



Evaluation of Surgical and Systemic Treatment Results in Patients with Ductal Carcinoma In Situ

Duktal Karsinoma In Situ Tanılı Hastalarda Cerrahi ve Sistemik Tedavi Sonuçlarının Değerlendirilmesi

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Abstract

Objective: The aim of this study was to evaluate the surgical method and systemic treatment results, recurrence and mortality rates in patients whose histopathological results were ductal carcinoma in situ (DCIS) following breast surgery in our general surgery clinic.

Material and Method: A retrospective review was made of the preoperative and postoperative histopathological results of all patients who underwent breast surgery in our general surgery clinic between January 2016 and January 2021. The demographic data, clinicopathological features, postoperative systemic treatments, local recurrence (LR) rate, and overall survival (OS) rate of patients whose histopathological results were reported as DCIS were obtained from the data system of our hospital and the national death reporting system.

Results: The study group consisted of 24 female patients with a histopathology result of DCIS. The average age of the patients was 49.96±10.61 years. In the localization of the lesions in the breast, 11 (45.8%) were observed as unifocal, 7 (29.2%) as multifocal and 6 (25%) as multicentric. The most common type of operation was lumpectomy (n=16, 66.7%). Sentinel lymph node biopsy was performed in 8 patients. The mean follow-up period of the patients after surgery was 32.20±18.22 months. Anti-estrogen hormone therapy (HT) was applied to 21 (87.5%) patients and radiotherapy (RT) to 14 (58.3%) after the operation. There was no recurrence in any of the patients and no mortality was observed.

Conclusion: With a multidisciplinary approach and good preoperative staging, as applied in our general surgery clinic, it can be recommended that the most appropriate surgical method is applied, and risk factors determined for DCIS patients. RT is recommended for eligible patients after BCS and HT in estrogen receptor+ patients.

Keywords: Ductal carcinoma in situ, lumpectomy, mastectomy, sentinel biopsy, radiotherapy, hormone therapy

Öz

Amaç: Bu çalışmada genel cerrahi kliniğimizde meme cerrahisi yapılan hastalarda histopatolojik sonucu duktal karsinoma in situ (DKİS) gelen hastalarımızın cerrahi yöntem ve sistemik tedavi sonuçlarını, rekürrens ve mortalite oranlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Ocak 2016 ile Ocak 2021 tarihleri arasında, genel cerrahi kliniğimizi meme cerrahisi geçiren tüm hastaların preoperatif ve postoperatif histopatolojik sonuçları incelendi. Histopatolojik sonucu DKİS gelen hastaların demografik verileri, klinikopatolojik özellikleri, reoperasyon sayısı, postoperatif radyoterapi (RT), anti-östrojen hormon tedavisi (HT), lokal rekürrens (LR) oranı, ve genel sağkalım (GS) oranı hastanemiz veri datasından ve ulusal ölüm bildirim sisteminden retrospektif olarak incelendi.

Bulgular: Çalışma grubu histopatolojik sonucu DKİS gelen toplam 24 kadın hastadan oluşmakta idi. Grubun ortalama yaşı 49,96±10,61'dir. Lezyonların meme içinde yerleşiminde, 11 (45,8%)'i tek odaklı, 7 (%29,2)'si multifokal ve 6 (%25)'si ise multisentrik olarak gözlenmiştir. En sık uygulanan operasyon tipi lumpektomidir (n=16, 66,7%). 8 hastaya sentinel lenf nodu biyopsisi yapılmıştır. Ortanca tümör boyutu 12,5 (4-70) mm'dir. En sık görülen moleküler tip Luminal A' dir (n=14, 58,3%). Lezyona en yakın cerrahi sınır uzaklığı ortalama 5 (0-20) mm'dir. Hastaların cerrahi sonrası ortalama takip süresi 32,20±18,22 aydır. Hastaların 87,5%'si (n=21) operasyon sonrası HT ve 58,3%'ü (n=14) RT almıştır. Hastaların hiçbirinde nüks gelişmemiştir ve mortalite gözlenmedi.

Sonuç: Genel cerrahi kliniğimizde multidisipliner yaklaşım ve iyi bir preoperatif evreleme ile DKİS hastalarına en uygun cerrahi yöntemi ve risk faktörlerini de değerlendirerek uygun hastalarda meme koruyucu cerrahi sonrası RT ve östrojen reseptör+ hastalarda HT'yi öneriyoruz.

Anahtar Kelimeler: Duktal karsinoma in situ, lumpektomi, mastektomi, sentinel biyopsi, radyoterapi, hormon tedavisi



INTRODUCTION

Breast cancer is the major cause of cancer-associated death among women worldwide.^[1] With the increase in screening mammography, the rate of early stage breast cancer and ductal carcinoma in situ (DCIS), which is a breast cancer precursor lesion, is gradually increasing. Today, DCIS constitutes 20% of breast cancer patients.^[2] DCIS is a non-invasive breast cancer characterized by atypical ductal cell proliferation within the ducts that make up the breast tissue that do not cross the basement membrane. The 10-year mortality rate is very low, at 1-3%.^[3] Studies have shown that approximately 13% to 50% of DCIS lesions can progress to invasive ductal carcinoma (IDC),^[4] but is estimated that 70% of these lesions will not show clinically significant findings.^[5] However, which DCIS lesions will become IDC cannot be fully predicted by clinicians. Prognostic factors and nomograms, including tumor grade (low, intermediate and high), comedonecrosis, tumor size, surgical margin status, morphological structure and, in recent years, genetic risk scoring systems are used to predict the aggressive nature of DCIS lesions and help in the selection of the treatment method.^[4]

There is a wide range of treatment protocols for DCIS disease including mastectomy (Mx), bilateral prophylactic mastectomy (PMx) with or without reconstruction, breast conserving surgery (BCS) with or without radiotherapy (RT) (lumpectomy) and anti-estrogen hormone therapy (HT) (tamoxifen, anastrozole).^[6] The high overall survival (OS) rate in DCIS disease and the fact that surgical methods reduce local recurrence (LR) more than OS and increase disease-free survival (DFS) has led to the questioning of unnecessary aggressive surgery. There are many studies currently being performed in multi centric randomised studies."

The aim of this study was to evaluate the surgical method and systemic treatment results, recurrence and mortality rates in patients with histopathological results of DCIS following BCS and Mx in our general surgery clinic.

MATERIAL METHOD

This study was approved by The Ethics Committee of Ankara Training and Research Hospital (approval date and number: 24.02.2021, 2021/21:598). Informed consent was not taken due to the retrospective nature of the study.

The preoperative and postoperative histopathological results of all patients who underwent breast surgery (modified radical mastectomy, simple mastectomy±sentinel lymph node biopsy, segmental mastectomy±sentinel lymph node biopsy, segmental mastectomy and axillary dissection, excisional biopsy) in the general surgery clinic of our training and research hospital between January 2016 and January 2021 were reviewed. Preoperative and postoperative clinicopathological characteristics of all patients, pathology results, surgery notes, radiology reports, laboratory results and epicrisis reports were reviewed by 3 general surgeons. 196 patients diagnosed with

invasive breast carcinoma, 164 patients with benign breast disease and patients whose data could not be accessed from the system were excluded from the study. Patients with preoperative imaging and / or tru cut biopsy results and postoperative histopathology results with DCIS were included in the study. Sixteen (66.7%) patients were diagnosed with mammography-guided lumpectomy after wire marking, and 8 (33.3%) patients with a palpable mass were diagnosed with core biopsy under sonography guidance. The demographic data, operation type, tumor size, localization, histological grade (grade 1, 2, 3), surgical margin status, molecular typing, number of reoperations, postoperative RT, HT, recurrence rate, and OS rate of patients with a histopathological result of DCIS were retrospectively analyzed from the electronic data system of our hospital and the national death reporting system.

Statistical Analysis

Normal distribution analysis of numerical data was performed using the Shapiro-Wilk test. Numerical data showing normal distribution were expressed as mean±standard deviation values, and those that did not show normal distribution were expressed as median (minimum-maximum) values. Categorical data were defined as number (n) and percentage (%).

RESULTS

The study group consisted of 24 female patients with a histopathology result of DCIS. The average age of the group was 49.96±10.61 years. In pre-operative imaging methods, lesions were most frequently observed in the Breast Imaging-Reporting and Data System (BIRADS) 4a (n=15, 62.5%) class. The location of the lesions was evenly distributed in the right and left breast. In the localization of the lesions in the breast, 11 (45.8%) were observed as unifocal, 7 (29.2%) as multifocal and 6 (25%) as multicentric. Of the 18 patients with a single focus and multifocal location, 4 were located in the upper outer quadrant, 5 were in the lower outer quadrant, 3 were in the lower inner quadrant, 2 were in the upper inner quadrant, and 4 were centrally located. Two-thirds of the patients were diagnosed from mammography-guided stereotaxic excisional biopsy. The most common type of operation was lumpectomy (n=16, 66.7%). Mx was applied to 6 (25%) patients with a multicentric location. Sentinel lymph node biopsy was performed in patients who underwent Mx and in 2 (8.3%) patients who underwent high-risk lumpectomy. The demographic characteristics and clinical results of the patients are shown in **Table 1**.

Tumor grade 3 was observed in half of the patients, and comedo variant was observed in 9 patients (37.5%). Median tumor size was 12.5 (4-70) mm. The most common molecular type was Luminal A (n=14.58.3%). No metastatic lymph node was found in any of the patients who underwent sentinel lymph node biopsy. The closest surgical border distance to the lesion was median 5mm (0- 20 mm). The histopathological results of the patients are shown in **Table 2**.

Table 1. Demographic characteristics and clinical results of the patients

Characteristics	DCIS (n=24)
Age (years)	49.96±10.61
BIRADS n(%)	
0	1 (4.2)
3	3 (12.5)
4a	15 (62.5)
4b	5 (20.8)
Tumor localization n(%)	
Right	12 (50)
Left	12 (50)
Tumor distribution n(%)	
Single focus,	11 (45.8)
Multifocal	7 (29.2)
Multicentric	6 (25)
Preoperative biopsy n(%)	
Core biopsy	8 (33.3)
Stereotaxic excisional biopsy	16 (66.7)
Operation type n(%)	
Lumpectomy	16 (66.7)
Lumpectomy+SLNB	2 (8.3)
Total mastectomy+SLNB	6 (25)

DCIS: Ductal carcinoma in situ, BIRADS: Breast Imaging-Reporting and Data System, SLNB: Sentinel lymph node biopsy

Table 2. Histopathological results of the patients.

	DCIS (n=24)
Histological grade (GR) n (%)	
GR1	4 (16.7)
GR2	8 (33.3)
GR3	12 (50)
Comedo type (yes) n (%)	9 (37.5)
Tumor size (mm)	12.5 (4-70)
Molecular subtype n (%)	
Luminal A	14 (58.3)
Luminal B	7 (29.2)
HER-2 positive	2 (8.3)
Triple negative	1 (4.2)
Ki-67 (<20) n (%)	22 (91.7)
Number of positive sentinel lymph node	-
Number of sentinel lymph nodes	2 (1-5)
Surgical margin (mm)	5 (0-20)

DCIS: Ductal carcinoma in situ

The mean follow-up period of the patients after surgery was 32.20±18.22 months. The follow-up of the patients was done every 6-12 months for 5 years by medical oncology, radiation oncology, and general surgery specialist with a multidisciplinary approach. The study included an interval history, physical examination, and breast ultrasound every six months. Mammography was performed every 12 months. Postoperatively, HT was applied to 87.5% (n=21) of the patients and RT to 58.3% (n=14). Postoperative RT was not given to 2 of the 16 patients as they had comorbid diseases and low grade DCIS was the histopathological results. There was no recurrence in any of the patients and no mortality was observed. Reoperation was performed in 4 patients (16.6%) because surgical margin negativity could not be achieved. The postoperative follow-up results of the patients are shown in **Table 3**.

Table 3. Postoperative follow-up results of patients.

	DCIS (n=24)
Hormone replacement therapy (yes) n (%)	21 (87.5)
Radiotherapy (yes) n (%)	14 (58.3)
Recurrence (yes) n (%)	0 (0)
Mortality (yes) n (%)	0 (0)
Reoperation (yes) n (%)	7 (29.2)
Reoperation type n(%)	
Reexcision	2 (8.3)
Mastectomy+SNLB	2 (8.3)
Follow-up period (months)	32.20±18.22

DCIS: Ductal carcinoma in situ, SLNB: Sentinel lymph node biopsy

DISCUSSION

With the increasing use of screening mammography methods, the rate of DCIS diagnoses, which is non-invasive breast cancer, is also increasing. Since DCIS is an early stage disease, it is diagnosed from the presence of punctate, linear and branching microcalcification in the ductus on mammography at a high rate, rather than a palpable mass.^[7,8] Very occasionally, it presents as a mass on mammography or sonography, or with bloody nipple discharge in Paget's disease. The diagnosis of DCIS should be confirmed by stereotaxic vacuum biopsy, or the second preference of stereotaxic excisional biopsy.^[9] Magnetic resonance imaging (MRI) is used in DCIS management to evaluate the extent and distribution of the disease and to evaluate the contralateral breast.^[10] It is also used for early diagnosis of invasive and non-invasive breast cancer in high-risk lesions.^[11] Although MRI has been shown to be significantly more sensitive than mammography for the diagnosis of DCIS, its specificity is lower and non-malignant lesions may be interpreted as malignancy, which may lead to unnecessary interventions.^[12,13] In the current study, MRI was also applied to the high-risk patient group to confirm the spread of the disease in the breast and suitability for BCS.

The diagnosis of DCIS after biopsy depends on the experience and interpretation of the pathologist. Since DCIS is a lesion between IDC and ADH, it may be interpreted in favor of ADH or in favor of IDC by pathologists with different levels of expertise.^[14] Therefore, in case of radiopathological incompatibility, it may be necessary to obtain a second expert opinion to prevent insufficient or unnecessary aggressive surgery. In the current study, adjuvant treatment (RT and/or HT) was planned for the patients with radiopathological incompatibility after the histopathological results were obtained from a second expert opinion.

Risk factors for IDC can be listed as positive family history, age, obesity, and high lifetime exposure to estrogen. Patients with the same risk factors are also at high risk for DCIS lesions.^[11] Although some previous studies have reported that a significant proportion of DCIS lesions do not transform into IDC, many studies have been conducted to determine which DCIS lesions can become IDC, and the various prognostic factors that predict the risk of recurrence after treatment. Clinically, palpable, multifocal localized tumours of increasing size,

comedo type, high grade and molecular subtype [estrogen receptor (ER) -, progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) +] lesions have been shown to be a greater risk in terms of recurrence.^[15-17] Nomograms with clinicopathological factors that predict the risk of relapse and IDC in DCIS patients have been developed. The Van Nuys Prognostic Index (VNPI) was the first risk scoring unit to be defined.^[18] Later, risk factors were further expanded and the Memorial Sloan-Kettering Nomogram was defined.^[19] In recent years, genetic risk scoring nomograms created with cancer genes have been developed, of which OncotypeDx is one. With these scoring systems, studies predicting the need for adjuvant RT treatment have been conducted by calculating the risk of recurrence after BCS treatment.^[20] In the current study, molecular subtype luminal A (14; 58.3%) and small tumor size (median 12.5 mm) were the indicators of good prognosis, while comedo variant (9; 37.5%), grade 3 (12; 50%) and We can list multifocal or multicentric (13; 54.16%) lesions as poor prognostic factors. Especially 4 patients with multifocal localized lesions were reoperated because negative surgical margins could not be achieved in the first operation.

Surgical methods applied in DCIS lesions do not affect the OS of the patient, but have been shown to affect LR rate in a 10-year follow-up study. The most important factor in minimizing LR in DCIS surgery is resection of the mass with negative surgical margins. There is a current trend moving from aggressive surgery to minimally invasive surgery, as a result of advances in imaging, pathology, treatment and tumor biology. The surgical method to be applied is decided as a result of good preoperative clinical staging with a multidisciplinary approach. Multicentric localized tumors >4 cm larger than breast size, failure to obtain negative surgical margins after BCS and Mx method are indicated for patient preference.^[4,21] In cases where Mx is not indicated, the primary approach is BCS. The advantage of Mx surgery compared to BCS surgery is that the LR rate is very low and adjuvant RT treatment is not required. In addition, unlike IDC, early reconstruction surgery can be applied in patients who undergo Mx because there is no need for RT treatment.^[22] In our clinic, Mx operation was preferred for 6 patients with multicentric location detected in preoperative staging. Although BCS was initially selected, as a safe negative surgical margin could not be provided for 4 patients with multifocal localization, 2 mastectomies and 2 re-excision surgeries were applied. Early re-operations are important to be able to provide safe negative surgery as evidenced by the absence of recurrence in the current patients.

Today, sentinel lymph node biopsy (SLNB) is recommended instead of routine axillary dissection in patients without clinical and radiological axillary metastasis in invasive breast cancer surgery. Axillary dissection is performed for patients with positive SLNB, although the American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) reported 10-year results of no clinically axillary metastasis with T1 and

T2 invasive breast cancer, even if 1 or 2 SLNBs are positive, and axillary dissection was performed in patients who received RT and systemic treatment after BCS, with no significant difference determined in terms of OS and DFS among those who received or did not receive these treatments.^[23] In DCIS lesions, which are non-invasive breast cancer, the rate of axillary metastasis is as low as 1-2%. Randomized studies (NSABP B-17 and B-24) have reported that the risk of nodal recurrence is very low, at a rate of 1%.^[24,25] It is appropriate to perform SLNB in DCIS lesions only in high-risk patients (palpable mass, comedo type, multicentric located) with suspicion of invasive cancer focus and in patients who will undergo Mx again after surgery. SLNB is not recommended for other lesions.^[26] In the current study, routine SLNB was applied to patients who underwent Mx. SLNB was performed in only 2 (8.3%) patients in the high risk group who underwent BCS, and SLNB was not positive in any of the patients who underwent biopsy.

Surgical margin status has been the subject of many studies of DCIS patients undergoing BCS and is still a matter of current debate. Since DCIS recurrences are 40-50% IDC, it is very important to obtain a negative surgical margin. In a study where the positive margin and the negative margin were compared, the negative margin width was discussed in terms of ipsilateral IDC recurrence, but the recurrence rate was significantly lower compared to the positive surgical margin.^[27] The Federation of French Cancer Centers (FNCLCC) recommended a surgical margin of 3 mm for DCIS in a multi-center study.^[28] In a subsequent meta-analysis, it was found that the surgical margin of 2 mm was significantly lower in patients who underwent BCS and RT, compared to operations performed with a lower surgical margin.^[29] The Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline recommends the negative surgical margin width as 2 mm in DCIS patients undergoing BCS and RT. It has been suggested that the decision for re-operation should be made for patients with negative margins of <2 mm by considering other risk factors affecting recurrence.^[30] The median value of the surgical margin distance in the current series patients who underwent BCS in our clinic was 5mm (range, 0-20 mm). Re-operation was performed for 4 patients when safe surgical margins could not be obtained in the first operation.

The LR rate is quite high after BCS. Randomized studies of EORTC, UK / ANZ, SweDCIS, NSABP B-17 were conducted to reduce LR after BCS and determine RT efficiency. The common result of those studies was that adjuvant RT administration after BCS reduced both ipsilateral IDC and DCIS recurrence.^[24,31-33] In addition to those studies, the necessity of RT treatment due to the increased morbidity and the fact that RT treatment does not affect the risk of LR in low-risk DCIS lesions has been the subject of studies. In low-risk DCIS lesions, BCS with a wide negative surgical margin and BCS+RT treatment have been compared and different results have been reported regarding the efficiency of RT

in low-risk DCIS lesions.^[34-36] Therefore, it can be considered that RT should be given after BCS in eligible patients until a definitive protocol defining the low-risk DCIS patient group is established. In the current study, BCS was applied to a total of 16 patients as a result of re-operations. Postoperative RT was not given to 2 of the 16 patients as they had comorbid diseases and low grade DCIS was the histopathological result, so only HT was given. The other 14 patients received RT after BCS.

Studies have been conducted showing the benefit of HT as adjuvant therapy after BCS and RT treatment in DCIS patients. In the NSABP-24 study, it was shown that tamoxifen treatment after BCS+RT treatment in DCIS patients reduced the incidence of ipsilateral and contralateral recurrence, DCIS and IDC in the ER+patient group. This benefit could not be demonstrated in ER- patients.^[37] In the treatment of NSABP-35, the efficacy of tamoxifen, an adjuvant therapy, and anastrozole, an aromatase inhibitor, in postmenopausal hormone-positive women was compared. While the recurrence of ipsilateral invasive breast cancer was lower in the anastrozole group aged <60 years, both treatments were found to reduce the recurrence and incidence of invasive breast cancer and DCIS at a similar rate in patients aged > 60 years.^[38] In the current study, 21 (87.5%) patients were in Luminal A or B molecular subtype and HT was applied.

CONCLUSION

DCIS is a non-invasive breast cancer disease and although various risk scoring nomograms have been developed and are in current use, which lesion will progress to IDC cannot be predicted exactly. The increasing rate of diagnosing DCIS with screening mammograms and applying aggressive treatment to low-risk DCIS patients has been criticized in some studies. In addition, the necessity of RT treatment after BCS in low-risk DCIS lesions is still a matter of research. With a multidisciplinary approach and good preoperative staging, RT can be recommended for eligible patients after BCS, and HT for ER+patients by evaluating the most appropriate surgical method and risk factors for DCIS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ankara Training and Research Hospital Ethics Committee (decision no: 598, date: 24/02/2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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