

# Saf Duktal Karsinoma İn situ'lu Hastalarda Adjuvan Radyoterapi Etkinliğinin Farklı Değişkenlere Göre Değerlendirilmesi

## Evaluation of Adjuvant Radiotherapy Efficacy in Pure Ductal Carcinoma In situ Patients According to Different Variables

Feryal KARACA<sup>1</sup>, Selahattin MENTES<sup>1</sup>, Timucin CIL<sup>2</sup>, Sıddık KESKİN<sup>3</sup>

<sup>1</sup> Adana City Training and Research Hospital, Department of Radiation Oncology, Adana, Turkey

<sup>2</sup> Adana City Training and Research Hospital, Department of Medical Oncology Adana, Turkey

<sup>3</sup> Van Yüzüncü Yıl University, Faculty of Medicine, Department of Biostatistics Van, Turkey

### Özet

**Amaç:** Duktal karsinoma in situ, meme kanserinin invaziv olmayan bir patolojisidir. Saf duktal karsinoma in situ, sıklıkla invaziv meme kanserleri ile birlikte görülmesine rağmen oldukça nadirdir. Bu çalışmanın amacı, adjuvan radyoterapi alan in situ duktal karsinom hastalarının farklı değişkenlere göre dağılımını ve birbirleriyle ilişkilerini incelemek ve bu hastalarda adjuvan radyoterapinin klinik takip üzerindeki etkilerini belirlemektir.

**Gereç ve Yöntemler:** Çalışmaya Adana Şehir Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi polikliniğine başvuran ve saf duktal karsinoma in situ tanısıyla adjuvan radyoterapi alan 27 hasta dahil edildi.

**Bulgular:** Hastaların premenopozal dönemde yaş ortalaması 45.33, postmenopozal dönemde 59.83 idi ve her iki grubun yaşları karşılaştırıldığında istatistiksel olarak anlamlı sonuç elde edildi ( $p = 0.001$ ). Yaş ile tümör çapı (% 38.8) değerlendirildiğinde istatistiksel olarak anlamlı bulundu ( $p < 0.05$ ). Yaş ilerledikçe, tümör çapının artma eğiliminde olduğu söylenebilir.

**Sonuç:** Yaş, tümör boyutu, reseptör durumu, operasyon sınırı, histopatolojik grade, multifokalite ve adjuvan tedaviler, duktal karsinom in situ hastalarının lokal nükslerinde ve sağkalımı üzerinde etkilidir.

**Anahtar kelimeler:** Duktal karsinoma in situ, Adjuvan radyoterapi, Lokal rekürrens, Meme kanseri

### Abstract

**Objective:** Ductal carcinoma in situ is a non-invasive pathology of breast cancer. Pure ductal carcinoma in situ is extremely rare, although it is often accompanied by invasive breast cancers. The aim of this study is to examine the distribution of ductal carcinoma in situ patients receiving adjuvant radiotherapy according to different variables and their relationship with each other and to determine the effects of adjuvant radiotherapy on clinical follow-up in these patients.

**Material and Methods:** The study included 27 patients who applied to the Adana City Training and Research Hospital Radiation Oncology outpatient clinic and received adjuvant radiotherapy with a diagnosis of pure ductal carcinoma in situ.

**Results:** The mean age of the patients was 45.33 year in the premenopausal period and 59.83 in the postmenopausal period, and a statistically significant result was obtained when the age of both groups was compared ( $p = 0.001$ ). Age and tumor diameter (38.8%) was assessed statistically significant ( $p < 0.05$ ). It can be stated that the tumor diameter tends to increase with increasing age.

**Conclusion:** Age, tumor size, receptor status, operation margin, histopathological grade, multifocality and adjuvant treatments are effective on local recurrences and survival in ductal carcinoma in situ patients. Patients diagnosed with ductal carcinoma in situ receive adjuvant radiotherapy after breast conserving surgery, reducing the risk of local recurrences.

**Keywords:** Ductal carcinoma in situ, Adjuvant radiotherapy, Local recurrence, Breast cancer

**Yazışma Adresi:** Feryal KARACA, Adana Şehir Eğitim ve Araştırma Hastanesi, Radyasyon Onkolojisi Anabilim Dalı, Adana, Türkiye

Telefon: +90 505 407 19 93 Mail: feryalkaraca@gmail.com

**ORCID No (Sırasıyla):** 0000-0002-1474-1382, 0000-0002-1371-7356, 0000-0002-5033-1479, 0000-0000-0001-9355-6558

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## INTRODUCTION

Ductal carcinoma in situ (DCI) is a non-invasive pathology of breast cancer (BC). Pure DCI is extremely rare, although it is often accompanied by invasive BCs. As with invasive BCs, the risk of developing DCI increases with age. Risk factors between DCI and invasive carcinoma are similar such as inherited factors, enhanced density of breast, weight gain, situation of not giving birth and giving birth at older ages. Mutations of BRCA1 and BRCA2 genes are risk factors for DCI as well as in ovarian cancer and invasive BC. A 5% mutation in these genes can lead to DCI development. DCI is rare in women under the age of 30. The risk of occurrence in patients between the ages of 40-49 increases 0.6 times, and between 70-84 years, 1.3 times.

The risk of metastasis or mortality is <1% (1). It is a known fact that not all DCI cases are prone to invasive BC progression. Although DCI is considered to be preinvasive, not all lesions display invasion (2). Increased DCI cases have been observed due to the widespread use of BC screening methods and digital mammography. Mammographic findings of DCI cases are calcified foci within the breast tissue. It should be borne in mind that, in mammography DCI foci can occur not only in calcified areas, but also in non-calcified ones (3,4).

Biopsy is performed for histopathological diagnosis and grade determination subsequent to the detection of the lesion by radiological scanning methods. DCI pathology differs due to epithelial proliferation, cellular atypia, cytoplasmic features, nuclear pleomorphism, mitotic activity and the arrangement of ductal cells such as cribriform, solid, micropapillary. The presence of comedonecrosis and invasive component in an extensive tumor suggests high grade lesion. Sentinel lymph node (SLN) biopsy is not recommended in DCI cases, except in patients with high-grade and lymphovascular invasion (LVI) (5).

The aim of this study is to examine the distribution of DCI patients receiving adjuvant radiotherapy (RT) according to different variables and their relationship with each other and to determine the effects of adjuvant RT on clinical follow-up in these patients.

## MATERIAL AND METHODS

In The study included 27 patients who applied to the Adana City Training and Research Hospital Radiation Oncology outpatient clinic and received adjuvant RT with a diagnosis of pure DCI between May 2016-November 2019. Our study was conducted retrospectively following the ethics committee approval obtained from Adana University Faculty of Medicine Ethics Committee (2019/21). This study was conducted in accordance with the Declaration of Helsinki. After the clinical and radiological evaluations of the patients, their staging was performed according to the "American Joint Committee on Cancer" (AJCC) 7th edition tumor, nodes, metastasis (TNM) system and accepted as Tis-E0 (6).

## Radiotherapy

Considering with age, histopathological features, accompanying chronic diseases and general condition, 50 Gy external curative RT was given to 7 (25.9%) patients by Intensity-modulated radiotherapy (IMRT) method. In 20 (74.07%) patients, a total of 60 Gy RT was applied by IMRT method by giving 50 Gy to the entire breast and 10 Gy boost to the operation loge.

## Statistical Analysis

SPSS (ver: 21) (Statistical Package for Social Sciences IBM Coop., New York) statistical program was used for all statistical computations. Descriptive statistics for the continuous variables were presented as Mean, Standard deviation, minimum and maximum values while count and percentages for categorical variables. Normality assumption was evaluated with Kolmogorov- Smirnov test. After determining that the normality assumption is not be provided. Mann- Whitney U test was used to compare pre and post menopause groups. In addition, Spearman correlation coefficients were performed to determine linear relationships among the continuous variables. Statistical significance level was considered as 5%.

## RESULTS

The mean age of the patients was 55 (min: 39 - max: 77) and 9 (33.3%) patients were premenopausal, 18 (66.7%) patients were in the postmenopausal period. On average, height (cm) was 162 (min: 157- max: 168) and weight (kg) was 73.2 (min: 65- max: 91). Breast conserving surgery (BCS) was fulfilled in all patients and histopathologically, only DCI was detected.

**Table 1. Descriptive statistics for categorical variables**

	n (%)
Multifocality	
No	27 (100)
Breast laterality	
Left Breast	11 (40.7)
Right Breast	16 (59.2)
DCI	27 (100)
E0	27 (100)
Calcification on mammography	
Absent	7 (25.9)
Present	20 (74.1)
Grade	23 (23.2)
1	19 (70.4)
2	5 (18.5)
3	3 (11.1)
ER	
No	4 (14.8)
Yes	23 (85.2)

PR	
No	3 (11.1)
Yes	24 (88.9)
Her2 receptor	
No	10 (37)
Yes	6 (22.2)
Unmeasured	11 (40.7)
Ki 67	
2	9 (33.3)
3	8 (29.6)
4	8 (29.6)
5	2 (7.4)
LVI	
No	27 (100)
SLN	
No	27 (100)
Axillary dissection	
No	27 (100)
Surgical margin (mm)	
1	8 (29.6)
2	2 (7.4)
3	10 (37)
≥4	7 (25.9)
Endocrine therapy	
Yes	9 (33.3)
No	18 (66.7)
RT	
Yes	27 (100)
Local recurrence	
No	27 (100)
Metastasis	
No	27 (100)
Surviving patients	
Yes	27 (100)

In the current study, calcification was detected in 20 (74.1%) patients on mammography, although 7 (25.9%) patients did not have calcification (**Table 1**). Histopathologically, 19 (70.4%) patients were grade 1, 5 (18.5%) patients were grade 2, 3 (11.1%) patients were grade 3 (**Table 1**). The estrogen (ER) receptors were positive in 23 (85.2%) patients and negative in 4 (14.8%) patients. The progesterone (PR) receptor was positive in 24 (88.9%) patients and negative in 3 (11.1%) patients (**Table 1**). Human epidermal growth factor receptor 2 (HER2) was not measured in 11 (40.7%) patients and was measured in 16 patients. Measurements were positive in 6 patients (22.2%) and negative in 10 (37%) patients (**Table 1**). The value of Ki 67 was 2 in 9 (33.3%) patients, 3 in 8 (29.6%) patients, 4 in 8 (29.6%) patients, and 5 in 2 (7.4%) patients (**Table 1**). Eight (29.6%)

patients had 1mm surgical margin, 2 (7.4%) patients had 2mm surgical margin, 10 (37%) patients had 3mm surgical margin, 7 (25.9%) patients had ≥4mm surgical margin (**Table 1**). None of the patients had LVI and none of them had SLN and axillary dissection. Adjuvant RT was given to all patients and 9 (33.3%) of those received endocrine therapy additionally. In our trial, progression-free survival continues in all patients (100%) receiving adjuvant RT (**Table 1**).

Some variables discussed in the study were evaluated according to the state of menopause (**Table 2**). The mean age of the patients was 45.33 in the premenopausal period and 59.83 in the postmenopausal period, and a statistically significance was seen/observed between the groups for age and RT dose (p values; 0.001 and 0.012 respectively) significance was seen between the groups for age and RT dose (p values; 0.001 and 0.045 respectively). In this case, it was assigned that the RT dose in the postmenopausal period was approximately 4 Gy higher.

Correlation between variables such as age and tumor diameter (38.8%) was assessed statistically significant (p <0.05) (**Table 3**). Accordingly, it can be stated that the tumor diameter tends to increase with increasing age. Similarly, a positive relationship was identified between height and follow-up duration after diagnosis.

## DISCUSSION

Increasing BC scanning methods recently causes an increase in DCI cases. DCI is a pathology that occurs within the basal membrane of the breast epithelium, ranging from low-grade lesions resembling atypical hyperplasia to high-grade or anaplastic lesions. Although it is generally a component of invasive BCs, it can rarely be seen as pure DCI (5). Evaluation of rare DCI cases in this study makes it valuable.

Mammography is a radiological imaging method in which not only invasive lesions of the breast can be detected, but also in situ lesions. Ernster et al., reported that DCI is more sensitive to mammography than invasive BCs (7). In mammography, DCI appears as calcified foci and thin linear branching of these calcifications indicates high grade DCI, while amorphous ones indicate low grade DCI. Pleomorphic calcifications can be observed in both low grade and high grade DCI cases. Also, DCI foci can give images compatible with soft tissue abnormalities as well as create tumor-like images in mammography (8). In this study we conducted, all patients were diagnosed with mammography. Greenwood et al., stated that magnetic resonance (MR) is much more sensitive than mammography in DCI. They also emitted that DCI foci do not demonstrate tumor compatible images in MR generally, and radiological findings compatible with tumor can be obtained less frequently. Even if they reported that high and intermediate grade DCI cases can be differentiated thanks to MR, mammography remains valid due to its easily accessible and widespread use (9).

**Table 2. Descriptive statistics and comparison results according to menopause status**

		n	Mean	Std. Dev.	Min.	Max.	p
Age	Premenopausal	9	45.33	4.062	39	49	0.001
	Postmenopausal	18	59.83	9.709	49	77	
	Total	27	55.00	10.735	39	77	
Weight	Premenopausal	9	75.33	10.025	65.0	91.0	0.781
	Postmenopausal	18	72.28	4.885	65.0	78.0	
	Total	27	73.29	6.977	65.0	91.0	
Follow-up duration after diagnosis (month)	Premenopausal	9	25.33	10.320	8	33	0.118
	Postmenopausal	18	24.44	2.995	21	29	
	Total	27	24.74	6.230	8	33	
RT dose (Gy)	Premenopausal	9	54.44	5.270	50	60	0.045
	Postmenopausal	18	58.89	3.234	50	60	
	Total	27	57.41	4.466	50	60	
Tumor Diameter	Premenopausal	9	1.90	0.578	1.50	2.90	0.820
	Postmenopausal	18	2.17	0.691	1.50	3.40	
	Total	27	2.08	0.658	1.50	3.40	

**Table 3. Correlation coefficients between variables**

	Age	Height	Weight	Follow-up duration after diagnosis	RT dose (Gy)	Tumor Diameter
Age	1					
Height	-0.302	1				
Weight	0.408*	0.487**	1			
Follow-up duration after diagnosis	-0.173	0.734**	0.282	1		
RT dose (Gy)	0.168	0.651**	0.186	-0.647**	1	
Tumor Diameter	0.388*	-0.231	0.029	-0.472*	0.507**	1

\*:  $p < 0.05$ ; \*\*:  $p < 0.01$

Histopathological grade and local recurrence (LR) are related in DCI. Solin et al., specified that 5 year local control is better in patients with grade 3 DCI with comedo architecture than 10 year local control (10). In EORTC's 10.5-year observation study, intermediately or poorly differentiated DCI patients were ascertained to have a higher risk of LR than well differentiated DCI patients (11). In our study, there were 19 (70.4%) patients with grade 1 tumors, but LR was not determined in any of the patients included in the study.

In DCI cases, ER, PR, Her2 receptors can be positive / negative (12). In our study, the receptor distribution in the whole group was different, and Ki 67 was found to be low in all patients.

SLN biopsy is an effective and accurate diagnostic method in patients with invasive breast carcinoma (13), but is controversial in DCI. SLN biopsy is not recommended in Pure DCI cases. In contrast, it is recommended in these situations such as suspected invasive cancer, solid mass, diffuse microcalcification, multicentric DCI foci, high grade tumor,

tumors larger than 3-4 cm and recurrence of any kind of BC (14). All of our patients were pure DCI and none had LVI. SLN biopsy and axillary dissection were not performed since the patients in the study did not have negative risk factors.

Patients with surgical margin continuity tend to have a higher risk of LR than those without (14). Various treatment modalities have been developed to avoid over or under treatment in DCI. In patients with surgical margins, cosmetic defects may occur following the resection. In recent studies, 2 mm margin has been defined as the standard in DCI cases (15). The risk of ipsilateral tumor recurrence is reduced in DCI removed with a 2 mm margin. Patients with Comedo necrosis, young patient age, negative ER status, high grade and large size of tumor have a high risk of ipsilateral tumor recurrence. Regardless of whether a RT is given to patients in these risk groups, excision with a margin of more than 2 mm is required. Patients operated with margin over 2mm and without additional treatment have been reported. In the meta-analysis of EBCTCG covering 10 years of research,

ch, patients with negative margin who were applied tumor excision alone were compared with those who received RT after the operation, and LR was found to be 26.0% vs 12.0%, respectively ( $p < 0.001$ ). In the same study, LR was shown to be 48.3% vs 24.2% ( $p < 0.001$ ), respectively, for patients with a positive margin (16). In a study involving 1266 patients with 10-year follow-up results, Van Zee *et al.*, compared the rate of surgical margin distance and LR in patients treated with excision alone. They determined the LR rate in the patients with negative margin to be 16% at  $> 10$ mm surgical margin, 23% between 2.2-10mm, and 27% for those less than 2mm. Simultaneously, they found that the LR rate in tumors with positive margin was 41% ( $p < 0.001$ ) (17). According to the results of these studies, surgical margin should be at least 2mm is recommended. In our study, only 8 (29.6%) patients had surgical margin distance of 1mm.

The recurrence rate in invasive BCs is higher than DCI and is responsible for about 50% of them. In some retrospective studies, approximately 33% of low grade DCI cases were observed to progress to invasive BC after 20 years of follow-up, and concordant histology and the same marker expression were found to increase the risk of recurrence in DCIs.

Hormonal therapy via Tamoxifen (Tmx) is a treatment option in ER receptor positive DCI cases and is not applied to postmenopausal DCI patients in many centers due to their side effects and inadequate clinical studies (18). There are two randomized clinical trials investigating the role of Tmx, which inhibits the ER receptor, in BCs. In the NSABP study, Tmx in DCI patients was comprehended to prevent the development of invasive carcinoma in the ipsilateral breast (18). In addition, DCI patients who did not receive RT and used Tmx displayed a decrease in the risk of recurrence in the ipsilateral breast (18). Endocrine treatment is used more frequently in USA than in other countries, and almost half of the patients who have positive ER receptors use Tmx (19). In this study, adjuvant Tmx therapy was fulfilled in 9 (33.3%) patients with premenopausal and positive ER receptors, and none of them had LR and metastases.

In previous studies, it was an option not to give adjuvant RT after excision in DCI cases with a tumor smaller than 1 cm, however, in a subsequent study, an increase in tumor recurrence in the ipsilateral breast was perceived in low-intermediate grade DCI cases with excision alone. Consequently, it was concluded that low grade DCI cases were not actually low risk for LR, and compared to high grade DCI cases, LR developed over a longer period of time (19).

In DCI cases, adjuvant whole-breast RT (WBRT) is recommended at level 1 and reduces the risk of ipsilateral breast tumor recurrence (IBTR) by the rate of 50%. It has recently been suggested that the application of WBRT to patients with high-risk DCI is associated with a statistically significant increase in survival. Therefore, WBRT is applied to DCI cases after local excision. In the current study, 27 (100%) patients who were followed up after RT are still alive without LR.

In our study, IBTR and distant metastasis were not defi-

ned as a result of follow-up of patients diagnosed with pure DCI who received a RT. Patients are still being followed up without any problems.

It has been represented that 4-8fx RT boost applied to tumor bed provides a statistically significant decrease in IBTR risk. There are very few studies about the efficacy of RT boost to recurrent DCI due to rare cases of IBTR, heterogeneous DCI lesions, and local recurrence emerging within the long time follow up. In addition, there are delays in the implementation of RT in DCI cases owing their lower incidence and less awareness compared to invasive BCs and RT is not given to these tumors following operation and LR in some centers. The status of comedo necrosis or hormonal receptors is not associated with boost, however, in patients with negative margin, boost is significantly effective. IBTR decreases in both elderly and young patients given boost. A significant reduction in IBTR is achieved by adding boost application to the tumor bed in patients whose survival is estimated between 10-15 years (20). In our study, 20 (74.07%) patients received boost RT to the tumor bed. The dose of RT given to patients in the postmenopausal period was found to be approximately 4 Gy more than in the premenopausal period, and this difference was statistically notable ( $p = 0.012$ ).

The incidence of DCI cases increases with age (21). In our study, DCI was more common in patients with a mean age of 59.83 compared to those 45.33 and a statistically meaningful result was effectuated in the comparison of these two age groups ( $p = 0.001$ ). Adjuvant RT applied to DCI cases reduces local recurrence. The data we obtained in our study were parallel to the results of Narod SA *et al.* (22).

In a recent study, the 5-year recurrence rate in DCI cases treated with mastectomy alone was 0.8%, in RT receiving patients following BCS was 4.1%, and in those who performed BCS alone was 7.2%. In the same study, when variables such as age, clinical presentation, and histopathological grade in DCI are evaluated, it is seen that local recurrence decreases with RT administration (23).

The correlation between age and tumor diameter was examined (38.8%), a statistically crucial ( $p < 0.05$ ) result was established and it was deduced that the tumor diameter tended to increase as patients aging.

There are limitations such as the retrospective study of a small number of patients, different follow-up times and short follow-up. However, since pure DCI cases are rare, it will take time to reach the desired number of patients. Despite all these limitations, we believe that this study, where rare DCI cases are evaluated, will shed light on the future studies.

As a conclusion, Age, tumor size, receptor status, operation margin, histopathological grade, multifocality and adjuvant treatments are effective on LR and survival in DCI patients. Patients diagnosed with DCI receive adjuvant RT after BCS, reducing the risk of LR.

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