

Are Determining Biological Markers Important in Ductal Carcinoma in Situ?

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Abstract

Aim: In the present study, we aimed to investigate the expressions of bcl-2 along with p53 and Ki67 ductal carcinoma in situ (DCIS) of breast cancer.

Method: Biopsy materials of 24 patients, were studied by immunohistochemistry using specific antibodies for Ki67, bcl-2 and p53 along with estrogen and progesteron receptor.

Results: Patients with high grade DCIS were more likely to express p53 compared to those with low-grade DCIS ($p < 0.05$). Contrarily, expressions of bcl-2, estrogen (ER) and progesteron receptors (PR) were found to be increased in low- grade DCIS compared to high grade DCIS ($p < 0.05$). No significant difference could be found in terms of Ki-67 expression in terms of grade classification. Similarly, no significant difference could be found in regards to p53, bcl-2, ER and PR expressions when compared intermediate grade DCIS to either low-or high grade DCIS.

Conclusion: Our findings suggest that studying Ki67 in DCIS seems to be unnecessary in management of DCIS. Similarly, determing the expressions of p53 and bcl-2 does not provide any useful information either for surgical treatment or for endocrine treatment over ER and PR for predicting hormone responsiveness.

Keywords: breast cancer, bcl-2, p53, Ki-67, ductal carcinoma in situ.

INTRODUCTION

The diagnosis of ductal carcinoma in situ (DCIS), has been found to be increased worldwide since implementation of routine mammographic screening [1]. Between 10 to 20 % of women who are treated with local treatment including breast conserving surgery with/without radiation therapy develop an ipsilateral breast cancer recurrence within 15 years, and more than half of those will recur as invasive cancer [2]. The clinical management of low risk DCIS is still controversial whether to proceed with active monitoring or local management strategies including surgery and/or radiotherapy [3]. Therefore, predictive biological markers might be important to distinguish which patients will recur and progress to invasive carcinoma [4-11].

Previous studies have demonstrated expression of p53 was associated with poor pathological features and local recurrence [4-6]. Similarly, DCIS lesions that were Ki67(+)

were statistically significantly associated with subsequent invasive cancer [7]. Nonrecurrent cases were more likely to have low Ki67 staining compared with recurrent cases ($p = 0.002$) [8]. However, no association could be found between aggressive biologic behavior of DCIS including Ki-67 or p53 expression with any vascular pattern or larger lesions in other studies [9, 10]. Furthermore, bcl-2 has been characterized as a protein that counteracts the apoptotic pathways [11]. Clarck et al have shown the anti-apoptotic bcl-2 protein was expressed in 69.1% of cases and was strongly positively correlated with ER and PR [12].

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Due to the few controversial reports, the present study aimed to investigate the expressions of bcl-2 along with p53 and Ki67 of patients diagnosed with DCIS at our institution.

MATERIAL AND METHODS

Patients who underwent surgery with a diagnosis of DCIS were included in the study. Tumor paraffin block sections were obtained from archival tissue material of either biopsy samples or surgical specimens. Expressions of bcl-2, p53, Ki-67, ER and PR were determined by immunohistochemical staining. Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine.

Patients and Tissue Material

Twenty-four patients had a diagnosis of DCIS based on the findings of the previous surgical pathology reports, at the Istanbul University Istanbul Faculty of Medicine, Department of General Surgery. Demographic and clinical characteristics were obtained from chart review. Holland criteria was used in classification of DCIS grade as well-differentiated (low-grade) (n=9), intermediately-differentiated (intermediate grade) (n=8), and poorly-differentiated (high grade) DCIS (n=7) as shown in Figure 1 [13]. The AJCC Staging 8th edition has been used in the clinical and pathological TNM classification [14].

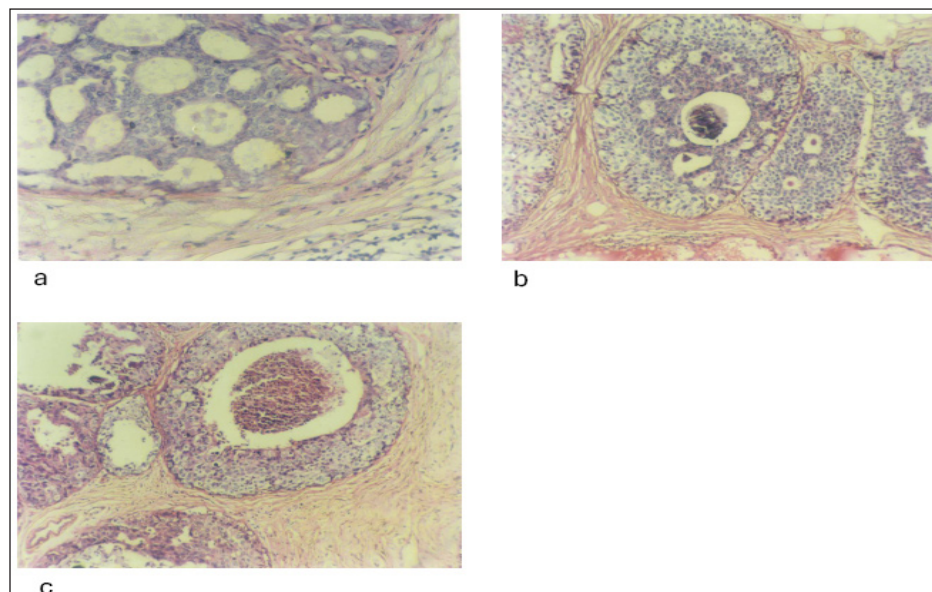


Figure 1. Classification of ductal carcinoma in situ (DCIS) according to grade (a). Well differentiated DCIS (H&E staining, X 310 magnification) (b). Intermediately- differentiated DCIS (H&E staining, X 125 magnification) (c). Poorly- differentiated DCIS (H&E staining, X 125 magnification)

Immunohistochemical Staining

Estrogen (ER) and progesterone receptors (PR), Ki-67, p-53, and bcl-2 were examined in tumor paraffin block sections of 24 patients by immunohistochemistry (IHC). by IHC. Expressions of biomarkers were studied on 5- μ m formalin-fixed paraffin-embedded slides. Sections were incubated with primary antibodies for ER (mouse mAb; NCL-ER-6F11, Novocastra) at 1:40 dilution, for PR (mouse

mAb; NCL-PGR, Novocastra) at 1:40 dilution, for Ki-67 (mouse mAb, Novocastra, NCL-Ki67-MM1) at 1:50 dilution, bcl-2 (mouse mAb; Clone-124, DAKO) at 1:40 dilution, and p-53 (mouse mAb; M 7001, DO-7 clone, DAKO) at 1:100 dilution. The avidin-biotin complex method was used to assess the immunohistochemical expression of biomarkers by using biotin-streptavidine-peroxidase system (LAB VISON; TR-125-HL).

Table 1. Evaluation of the immunohistochemical staining of Ki67, p53, and bcl-2 expressions

Percentage (%)	Score A	Staining Intensity	Score B	Total Score (≤ 1)
0%	0	No	0	A+B/8
0-<1%	1	faint	1	
1-10%	2	intermediate	2	
10-33%	3	strong	3	
33-67%	4			
67-100%	5			

Immunohistochemical Evaluation

Sections were counterstained with hematoxylin and eosin, and the percentage of stained cells was calculated by counting >500 tumor cells. The intensity of the staining, the staining percentage, and pattern of staining (nuclear, membranous, cytoplasmic) were determined for each marker. The intensity was scored as low, moderate, and strong compared with background staining. The staining patterns were nuclear for ER, PR, Ki67, p-53, whereas the staining was cytoplasmic for bcl-2 (Figure 2). ER and PR were considered positive if the nuclear staining was >5%. A semiquantitative scoring system was utilized in evaluation of immunohistochemical staining of bcl-2, p53 and Ki67 reported by Allred et al as explained in Table 1

[15]. Briefly, the total score was calculated by dividing the sum of the scores based on the extent and intensity of the staining marker by 8. Therefore, scores of each marker were found to be between 0 to 1 as shown in Table 5. A score ≥ 0.37 was found to be as positive expression for bcl-2.

Statistical analysis

The SPSS software package program (SPSS, Inc., Chicago, IL) was used for statistical analysis. Mann Whitney-U test was used for evaluating the continuous variables, whereas categorical variables were evaluated by Fisher's exact test. A p value equal or less than 0.05 was defined as statistically significance.

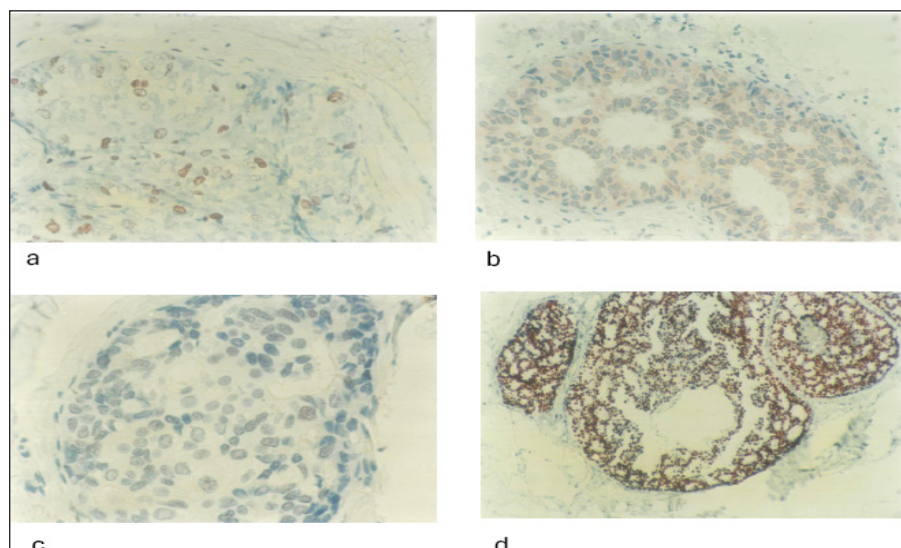


Figure 2. Expression of biomarkers. (a). Ki-67 expression (nuclear staining, X 310 magnification) (b). bcl-2 expression (cytoplasmic staining, X 310 magnification. (c). p53 expression (nuclear staining, X 500 magnification) (d) High ER expression (strong nuclear staining, X 125 magnification)

Table 2. Clinical, radiological and pathological characteristics of patients

Characteristics (n=22)	N (%)
*Symptom (n=22)	
Breast mass	8 (36.4%)
Nipple discharge	1 (4.5%)
Nippleareola complex changes (Paget' disease)	2 (9.1%)
Breast pain	1 (4.5%)
Asymptomatic	10 (45.5%)
*Mammographic findings (n=22)	
Suspicious microcalcifications only	10 (45.4%)
Mass finding	4 (18.2%)
Asymetric density	3 (13.6%)
Mass with suspicious microcalcifications	3 (13.6%)
Asymetric density with suspicious microcalcifications	2 (9.1%)
DCIS grade (n=24)	
Low grade	37.5% (n=9)
Intermediate grade	33.3% (n=8)
High grade	29.2% (n=7)

*Missing data was excluded (n=2).

RESULTS

The median age was 50.5 (range, 35-77). Of 24 patients, 10 (41.7%) were premenopausal, whereas the remaining were postmenopausal. The majority of the patients were asymptomatic (45.5%), and the most common symptom was breast mass (36.4%). Of those, 2 had nipple areola complex changes suspicious of Paget's disease. All patients had a mammogram, and ultrasound. The most common mammographic abnormalities included suspicious pleomorphic microcalcifications (68.2%) and finding of mass (31.8%). Patients were either treated with breast conserving surgery (37.5%, n=9) or mastectomy (62.5%, n=15) (Table 3).

Pathological Findings

Overall, 9 patients (37.5%) had low grade DCIS, and 8 patients (33.3%) had intermediate grade DCIS, whereas 7 patients (29.2%) had high grade DCIS (Table 4). Of 24 patients, all sections that were studied have shown any positive staining of p53 (Figure 1). Overall, the median scores (range, min-max) of p53, Ki67 and bcl-2 were 0.58 (range, 0.25-0.87), 0.51 (range, 0.25-0.87), and 0.40 (0-0.87). The p53 scores according to the DCIS grade were shown in Table 5. Patients with high grade DCIS were more found to have increased p53 scores ($p<0.05$) compared to those with low grade DCIS, whereas no significant difference could be found in p53 scores between low-grade and intermediate grade tumors and between intermediate grade and high grade DCIS.

Similarly, all sections (n=22) that were studied for Ki67 have shown any staining for Ki67 (Figure 1). However, no significant difference could be found between groups in terms of Ki67 scores. Unlike p53 and Ki67, no staining could found in bcl-2 staining in 7 cases of 22 slides (31.8%).

Regarding the cut-of score 0.37, 13 cases (59.1%) had positive expression of bcl-2. The distribution of bcl-2 expressions was shown in Table 6. Contrary to p53, patients with low grade DCIS were more likely to have bcl-2 expressions compared to those with high grade DCIS ($p<0.05$). Nevertheless, no significant difference could be found between low grade and intermediate DCIS and intermediate grade and high grade DCIS in terms of bcl-2 expressions ($p>0.05$).

Of 24 patients, 15 patients (62.5%) had ER- and PR-positivities. The distribution of ER- and PR positivities were shown in Table 6 according to the tumor grade. Similar to bcl-2 expressions, patients with low grade DCIS were more likely to have ER- or PR-positivities compared to those with high grade DCIS ($p<0.05$). However, no significant differences could be found between low-grade and intermediate grade, and intermediate and high grade DCIS ($p>0.05$).

Adjuvant Treatment

Patients were either treated with breast conserving surgery (37.5%) or mastectomy (62.5%) (Table 3). Patients (n=10, 41.7%) with hormone receptor (ER and/or PR) positive breast cancer received tamoxifen as part of their treatment protocol. The majority of the patients (7/9, 77.8%) with breast conserving surgery also received radiotherapy followed by surgery including a chest wall irradiation of 50 Gy.

Outcome

The median follow-up time after surgery was 19.1 months (range, 3-36 months). Only 1 patient with Paget's disease associated with DCIS had a contralateral invasive breast cancer at the 28th month. None of the remaining other patients developed a local or distant recurrence.

Table 3. Management of ductal carcinoma in situ

Management of patients (n=24)	N (%)
Simple mastectomy	6 (25%)
Simple mastectomy+tamoxifen	4 (16.7%)
Simple mastectomy+nodal sampling	1 (4.2%)
Simple mastectomy+nodal sampling+tamoxifen	3 (12.5%)
Skin sparing mastectomy with reconstruction	1 (4.2%)
Segmental mastectomy only	1 (4.2%)
Segmental mastectomy+tamoxifen	1 (4.2%)
Segmental mastectomy followed by radiotherapy	5 (20.8%)
Segmental mastectomy followed by radiotherapy and tamoxifen	2 (8.3%)

Table 4. The distribution of biomarker evaluation of patients diagnosed with ductal carcinoma in situ (DCIS) according to their tumor grade and biomarker that were studied in the present cohort

Biomarker	Overall	Low-grade DCIS	Intermediate Grade DCIS	High-grade DCIS
p53	24	9	8	7
Bcl-2*	22	8	7	7
Ki-67*	22	8	7	7
ER	24	9	8	7
PR	24	9	8	7

ER= estrogen receptor, PR=progesterone receptor.

*Two cases were excluded due to the technical reasons.

Table 5. Median values of scores (min-max) of biomarker expressions according to tumor grade in patients diagnosed with ductal carcinoma in situ (%)

Biomarker expression	Low grade DCIS	Intermediate grade DCIS	High grade
p53 ^{a,b,c}	0.51 (0.25-0.75)	0.54 (0.25-0.87)	0.71 (0.62-0.87)
Ki67 ^{a,b,c}	0.49 (0.25-0.75)	0.55 (0.37-0.62)	0.49 (0.25-0.87)
Bcl-2 ^{a,b,c}	0.52 (0-0.87)	0.44 (0-0.87)	0.21(0-0.75)

^ap53: low grade vs high grade; $p<0.05$; ^bp53: low grade vs intermediate grade; $p>0.05$; ^cp53: intermediate grade vs high grade; $p>0.05$

^aKi67: low grade vs high grade; $p<0.05$; ^b Ki67: low grade vs intermediate grade; $p>0.05$; ^cKi67: intermediate grade vs high grade; $p>0.05$

^aBcl-2: low grade vs high grade; $p<0.05$; ^c: low grade vs intermediate grade; $p>0.05$; ^cp53: intermediate grade vs high grade; $p>0.05$

Table 6. Expressions of ER, PR and bcl-2 according to DCIS grade

Biomarker expression	Low grade DCIS	Intermediate grade DCIS	High grade
ER ^{a,b,c}	77.7% (7/9)	75% (2/8)	28.5% (2/7)
PR ^{a,b,c}	88.8% (1/9)	62.5% (3/8)	28.5% (2/7)
Bcl-2 ^{a,b,c}	87.5% (7/8)	57.1% (3/7)	28.5% (2/7)

ER= estrogen receptor, PR=progesterone receptor

^aER: low grade vs high grade; $p<0.05$; ^bER: low grade vs intermediate grade; $p>0.05$; ^cER: intermediate grade vs high grade; $p>0.05$

^aPR: low grade vs high grade; $p<0.05$; ^bPR: low grade vs intermediate grade; $p>0.05$; ^cPR: intermediate grade vs high grade; $p>0.05$

^aBcl-2: low grade vs high grade; $p<0.05$; ^bBcl-2: low grade vs intermediate grade; $p>0.05$; ^cBcl-2: intermediate grade vs high grade; $p>0.05$

DISCUSSION

Detection of DCIS has risen in the era of mammographic screening. Breast conserving surgery with radiotherapy has been the preferred treatment modality in management of this cancer type that was associated with low breast cancer mortality risk. This approach has been reported to have an annual ipsilateral breast cancer recurrence (IBCR) less than 1% [2]. Long term findings from the joint analysis of NSABP-17 and NSABP-24 have indicated that 53.7% of IBTR occur as invasive breast cancer which was potentially associated with a subsequent risk of breast cancer mortality. Different approaches including molecular gene assays and biological markers based on

immunohistochemistry staining have been developed to assess the individual risk prediction for IBCR after surgery to deescalate the management of DCIS of the breast followed by breast conserving surgery [16]. Due to the decreased cost-effectiveness of expensive gene assays, the clinical utility of other biomarkers should be studied in future clinical studies that could replace these molecular tests. We therefore have investigated expressions of p53, Ki-67 and bcl-2 in patients with a diagnosis of DCIS who were treated with surgery with/without radiotherapy.

In the present study, we have found that patients with high grade DCIS were more likely to express p53 compared to those with low-grade DCIS ($p<0.05$). In concordance

with this finding, previous studies have demonstrated expression of p53 was associated with poor pathological features and local recurrence [4-6]. Frequency of staining for p53 increased with increasing grade of DCIS [5]. Takahashi et al have evaluated 145 HER2+ and 85 triple negative (TN) DCIS cases. HER2 positive DCIS were more likely to have nuclear p53 immunoreactivity ($p = 0.002$) compared to those with TN DCIS. Furthermore, younger patients (age <40) with HER2+ DCIS were found to have a significantly poorer prognosis when their tumor also coexpressed p53 ($p = 0.033$). Similarly, Allred et al investigated the extent of diversity for conventional histologic grade and several prognostic biomarkers assessed by immunohistochemistry comparing a series of pure DCIS ($n = 200$) with a series of invasive breast cancers (IBC; $n = 200$) [18]. They significantly found that diversity of DCIS was highly correlated with mutated p53 ($p = 0.0007$) suggesting that poorly differentiated DCIS may gradually evolve from well-differentiated DCIS by randomly acquiring genetic defects.

Finally, a consecutive series of patients treated for pure ductal carcinoma in situ (DCIS, $n = 110$) and invasive ductal carcinoma (IDC, $n = 243$) was studied [19]. At a median follow-up of 49.8 months, p53 overexpression (HR 3.0, 95% CI 1.1-8.2, $P = 0.036$ and HR 4.4, 95% CI 1.5-12.9, $P = 0.008$) and adjuvant radiotherapy (HR 0.2, 95% CI 0.1-0.8, $P = 0.026$) were found to be independent common predictors of local recurrence in patients treated with breast conserving therapy for both DCIS and IDC. These findings suggest that utilizing p53 as a predictive marker of local recurrence after breast conservation might have clinical implications to decide on surgical management of patients with DCIS.

Unlike p53, expressions of bcl-2, ER and PR were found to be increased in low- grade DCIS compared to high grade DCIS ($p > 0.05$) in the present study. The bcl-2 gene, encodes a protein which appears to play a key role in cell regulation by inhibiting apoptosis [11]. There are few reports on the significance of bcl-2 in DCIS. Clarck et al have studied the expression of bcl-2 in tissue microarray for 188 cases of DCIS. They have shown the anti-apoptotic Bcl-2 protein was expressed in 69.1% of cases and was strongly positively correlated with ER and PR [12]. Quinn et al similarly investigated the expression of bcl-2, ER, c-erbB-2 and p53 proteins expression in a series of 108 cases of DCIS by immunohistochemically staining [20]. In concordance with our findings, the bcl-2 expression was detected in 57 cases (53%) that was adversely associated with the histological grade of DCIS ($p < 0.0001$) indicating that all cases of well-differentiated DCIS were bcl-2 positive and loss of bcl-2 expression was almost exclusively seen

in high grade DCIS lesions. Of note, bcl-2 expression was significantly associated with ER expression ($P < 0.0001$). Forty-seven of 57 (82%) bcl-2 positive cases were ER positive, while 49/51 (96%) bcl-2 negative cases were ER negative. There was a significant inverse correlation between bcl-2 expression and both p53 protein expression ($P = 0.0004$) suggesting that loss of bcl-2 expression and ER and expression of p53 were associated with poorly differentiated DCIS.

Similar to p53 and bcl-2, Ki-67 as a proliferative marker of tumors was also studied in DCIS lesions in order to categorize DCIS in distinct subgroups. Kerlikowske et al analyzed 1162 women who were diagnosed with DCIS and treated by lumpectomy alone [7]. Of those, 324 cases had a recurrence either in ipsilateral breast or regional or distant at 8-year follow-up. In a multivariable model, DCIS lesions that were p16(+) COX-2(+) Ki67(+) or those detected by palpation were found to be statistically significantly associated with subsequent invasive cancer. A total of 87% of nonrecurrent cases had low Ki67 staining (0% to 10%) compared with 50% among the recurrent cases ($P = 0.002$) [8]. However, no association could be found between aggressive biologic behavior of DCIS including Ki-67 or p53 expression with any vascular pattern or larger lesions in other studies [9, 10]. Similar to these studies, no significant difference could be found in terms of Ki-67 expression in terms of grade classification in the current study.

Unlike our findings, however, Megha et al reported higher proliferative activity (MIB-1 positive cells) in cases with intermediately or poorly differentiated DCIS with a stem cell phenotype compared to those with intermediately or well differentiated DCIS with a luminal cell phenotype in 37 cases of DCIS [21]. Williams et al similarly studied different biomarkers including Ki-67 in 314 women with DCIS [22]. Independent predictors for invasive recurrence on multivariate analysis at 5-year were high Ki67 expression (HR 1.04, $P = 0.021$) and molecular phenotype (HR 13.4, $P = 0.014$ for Luminal B; HR 11.4, $P = 0.027$ for HER2 type and HR 10.3, $P = 0.031$ for triple negative compared with Luminal A DCIS).

In conclusion, our findings suggest that studying biomarkers including Ki67 may provide little benefit in management of DCIS. Whether determining the expressions of p53 or bcl-2 may provide any useful information either for local treatment or for endocrine treatment over ER and PR to predict endocrine therapy responsiveness, should be proven in future studies.

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Author Contributions

Study conception or design: MÇ, NC, EY, TD, AI.

Data acquisition and analysis of data: EY, ST, AI, TD, MM, VO

Methodology and immunohistochemistry and analysis of the data: NC, MÇ, ST, EY

Writing of the manuscript: NC, MÇ, EY

Review-editing of the manuscript: EY, ST, AI, TD, MM, VO

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