due to DCIS, and the others were due to invasive cancer. The tumor sizes in these cases were above the average tumor size in the study.

Conclusion: Although the absence of axillary metastasis in our study is attributed to the low number of patients and small mean tumor size, routine SLNB might not be performed in patients with DCIS due to the low rate of axillary metastasis. SLNB may be preferred only in cases where mastectomy will be performed.

Keywords: Axilla; ductal carcinoma *in situ*; metastasis; recurrence; sentinel lymph node.

ÖZET

Amaç: Mamografi taramasındaki yaygınlaşma ile duktal karsinoma in situ (DKİS) tanısı konulan hasta sayısı son 20 yılda artış göstermiştir. DKİS, prekanseröz bir lezyon olarak tanımlanmakla birlikte metastaz yapmadığı kabul edilmektedir, ancak literatürde pür DKİS hastalarının %1'inde aksilla metastazı görülmektedir. Çalışmanın amacı, DKİS tanılı hangi hastalara sentinel lenf nodu biyopsisi yapılması gerektiğini araştırmaktır.

Yöntem: 2008-2023 yılları arasında genel cerrahi kliniğinde DKİS tanısı alan hastalar retrospektif olarak değerlendirildi. Hastaların yaş, klinik özellikler, tümör nükleer derecesi, komedonekroz varlığı, tümör çapı, hormon reseptörü, mikroinvaziv komponent varlığı, aksilla patolojileri, yapılan cerrahi girişimler, lökorejiyonal nüksler, genel ve hastalıksız sağkalım bilgileri değerlendirildi.

Bulgular: Ortalama yaşı 52,2±12,4 (25-76) yıl olan 48 hasta çalışmaya alındı. On altısına mastektomi, 32'sine meme koruyucu cerrahi, 21'ine sentinel lenf nodu biyopsisi, üçüne aksiller diseksiyon yapılırken, 24 hastada aksillaya yönelik girişim yapılmadı. Hastaların 44'ünde pür DKİS, 4'ünde (%8,3) mikroinvaziv komponent saptandı. Aksilla örneklemeleri sonucunda metastaz saptanmadı. Aksilla girişimi yapılan hastaların daha yüksek oranda mastektomi grubunda olması ve mamografilerinde difüz mikrokalsifikasyon görülmesi istatistiksel olarak anlamlı bulundu (p<0,001 ve p=0,009). Hastalar ortalama 82,5 ay takip edildi, takip sonucunda üç (%6,25) hastada lökorejyonel nüks saptandı. Saptanan nükslerin biri DKİS, diğerleri invaziv kansere bağlıydı. Bu olgulardaki tümör boyutları çalışmadaki ortalama tümör boyutunun üzerinde idi.

Sonuç: Çalışmamızda aksiller metastaz görülmemesi düşük hasta sayısı ve ortalama tümör boyutunun küçük olmasına bağlanmakla birlikte düşük aksiller metastaz oranı nedeniyle DKİS hastalarına rutin sentinel lenf nodu biyopsisi yapılmayabilir. Sadece mastektomi yapılacak olgularda sentinel lenf nodu biyopsisi tercih edilebilir.

Anahtar sözcükler: Aksilla; duktal karsinoma in situ; metastaz; rekürrens; sentinel lenf nodu.

Breast cancer is the most common cancer worldwide.[1] With the widespread use of mammography and early diagnosis, mortality due to breast cancer has decreased.[2] At the same time, improved chemoradiotherapy has increased survival expectancy. The increase in screening with mammography has also increased the number of patients diagnosed with ductal carcinoma *in situ* (DCIS). DCIS is a proliferative disease limited to ducts and lobules and does not cross the basement membrane. It is known as a precursor lesion of breast cancer. By definition, it has no metastatic capacity, but it has been reported that invasive foci that are not recognized at the time of diagnosis may metastasis.[3] The most common site of these metastases is the axillary. The optimal treatment for patients with DCIS is still controversial in the literature. The local treatment is mastectomy or breast-conserving surgery (BCS). Adjuvant radiotherapy (RT) after BCS may be required in most cases. Although mastectomy is associated with more radical and definitive outcomes, it can be a drastic decision in many cases.

In the literature, the rate of axillary metastasis in patients with pure DCIS is around 1%. However, patients with a pre-operative diagnosis of DCIS are diagnosed with invasive cancer with a postoperative final pathology rate of 13–40%.[4] In this case, axillary sampling should be performed. Sentinel lymph node biopsy (SLNB) can be performed from the axillary with the second operation in patients who have undergone BCS, but this chance will disappear in patients who have undergone mastectomy because the lymphatic drainage will change.

While SLNB is recommended in patients who are scheduled for mastectomy due to DCIS, the recommendation for SLNB in patients who will undergo BCS is controversial. Although SLNB is considered a low-risk procedure, it is associated with morbidities such as lymph edema, pain, numbness in the arm, and anaphylaxis due to the dye used, which may decrease patient comfort. Therefore, it is important to identify which patients should undergo SLNB. Detection of axillary lymph node metastasis is one of the most valuable parameters in determining the patient's prognosis and adjuvant treatment decision.

The aim of our study was to evaluate the types of surgery, axillary approaches and associated parameters in patients with DCIS and to identify variables that may indicate axillary metastasis or invasive component. To investigate which patients with DCIS should undergo SLNB.

Methods

This study was a retrospective review of patients operated on for breast tumors in the General Surgery Clinic between January 2008 and January 2023. This study was approved by the Goztepe Prof. Dr. Suleyman Yalcin City Hospital Clinical Research Ethics Committee (date: October 27, 2021-number: 2021/0542) and carried out in compliance with the Helsinki Declaration. Written informed consent was obtained from all participants. The pathology reports of the patients were reviewed, and those with DCIS or DCIS with microinvasive components were included in the study. Patients with a history of invasive breast carcinoma or other systemic malignancy were excluded. A total of 48 female patients over 18 years of age who met the study criteria were included in the study, and age, menopausal status, tumor side information, radiological TNM stage, ultrasonography (USG), magnetic resonance imaging (MRI), and mammography findings were recorded. A histologic subtype, nuclear grade, presence of comedo necrosis, hormone receptor status, and tumor diameters reported by postoperative pathological examination were determined. Surgery was performed on the breast and axillary, and the number of excised sentinel lymph nodes was analyzed. Patients were divided into two groups according to the technique of breast surgery as mastectomy and BCS, axillary intervention (SLNB or ALND) and non-intervention (SLNB or ALND) and compared in terms of pathologic features, TNM staging, imaging, treatment methods, nuclear grade, and prognosis.

Follow-ups were performed every 6 months for the first 2 years and annually thereafter. Recurrence in the breast quadrant and thoracic wall was defined as local recurrence, and recurrence in the axillary was defined as regional recurrence. Postoperative RT, hormone therapy, locoregional, and distant metastasis findings of the patients were recorded.

The duration between surgery and recurrence or death was accepted as disease-free survival (DFS). The period between the date of surgery and death by any cause was defined as overall survival (OS). The presence of distant metastasis and mortality rates of the patients were compared. In addtion, analyses for DFS and OS were carried out.

Statistical Analysis

Descriptive statistics were presented as number and percentage for categorical variables and mean±standard deviation or median (minimum–maximum value) for continuous variables. The presence of normal distribution was determined by histograms, Q-Q plots, and normal distribution tests (Kolmogorov–Smirnov or Shapiro–Wilk). Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test when assumptions were not met. When comparing continuous variables between two groups, independent samples t-test or Mann–Whitney U test was used according to the presence or absence of normal distribution. Survival analysis was performed for all patients for recurrence, and 1-year and 5-year DFS probabilities were calculated. Since the number of recurrences was small (n=3), no comparison was made between groups. Two-way p<0.05 was considered statistically significant. Data analysis was performed with R version 4.2.2.

Results

Forty-eight female patients who met the study criteria were included in the study. The mean age of the patients was 52.2+12.4 years (25–76). The number of patients in whom a mass was palpated on physical examination at presentation was 17. Nineteen cases were operated for right-sided disease, 28 for left-sided disease, and 1 for bilateral disease. The diagnosis was made by tru-cut biopsy in 21 patients, surgical excision in 26 patients in whom DCIS was not diagnosed by previous biopsies and surgical indications such as atypia and suspected malignancy, and punch biopsy in 1 patient.

According to radiologic TNM staging, 32 patients were evaluated as T0, 7 as T1, and 9 as T3. While 1 patient was classified as N1, the remaining 47 patients were recorded as N0. All patients were M0 (Table 1). USG showed a suspicious lymph node in the axillary in 1 case, while no suspicious lymph node was detected in 47 cases. When mammography

Table 1. Numerical ratios of patients' pathological features, TNM staging, and imaging methods

	n (%)
Pathological Features	
Cribriform	18 (37.5)
Micropapillary	3 (6.25)
Papillary	10 (20.8)
Solid	20 (41.7)
Flat	3 (6.25)
Komedo	26 (54.2)
Final pathology:	
Pure DCIS	44 (91.7)
Microinvasive DCIS	4 (8.3)
Nuclear grade:	
Low	10 (20.8)
Middle	14 (29.2)
High	24 (50.0)
Comedonecrosis	17 (35.4)
ER+	36 (75.0)
PR+	34 (70.8)
HER2+	16 (33.3)
Triple Negative	4 (8.3)
TNM Staging	
Tumor Stage	
0	32 (66.7)
1	7 (14.6)
2	9 (18.7)
Nodal Status	
No	47 (97.9)
USG, PET suspect	1 (2.1)
M	
0	48 (100)
Imaging Methods	
USG, n=48	
No doubt	47 (97.9)
There is doubt	1 (2.1)
MMG, n=47	
No pathology	2 (4.3)
Focal microcalcification	33 (70.2)
Diffuse microcalcification	12 (25.5)
MRI, n=34	
No contrast	11 (32.4)
Focal contrast enhancement	14 (41.2)
Diffuse contrast enhancement	7 (20.6)
Diffuse-bilateral contrast enhancement	2 (5.8)
PET CT, n=2	
No doubt	1 (50)
There is doubt	1 (50)

US: Ultrasonography; MMG: Mammography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography–computerized tomography scan.

findings were evaluated, focal microcalcifications were observed in 33 patients and diffuse microcalcifications were observed in 12 patients, while no pathologic findings were detected in 2 patients. MRI was performed in 34 of the 48 patients included in the study. Focal contrast enhancement was seen in 14 of them, no pathologic contrast enhancement was seen in 11 patients, and diffuse contrast enhancement was seen in 7 patients. Bilateral diffuse contrast enhancement was observed in 2 cases.

Tumor nuclear grade was high in 24 cases, moderate in 14 patients, and low in 10 patients. Comedonecrosis was seen in 17 patients. Regarding hormone receptors, 36 patients were estrogen receptor (ER) positive, 34 were progesterone receptor (PR) positive, 16 were human epidermal growth factor positive and 4 were triple negative. In the final pathology report of the patients operated for DCIS, 44 patients were found to have DCIS, and 4 patients had DCIS with microinvasive components.

Mastectomy was performed in 16 of the patients, while 32 patients underwent BCS. The number of patients who underwent re-excision due to positive or suspected positive surgical margins was 11. The mean tumor diameter was 12 mm (2–85 mm) (Table 2). SLNB was performed in 21 patients, while ALND was performed in 3 patients. The mean number of lymph nodes removed in patients who underwent SLNB was 1.[1-3] No axillary-directed intervention was performed in 24 patients. No lymph node metastasis was detected in the final pathology of axillary interventions. RT was given to 25 patients, and hormonotherapy to 31 patients.

Local recurrence was detected in 1 of 47 patients whose 1st year follow-up was completed. She had previously undergone mastectomy, SLNB, RT, and hormone therapy. She was operated after neoadjuvant chemotherapy because of Paget's recurrence of invasive breast cancer 12th month postoperatively. A 5-year follow-up was performed on 29 patients. In a second patient, a mastectomy was performed at the 60th month due to the recurrence of DCIS in the operated breast. She had previously undergone BCS and SLNB and received hormone therapy. When all follow-up periods were included, a third patient had a recurrence of invasive cancer in the axilla in 84th month. Mastectomy and SLNB were performed, and HT was given. ALND was performed, and RT was applied. Tumor sizes were 65, 40, and 85 mm, respectively. No distant metastasis was detected in any of the patients. Mortality was seen in 2 patients during the follow-up. These patients died 81 and 84 months after surgery due to myocardial infarction and cerebrovascular accident. The mean OS was 82.5 (1–175) months.

The mean age of the patients without axillary intervention was 54.2±12.1 years, while the mean age of the group that un-

Table 2. Numerical ratios of the treatment modalities and prognosis of the patients

	n (%)
Treatment Method	
DCIS diameter (mm), median (min-max)	12 (2−85)
Breast surgery	
Mastectomy	16 (33.3)
Breast-conserving Surgery	32 (66.7)
Axillary management	
No	24 (50.0)
SLNB	21 (43.8)
AD	3 (6.2)
Median (min-max) number of SLNBs, n=21	1 (1-3)
RT	25 (52.1)
HT	31 (64.6)
Prognosis	
Local recurrence within 1 year, (n=47)[a]	1 (2.2)
Local recurrence within 5 years, (n=29)[b]	2 (6.9)
Regional recurrence (n=48)	1 (2.1)
Distant metastasis (n=48)	0 (0)
Number of locoregional recurrences (n=48)	3 (6.25)
Disease-free survival, median (min-max) (n=48)	82.5 (1-175)
Exitus (n=48)	2 (4.2)

[a]Among patients who completed 1 year of follow-up; DCIS: Ductal carcinoma in situ; SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; RT: Radiotherapy; HT: Hormonotheraphy.

derwent SLNB or ALND was 50.2±12.6 years, with no statistically significant difference (p=0.27). There was no significant difference between axillary intervention groups in terms of menopausal status, palpable mass, side, preoperative radiologic T stage, and MRI findings. In the group without axillary intervention, 70.8% were diagnosed by surgical excision, while this rate was statistically significant with 37.5% in the group with intervention (p=0.04). Diffuse microcalcification on MMG was seen in 8% of the group without axillary intervention, while diffuse microcalcification was seen in 43.5% of the group with axillary intervention (p=0.009).

Among histologic subtypes, comedo detection rates were significantly lower in those without axillary intervention (p=0.04). While there was no significant difference between the two groups in terms of final pathology (p=0.61), there was a significant difference in terms of nuclear grade (p=0.04). High nuclear grade was found in 66.7% of the group with axillary access. There was no significant difference in ER and PR receptor positivity between the groups (p=0.32 and p=0.34, respectively). HER2 positivity was significantly higher in the group with axillary access (p=0.03) (Table 3).

BCS was performed in 95.8% of the group without axillary

Table 3. Comparison of numerical rates and ratios of axillary management according to pathological features, TNM staging, and imaging methods of the patients

	Axillary management		p
	None, n=24	SLNB or AD, n=24	
Pathological Features			
Cribriform:			0.77
No	14 (58.3)	16 (66.7)	
Yes	10 (41.7)	8 (33.3)	
Micropapillary:			0.23
No	21 (87.5)	24 (100)	
Yes	3 (12.5)	0 (0.0)	
Papillary:			0.72
No	18 (75.0)	20 (83.3)	
Yes	6 (25.0)	4 (16.7)	
Solid:			0.38
No	12 (50.0)	16 (66.7)	
Yes	12 (50.0)	8 (33.3)	
Flat:			0.23
No	21 (87.5)	24 (100)	
Yes	3 (12.5)	0 (0.0)	
Komedo:			0.04*
No	15 (62.5)	7 (29.2)	
Yes	9 (37.5)	17 (70.8)	
Final pathology:			0.61
Pure DCIS	23 (95.8)	21 (87.5)	
Microinvasive DCIS	1 (4.2)	3 (12.5)	
Nuclear grade:			0.04*
Low	8 (33.3)	2 (8.3)	
Middle	8 (33.3)	6 (25.0)	
High	8 (33.3)	16 (66.7)	
Comedonecrosis:			0.55
No	17 (70.8)	14 (58.3)	
Yes	7 (29.2)	10 (41.7)	
ER:			0.32
No	4 (16.7)	8 (33.3)	
Yes	20 (83.3)	16 (66.7)	
PR:			0.34
No	5 (20.8)	9 (37.5)	
Yes	19 (79.2)	15 (62.5)	
HER2:			0.03*
No	20 (83.3)	12 (50.0)	
Yes	4 (16.7)	12 (50.0)	
Triple Negative:			>0.99
No	22 (91.7)	22 (91.7)	
Yes	2 (8.33)	2 (8.33)	
TNM Staging			
T			0.22
0	18 (75.0)	14 (58.3)	
1	4 (16.7)	3 (12.5)	
2	2 (8.3)	7 (29.2)	
N			>0.99
No	24 (100)	23 (95.8)	
USG, MRI, PET suspect	0 (0.0)	1 (4.2)	
Imaging Methods			
MMG, n=47			0.009*
No pathology	1 (4.2)	1 (4.3)	
Focal microcalcification	21 (87.5)	12 (52.2)	
Diffuse microcalcification	2 (8.3)	10 (43.5)	
MRI, n=34	5 (31.2)	6 (33.3)	
No contrast			0.73
Focal contrast enhancement	8 (50.0)	6 (33.3)	
Diffuse contrast enhancement	2 (12.5)	5 (27.8)	
Diffuse-bilateral contrast enhancement	1 (6.3)	1 (5.6)	

SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; DCIS: Ductal carcinoma in situ; US: Ultrasonography; MMG: Mammography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography-computerized tomography scan.

intervention, while 37.5% of the group with axillary intervention underwent BCS (p<0.001). There was no significant difference between the groups in the rates of RT and hormonotherapy after surgical treatment (p=0.248 and p>0.99, respectively). There was no significant difference between the groups in terms of 1-year and 5-year local recurrence and axillary recurrence (p>0.99, p=0.49 and p>0.99, respectively). While no local recurrence was observed at 1 and 5 years in the group without axillary intervention, these rates were 4.2% and 12.5% in the group with axillary intervention. While no axillary recurrence was observed in the group without axillary access, this rate was 4.2% in the group with axillary access (Table 4).

The mean age of the patients who underwent mastectomy was 54.3±11.3 years, while the mean age of the group who underwent BCS was 51.1±12.9 years. There was no significant difference in age between the groups (p=0.39). Diffuse microcalcifications were seen on mammography in 68.8% of the group that underwent mastectomy, whereas diffuse microcalcifications were seen in 3.2% of the group that underwent BCS (p<0.001). Histologic subtypes, final pathology, comedonecrosis rate, nuclear grade, and hormone receptor levels were not significantly different between the groups. The mean diameter of DCIS was 21 mm (7.5–85) in the mastectomy group and 10.8 mm (2–40) in the BCS group (p=0.009) (Table 5). There was no significant difference in

Table 4. Comparison of the numerical rates and ratios of axillary administrations according to the treatment modalities and patient prognoses

	Axillary management		p
	None, n=24	SLNB or AD, n=24	
Treatment Method			
Re-excision			>0.99
No	19 (79.2)	18 (75.0)	
Yes	5 (20.8)	6 (25.0)	
DCIS diameter (mm), median (min-max)	11.2 (2-40)	15 (3-85)	0.078
Breast surgery			<0.001*
Mastectomy	1 (4.2)	15 (62.5)	
Breast Conserving Surgery	23 (95.8)	9 (37.5)	
RT			0.248
No	9 (37.5)	14 (58.3)	
Yes	15 (62.5)	10 (41.7)	
HT			>0.99
No	9 (37.5)	8 (33.3)	
Yes	15 (62.5)	16 (66.7)	
Prognosis			>0.99
Local recurrence within 1 year, (n=47)a			
No	23 (100)	23 (95.8)	
Yes	0 (0.0)	1 (4.2)	
Local recurrence within 5 years, (n=29)b			0.49
No	13 (100)	14 (87.5)	
Yes	0 (0.0)	2 (12.5)	
Recurrence in the axillary			>0.99
No	24 (100)	23 (95.8)	
Yes	0 (0.0)	1 (4.2)	
Disease-free survival, median (min-max)	80.5 (1-175)	90.5 (20-167)	0.40
Exitus			0.49
No	22 (91.7)	24 (100)	
Yes	2 (8.3)	0 (0.0)	

aAmong patients who completed 1 year of follow-up; bPatients who completed 5 years of follow-up included; DCIS: Ductal carcinoma in situ; SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; RT: Radiotherapy; HT: Hormonotheraphy.

Table 5. Comparison of the numerical rates of breat surgery methods according to the treatment methods applied to the patients and the prognosis of the patients			
	Breast surgery		p
	Mastectomy, n=16	BreastConserving Surgery, n=32	
Treatment Method			
Re-excision			0.73
No	13 (81.2)	24 (75.0)	
Yes	3 (18.8)	8 (25.0)	
DCIS diameter (mm), median (min-max)	21 (7.5−85)	10.8 (2−40)	
Median (min-max) number of SLNBs, n=21	1 (1−3)	1.5 (1−3)	
RT			0.009*
No	13 (81.2)	10 (31.2)	0.59
Yes	3 (18.8)	22 (68.8)	0.003*
HT			>0.99
No	6 (37.5)	11 (34.4)	
Yes	10 (62.5)	21 (65.6)	
Imaging Methods			
MMG, n=47			<0.001*
No pathology	1 (6.2)	1 (3.2)	
Focal microcalcification	4 (25.0)	29 (93.6)	
Diffuse microcalcification	11 (68.8)	1 (3.2)	
MRI, n=34			0.182
No	4 (36.4)	7 (30.4)	
Focal contrast enhancement	2 (18.2)	12 (52.2)	
Diffuse contrast enhancement	4 (36.4)	3 (13.0)	
Diffuse-bilateral contrast enhancement	1 (9.0)	1 (4.4)	
Prognosis			0.34
Local recurrence within 1 year, (n=47)[a]	15 (93.8)	31 (100)	
No	1 (6.2)	1 (0.0)	
Yes			>0.99
Local recurrence within 5 years, (n=29)[b]	10 (90.9)	17 (94.4)	
No	1 (9.1)	1 (5.6)	
Yes			0.33
Recurrence in the axillary	15 (93.8)	32 (100)	
No	1 (6.2)	0 (0.0)	
Yes			
Disease-free survival, median (min-max)			
Exitus	90.5 (31−130)	80.5 (1−175)	0.53
No	16 (100)	30 (93.8)	0.55
Yes	0 (0.0)	2 (6.2)	

[a]Among patients who completed 1 year of follow-up; [b]Patients who completed 5 years of follow-up included; DCIS: Duktal carsinoma in situ; RT: Radiotheraphy; HT: Hormonotheraphy; MMG: Mammography; MRI: Magnetic resonance imaging.

1-year and 5-year local recurrence and axillary recurrence in terms of surgery performed on the breast (p=0.34, p>0.99, and p=0.33, respectively). Local recurrence rates at 1 and 5 years were 6.2% and 9.1% in the group that underwent mastectomy, while recurrence rates were 0% and 5.6% in the group that underwent BCS. Axillary recurrence was seen in 6.2% of patients who underwent mastectomy, while no recurrence was detected in patients who underwent BCS.

The mean DFS was 90.5 months (31–130) in the group that underwent mastectomy and 80.5 months (1–175) in the group that underwent BCS, with no significant difference in DFS

(p=0.53). The probability of DFS was 97.9% at 1 year, 94.4% at 5 years, and 90% at 7 years. There was no significant difference in DFS between the groups (p=0.4). The mean DFS was 80.5 months (1–175) in the group without axillary intervention and 90.5 months (20–167) in the group with axillary intervention (Fig. 1).

Discussion

Ductal carcinoma *in situ* is considered a precursor lesion of invasive breast cancer. With the widespread use of mammography in breast cancer screening, there has been a significant increase in the incidence of this disease. DCIS is a localized disease without regional spread. Moreover, axillary lymph node metastasis may be seen with the presence of an undiagnosed invasive component. This is more common if the diagnosis of the disease is made by core biopsy of the breast.[5]

The potential of DCIS to harbor malignancy was found to be associated with lesion diameter and nuclear grade in the study by Chin-Lenn et al.[6] There are many studies in the literature investigating lymph node metastasis in patients with DCIS, but which patients should undergo lymph node biopsy in practice is still controversial. In patients undergoing mastectomy, if the final pathology shows an invasive component, SLNB is recommended because SLNB cannot be performed with a second operation, but the recommendations are not clear in patients undergoing BCS. Lymph node

Figure 1. Cumulative probability of harm by month for disease-free survival among all patients and number at risk by month.

status is of great importance in predicting the prognosis of the disease and in the decision of adjuvant treatment.

Studies have shown very low sentinel lymph node positivity in patients with pure DCIS, and since lymph node biopsies and dissections have significant complications and morbidity, patient selection for axillary examination is important. In a single-center study, 307 patients with DCIS were retrospectively analyzed, and invasive cancer was seen in 19% of the final pathologies. It was found that diagnosis with core biopsy, mass appearance on ultrasound, and negative progesterone receptor (PR) status were risk factors for invasive cancer.[7] Metastasis was detected in 1.9% of patients in SLNB, and it was observed that all of these patients were patients who had undergone mastectomy. SLNB was performed in 37.2% of 145 patients and 91.4% of 162 mastectomy patients who underwent BCS, and as a result, it was recommended that SLNB should be performed in mastectomy patients diagnosed with core biopsy and should not be performed in patients in whom BCS is planned.

In a cohort of 398 DCIS patients, 37.6% underwent mastectomy and 62.4% underwent BCS and invasive cancer was detected in 23% of them.[8] In the multivariate analysis, it was emphasized that the increase in diagnosis to invasive cancer was only associated with increasing tumor diameter. When the group that underwent mastectomy was compared with the group that underwent BCS, it was observed that tumor size and palpability of the mass were statistically significantly different. Similarly, in our study, there was a statistically significant difference in tumor size when mastectomy and BCS groups were compared. While the mean tumor size was 21mm in patients who underwent mastectomy, it was 10.8mm in the BCS group. The mean age of the patients in our study was 52.2 years. The palpable mass rate (35.4%) did not show a statistically significant difference in terms of surgical interventions. In the literature, presentation with palpable mass varies between 8 and 47.4%.[7-10] While a microinvasive component was seen in 8.3% of the patients, invasive cancer was not detected. The incidence of microinvasive components is similar to the literature.

SLNB or AD was performed in 93.75% of 16 patients who underwent mastectomy and 28.12% of 32 patients who underwent BCS. No metastasis was observed after axillary interventions. In the literature, axillary metastasis is seen in 1–2% of patients with DCIS and 1–10% in those with microinvasive components. Our axillary metastasis rate was below the rate in the literature. In a study of 44 patients, similarly,
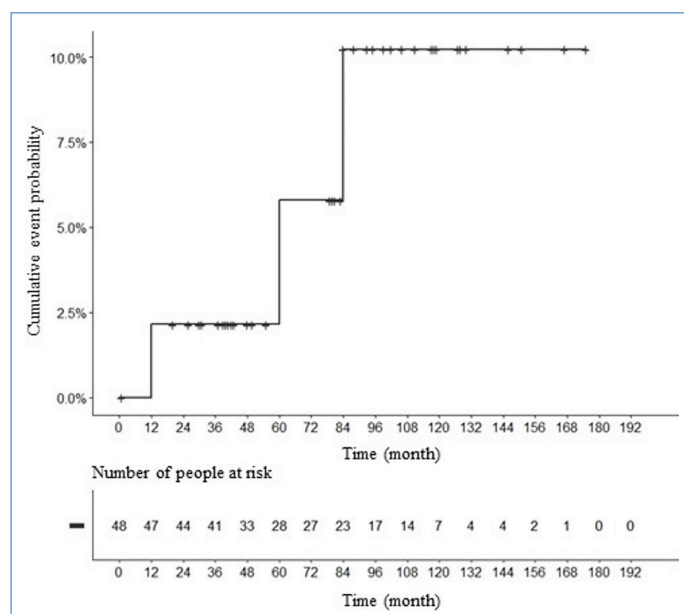
all SLNBs were found to be negative.[11] The reason for the absence of metastasis in our study may be the low sample size, small tumor size (mean 12 mm), and high rate of diagnosis by surgical excision (54.2%).

In a study, 85 of 92 patients with DCIS underwent mastectomy, and macrometastasis in the axillary was found in 6.5% and micrometastasis in 10%.[12] In the same study, 24 of 36 patients with microinvasive cancer underwent mastectomy, and macrometastasis in the axillary was found in 8% and micrometastasis in 7%. The high rate of mastectomy and large tumor sizes are striking in this study. Tumor size was larger than 3 cm in 90% of patients with DCIS and 64% of patients with microinvasive component. High nuclear grade was 82% in the DCIS group and 76% in the group with microinvasive components.

In a prospective multicentric study, 530 radiologically axillary negative patients diagnosed with DCIS by core or excisional biopsy were evaluated, and 77% of these patients underwent SLNB.[13,14] Axillary metastasis was found in 7.2% of patients, and this rate was found to be 2.15% when patients with invasive cancer (17.4%) were excluded. Microinvasive component was observed in 7.2% of patients. It was recommended that SLNB should be performed in patients who are not suitable for BCS, diagnosed with core biopsy, BIRADS 5, and lymphovascular invasion. In a meta-analysis, data from 52 studies were collected, and it was revealed that invasive cancer was observed in 23.6% of patients after excision in 7350 patients diagnosed with DCIS in core biopsy.[7] When patients with invasive cancer were compared with patients with DCIS, the presence of a palpable mass, lesion size >2 cm, nuclear grade, diameter of the device used in biopsy, BIRADS grade, and appearance of a mass on mammography were found to be statistically significantly different between the two groups. In the same study, a similar relationship could not be established with comedonecrosis.

In another study, 87 patients diagnosed as pure DCIS on core biopsy were examined, and metastasis in the axillary was found in 6% of the patients.[15] Comedo or solid tumors were observed in at least one DCIS focus in 4 of 5 patients with axillary metastasis. In our study, 54.2% of the patients had comedo, 41.7% had solid histologic subtype, and 35.4% had comedonecrosis. In a study by Klauber et al.,[16] palpable mass, suspicion of histologic microinvasion, multicentric disease requiring mastectomy, high nuclear grade, or necrosis were defined as high-risk DCIS and 12% of these 76 patients had axillary metastases. It was reported that 77.7%

of these metastases were micrometastases.

In a study using the patient groups of two large prospective studies, a total of 2612 patients diagnosed with DCIS and treated with BCS were followed up for a mean of 15 years, and the results showed that invasive recurrence in DCIS patients increased the risk of breast cancer-related mortality, and RT and hormonotherapy were effective in reducing invasive recurrence.[5]

Invasive cancer recurrence was observed in 1 patient (2.2%) in the 1-year follow-up of our study. This patient underwent a mastectomy and received adjuvant RT and HT. Recurrence was seen in 2 more patients during our follow-up period. One of them was DCIS recurrence in the 5th year. This patient underwent BCS and received adjuvant HT and no RT. One of our patients had a recurrence of invasive cancer in the axillary at 84 months, who had previously undergone mastectomy and received adjuvant HT. The mean follow-up period in our study was 82.5 months. The locoregional recurrence rate was 6.25%, and invasive cancer recurrence rate was 4.16%. Recurrence of DCIS was seen in 1 (5.6%) of 32 patients who underwent BCS.

In a cohort study, the recurrence rate was 14.4%, and the invasive cancer recurrence rate was 7.5% in DCIS patients who underwent BCS without RT.[17] In a 543-patient study, patients diagnosed with DCIS were followed up, and 2 control group patients without recurrence were compared for invasive or pure DCIS recurrence patients.[18] In the study, ER-positive patients with ER-negative or ER-negative DCIS foci (multiclonal) showed higher recurrence compared to ER-positive patients. When recurrences were divided into invasive and DCIS recurrence, it was shown that receptor status only increased the risk of DCIS but not the risk of invasive cancer recurrence. In our study, 75% of the patients were ER positive. We have no data on ER+ patients showing ER- extra focus in pathologic evaluation. When we evaluated the hormone receptor levels of our recurrence patients, it was observed that all patients were ER receptor positive and received hormone therapy.

In a similar study, patients with DCIS were evaluated according to their hormonal status and nuclear grade in a 5-year follow-up, and 7.6% recurrence was observed in luminal-A DCIS patients in 5 years, while 15–36% recurrence was observed in other groups.[19] They also defined high nuclear grade as an independent risk factor for recurrence. In our study, 50% of the patients had a high nuclear grade. All

of the patients in whom we found recurrence belonged to the intermediate nuclear grade group. In a cohort study, 773 DCIS patients from two studies were compared in terms of recurrence and a significant difference was observed in the risk of recurrence when tumor size larger than 2.5 cm was compared with those smaller than 1 cm.[20]

In our study, tumor diameters of patients with recurrence were 85, 65, and 40 mm. When all study data are considered, it is striking that the mean tumor diameter was 12 mm, while the mean of patients with recurrence was 63.3.

Conclusion

While routine SLNB may be avoided in patients undergoing surgery for ductal carcinoma *in situ*, SLNB may be considered in patients scheduled for mastectomy. We found that all patients with recurrence due to DCIS were associated with larger tumor diameters. In our study, no axillary metastasis was detected in any patient after sentinel node biopsies and axillary lymph node dissections. At the same time, locoregional recurrence was not observed in the follow-up of patients who did not undergo axillary intervention. Therefore, since there was no axillary involvement group to compare, a statistical comparison could not be made. This was attributed to the small sample size and small tumor size. These findings should be supported by future prospective studies with larger samples.

Disclosures

Ethics Committee Approval: This study was approved by the Goztepe Prof. Dr. Suleyman Yalcin City Hospital Clinical Research Ethics Committee (Date: October 27, 2021-number: 2021/0542) and carried out in compliance with the Helsinki Declaration

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References

1. Curigliano G. Breast cancer. Lancet 2021;397:1750−69.
2. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med 2016;375:1438−47.
3. Barrio AV, Van Zee KJ. Controversies in the treatment of ductal carcinoma in situ. Annu Rev Med 2017;68:197−211.
4. Si J, Guo R, Huang N, Xiu B, Zhang Q, Chi W, et al. Axillary evaluation is not warranted in patients preoperatively diagnosed with ductal carcinoma in situ by core needle biopsy. Cancer Med 2019;8:7586−93.
5. Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103:478−88.
6. Chin-Lenn L, Mack LA, Temple W, Cherniak W, Quinn RR, Ravani P, et al. Predictors of treatment with mastectomy, use of sentinel lymph node biopsy and upstaging to invasive cancer in patients diagnosed with breast ductal carcinoma in situ (DCIS) on core biopsy. Ann Surg Oncol 2014;21:66−73.
7. Brennan ME, Turner RM, Ciatto S, Marinovich ML, French JR, Macaskill P, et al. Ductal carcinoma in situ at core-needle biopsy: Meta-analysis of underestimation and predictors of invasive breast cancer. Radiology 2011;260:119−28.
8. Yen TW, Hunt KK, Ross MI, Mirza NQ, Babiera GV, Meric-Bernstam F, et al. Predictors of invasive breast cancer in patients with an initial diagnosis of ductal carcinoma in situ: A guide to selective use of sentinel lymph node biopsy in management of ductal carcinoma in situ. J Am Coll Surg 2005;200:516−26.
9. Bonnett M, Wallis T, Rossmann M, Pernick NL, Carolin KA, Segel M, et al. Histologic and radiographic analysis of ductal carcinoma in situ diagnosed using stereotactic incisional core breast biopsy. Mod Pathol 2002;15:95−101.
10. Shin YD, Lee HM, Choi YJ. Necessity of sentinel lymph node biopsy in ductal carcinoma in situ patients: A retrospective analysis. BMC Surg 2021;21:159.
11. Davey MG, O'Flaherty C, Cleere EF, Nohilly A, Phelan J, Ronane E, et al. Sentinel lymph node biopsy in patients with ductal carcinoma in situ: Systematic review and meta-analysis. BJS Open 2022;6:zrac022.
12. Sakr R, Barranger E, Antoine M, Prugnolle H, Daraï E, Uzan S. Ductal carcinoma in situ: Value of sentinel lymph node biopsy. J Surg Oncol 2006;94:426−30.
13. Bellver G, Buch E, Ripoll F, Adrianzen M, Bermejo B, Burgues O, et al. Is axillary assessment of ductal carcinoma in situ of the breast necessary in all cases? J Surg Res 2022;271:145−153.
14. Park HS, Park S, Cho J, Park JM, Kim SI, Park BW. Risk predictors of underestimation and the need for sentinel node biopsy in patients diagnosed with ductal carcinoma in situ by preoperative needle biopsy. J Surg Oncol 2013;107:388−92.
15. Pendas S, Dauway E, Giuliano R, Ku N, Cox CE, Reintgen DS. Sentinel node biopsy in ductal carcinoma in situ patients. Ann Surg Oncol 2000;7:15−20.
16. Klauber-DeMore N, Tan LK, Liberman L, Kaptain S, Fey J, Borgen P, et al. Sentinel lymph node biopsy: Is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol 2000;7:636−42.

17. Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-Year results from the ECOG-ACRIN E5194 study. J Clin Oncol 2015;33:3938–44.

18. Thorat MA, Levey PM, Jones JL, Pinder SE, Bundred NJ, Fentiman IS, et al. Prognostic value of ER and PgR expression and the impact of multi-clonal expression for recurrence in ductal carcinoma in situ: Results from the UK/ANZ DCIS trial. Clin Cancer Res 2021;27:2861–7.

19. Williams KE, Barnes NLP, Cramer A, Johnson R, Cheema K, Morris J, et al. Molecular phenotypes of DCIS predict overall and invasive recurrence. Ann Oncol 2015;26:1019–25.

20. Rakovitch E, Gray R, Baehner FL, Sutradhar R, Crager M, Gu S, et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: A combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat 2018;169:359–69.