



# Long-term Follow-up Results of Our Patients Diagnosed with Ductal Carcinoma *In Situ*: Usefulness of the Van Nuys Prognostic Index

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## ABSTRACT

**Objective:** The aim of the study was to investigate the relationship between the Van Nuys prognostic index (VNPI) score and disease-free survival (DFS) as well as overall survival (OS) in patients with ductal carcinoma *in situ* (DCIS).

**Material and Methods:** Ninety-five female patients diagnosed with pure DCIS, who were treated and followed up at Kartal Dr. Lütfi Kırdar City Hospital between January 2008 and December 2018, were evaluated retrospectively. Data regarding age, DCIS diameter, grade, presence of necrosis, and surgical margin -factors used to calculate the VNPI score- were extracted from patient records. DFS was defined as the time from diagnosis to the development of ipsilateral or contralateral DCIS or invasive breast cancer. OS was defined as the time from primary DCIS diagnosis to death or the last contact.

**Results:** A statistically significant correlation was found between the VNPI score and OS and DFS in both univariate and multivariate analyses [for OS hazard ratio (HR): 7.05, 95% confidence interval (CI): 2.57-19.35,  $p < 0.001$ ; for DFS HR: 8.8, 95% CI: 3.62-21.76,  $p < 0.001$ ]. The addition of radiotherapy to local excision showed limited benefits in the patient group with low VNPI scores. As the VNPI score increased, the contribution of radiotherapy to DFS improved.

**Conclusion:** VNPI score can be a helpful guide in determining treatment decisions for pure DCIS.

**Keywords:** Ductal carcinoma *in situ*; Van Nuys prognostic index; disease free survival; overall survival; radiotherapy

## INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is characterized by the abnormal proliferation of epithelial cells within the breast ducts. The incidence of DCIS increased from 5.8 per 100,000 women in the 1970s to 32.5 per 100,000 in 2004, after which it plateaued.<sup>1-3</sup> The widespread use of mammography for breast cancer screening is the main reason for this rise. Although DCIS is less prevalent than invasive breast cancer, its incidence increases with age.<sup>1,4</sup> Shared risk factors for both DCIS and invasive breast cancer include a family history of breast cancer, higher breast density, obesity, nulliparity, and late age at first childbirth.<sup>5-9</sup>

The risk of metastasis or death in patients diagnosed with pure DCIS is rare (<1%).<sup>10</sup> Although DCIS is considered a premalignant lesion, it exhibits a spectrum of tumor biology.<sup>11</sup> Breast-conserving surgery (BCS) is the standard treatment for DCIS, and postoperative radiation therapy (RT) is frequently used. Numerous randomized studies have shown that RT following BCS reduces the risk of local recurrence.<sup>12</sup> However, the survival benefit of RT for patients with DCIS remains unproven. The primary goal of systemic therapy is to reduce the risk of invasive breast cancer in the ipsilateral and/or contralateral breast. For ER-positive DCIS patients who do not undergo bilateral mastectomy, endocrine therapy

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with tamoxifen or anastrozole is recommended. Although endocrine therapy has not been shown to improve survival, it has been found to reduce recurrence rates.<sup>13</sup> The Van Nuys prognostic index (VNPI) is a model used to estimate the risk of ipsilateral breast recurrence. Introduced in 2003, the University of Southern California/VNPI is a numerical system that helps assess recurrence risk. The risk factors for recurrence in this model include tumor size, patient age, surgical margin width, nuclear grade, and the presence of comedo-type necrosis. Each factor is assigned a value between 1 and 3, with 1 representing the most favorable prognosis and 3 the least favorable. The final score, ranging from 4 to 12, is the sum of the individual scores. A score between 4 and 6 indicates low risk, 7 to 9 indicates moderate risk, and 10 to 12 indicates high risk.<sup>14</sup>

In this study, we aimed to investigate the relationship between the VNPI score and disease-free survival (DFS), and overall survival (OS) in patients with pure DCIS followed up at our center.

## MATERIAL AND METHODS

This study included female patients diagnosed with DCIS who were treated and followed up at the Medical Oncology Clinic of Kartal Dr. Lütfi Kırdar City Hospital between 2008 and 2018. Patients were excluded from the study if they had microinvasive or invasive disease, positive surgical margins, incomplete data required for calculating the VNPI score, were lost to follow-up, had missing file data, or had a history of secondary malignancies. Nuclear grade was assessed by comparing the nuclei of ductal epithelial cells to normal breast tissue. All pathology samples were evaluated by the same pathologist. Only female patients were included in the study. Patient records were retrospectively reviewed for the following data: age at diagnosis, menopausal status, smoking and alcohol history, number of pregnancies, breastfeeding duration, family history, type of surgery performed, DCIS diameter, nuclear grade, surgical margin status, radiotherapy and endocrine therapy status, presence of local recurrence, development of ipsilateral or contralateral invasive breast cancer, and patient final outcomes. VNPI scoring was performed for each patient.

### Statistical Analysis

Statistical analysis was performed using the SPSS 22.0 program (SPSS Inc., Chicago, Illinois). Fisher's exact test and chi-square test were used for categorical variables. The Student's t-test was used for comparing numerical variables between two independent groups, assuming normal distribution. If not, the Mann-Whitney U test was applied. DFS was defined as the time from diagnosis to the onset of ipsilateral or contralateral

invasive breast cancer or DCIS. OS was defined as the time from the diagnosis of primary DCIS to death or last contact. Kaplan-Meier analysis was used to estimate the impact of clinical and pathological features on DFS and OS. Multivariate Cox regression analysis was used to assess survival-related factors. A significance threshold of 0.05 was applied. The Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital approved the study (date: September 30, 2023, approval number: 2023/514/260/17). The study was conducted in accordance with the principles of the Declaration of Helsinki.

## RESULTS

Files of 1214 patients diagnosed with DCIS and treated at our center between 2008 and 2018 were retrospectively reviewed, with a minimum follow-up period of 5 years. After applying the inclusion and exclusion criteria, 95 female patients were included in the study. The patients' ages at diagnosis ranged from 24 to 77 years, with a median age of  $49.55 \pm 11.64$  years. The median follow-up duration was 136.9 months (range: 27.4–286.3 months). Of the 95 patients, 80 were alive and 15 had passed away. Of the patients who died, two died of invasive breast cancer, two from secondary malignancies (colon cancer and gastrointestinal stromal tumors), and 11 from other causes. Forty-four (46.3%) patients were premenopausal, and 51 (53.7%) were postmenopausal. BCS was performed on 56 (58.9%) patients, while modified radical mastectomy (MRM) was performed on 39 (41.1%) patients. Fifty-one (53.7%) patients received adjuvant radiotherapy, while 44 (46.3%) did not. Seventy-two (75.8%) patients received adjuvant hormonal therapy, and 23 (24.2%) did not. The median DCIS diameter was  $25.48 \pm 20.33$  mm (range: 3–90 mm). Sixteen patients (16.8%) had a surgical margin of less than 20 mm, and 7 (7.5%) of these patients had positive surgical margins, all of whom underwent re-excision to achieve negative margins. Seventy-two patients (75.8%) had positive estrogen receptor (ER) status, while 23 (24.2%) had negative ER status. Patient characteristics are summarized in Table 1.

Upon evaluation of the VNPI, 29 (30.5%) patients were classified as low risk (score 4–6), 55 (57.9%) as moderate risk (score 7–9), and 11 (11.6%) as high risk (score 10–12) (Table 2).

Relapse occurred in 15 (15.8%) patients. Of these, 4 (4.2%) had DCIS recurrence in the same breast, 5 (5.3%) had invasive breast cancer in the same breast, and 6 (6.3%) had invasive breast cancer in the contralateral breast. The median DFS could not be reached, but the median OS was found to be 281.9 months [95% confidence interval (CI): 126.2–437.6 months]. The 5-year estimated OS was 77% and DFS was 67% while the 3-year estimated OS was 92% and DFS was 86%. The 10-year OS and DFS rates according to VNPI score are shown in Table 3 and Figures 1 and 2.

After adjusting for confounding factors (age, menopausal status, smoking history, type of surgery (BCS vs. MRM), adjuvant radiotherapy, and adjuvant endocrine therapy), VNPI was found to be an independent prognostic factor for both OS [hazard ratio (HR): 7.05, 95% CI: 2.57-19.35,  $p < 0.001$ ] and DFS (HR: 8.8, 95% CI: 3.62-21.76,  $p < 0.001$ ). Univariate and multivariate analyses of OS and DFS are presented in Tables 4 and 5.

According to VNPI, in patients who underwent BCS, 19 were in the low-risk group, 34 in the moderate-risk group, and 3 in the high-risk group. The relationship between VNPI and DFS was statistically nonsignificant, but patients with lower VNPI scores showed longer DFS. In the BCS group, the additional contribution of radiotherapy to DFS was nonsignificant

( $p = 0.5$ ). Similarly, no significant contribution of endocrine therapy to DFS was observed ( $p = 0.2$ ) (Table 6). As the VNPI score increased, the contributions of radiotherapy and endocrine therapy to DFS became more pronounced.

## DISCUSSION

DCIS is a heterogeneous lesion, and there is no uniform approach to its treatment. For some patients, local excision alone is sufficient, while others may require adjuvant radiotherapy, and in some cases, mastectomy is considered. Treatment decisions are based on clinical, radiological, and pathological data. However, the risk of overtreatment for low-risk patients and undertreatment for high-risk patients remains a challenge.

TABLE 1: Patient characteristics.	
Categorical variables	n (100%)
<b>Diagnostic age</b>	
≤60 years	79 (83.2)
>60 years	16 (16.8)
<b>Menopausal status</b>	
Premenopausal	44 (46.3)
Postmenopausal	51 (53.7)
<b>Smoking history</b>	
Current	13 (13.7)
Past	82 (86.3)
<b>Surgical method</b>	
MRM	39 (41.1)
BCS	56 (58.9)
<b>Hormone receptor status</b>	
Positive	72 (75.8)
Negative	23 (24.2)
<b>Radiotherapy</b>	
Yes	51 (53.7)
No	44 (46.3)
<b>Endocrine therapy</b>	
Yes	72 (75.8)
No	23 (24.2)
n: number; MRM: Modified radical mastectomy; BCS: Breast conserving surgery.	

TABLE 2: Distribution of patients according to VNPI score.	
VNPI score	n (100%)
Low	29 (30.5)
Intermediate	55 (57.9)
High	11 (11.6)
Low risk: scores between 4 to 6, intermediate risk: scores between 7 to 9, high risk: scores between 10 to 12. VNPI: Van Nuys prognostic index.	

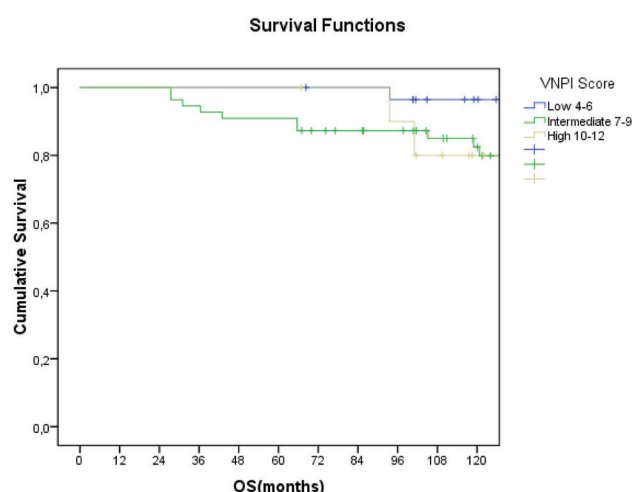


FIGURE 1: Estimated 10 years OS according to VNPI score.

VNPI: Van Nuys prognostic index; OS: Overall survival

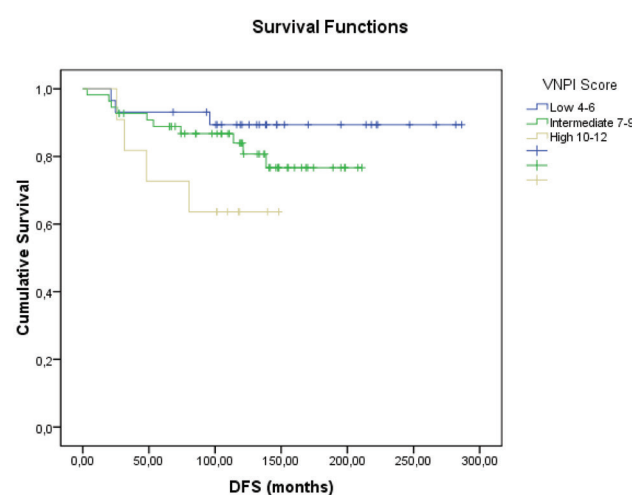


FIGURE 2: Estimated 10 years DFS according to VNPI score.

VNPI: Van Nuys prognostic index; DFS: Disease free survival

Currently, the standard treatment for many patients consists of local excision followed by radiation therapy. While 10-year breast cancer-specific mortality is low regardless of surgical treatment (1.9-2.0% for BCS vs. 1.3% for mastectomy), local recurrence following BCS for DCIS is more common than after mastectomy (13-25% vs. 3% after 10 years).<sup>15</sup> While most local recurrences after mastectomy are invasive, approximately half of all recurrences following BCS are DCIS.<sup>15,16</sup> Factors such as larger tumor size, palpable mass, grade III disease, surgical margin  $\leq 2$  mm, ER-negativity, and age, increase the likelihood of local recurrence.<sup>17</sup>

Studies have shown that local excision alone is sufficient in patients with low VNPI scores. In a study by Silverstein et al., it was reported that in cases with a VNPI score of 3 or 4,

there was no significant difference in local recurrence-free survival (100% vs. 97%;  $p$ =not significant) with or without radiotherapy after 8 years of follow-up. The addition of radiotherapy contributed to an increased benefit in patients with a VNPI score of 5, 6, or 7, (85% vs. 68%;  $p$ =0.017), with the most significant contribution observed in patients with a VNPI score of 8 or 9.<sup>18</sup> Similarly, a study of 215 patients with DCIS who underwent BCS without radiotherapy or hormonal treatment found a significant prognostic relationship between VNPI score and DFS ( $p$ <0.05).<sup>19</sup>

In our study, non-invasive and invasive recurrence rates were significantly lower in patients with low VNPI scores compared to those with intermediate and high VNPI scores. Moreover,

**TABLE 3: Estimated 10 years OS and DFS according to VNPI score.**

VNPI score	Life tables			
	10 years OS rates	p	10 years DFS rates	p
Low	91%	Low vs. others $p$ =0.038 High vs. others $p$ =0.723	96%	Low vs. others $p$ =0.232 High vs. others $p$ =0.073
Intermediate	88%		76%	
High	61%		25%	

VNPI: Van Nuys prognostic index; OS: Overall survival; DFS: Disease free survival.

**TABLE 4: Univariate and multivariate analysis for OS.**

Univariate analysis for OS				Multivariate analysis for OS		
Categorical variables	p	Hazard ratio	CI 95%	p	Hazard ratio	CI 95%
Diagnostic age						
≤60 years	0.12	2.4	0.77-8.00			
>60 years						
Menopausal status						
Premenopausal	0.30	1.7	0.59-5.12			
Postmenopausal						
Smoking history						
Current	0.48	2.0	0.26-15.82			
Past						
Surgical method						
MRM	0.15	0.4	0.16-1.32			
BCS						
Radiotherapy						
Yes	0.14	2.24	0.76-6.56			
No						
Endocrine therapy						
Yes	0.17	2.06	0.72-5.87			
No						
VNPI score						
Low vs. Intermediate vs. high	0.001	4.44	1.5-10.63	<0.001	7.05	2.57-19.35
Low vs. others	0.12	3.83	0.35-41.8			
High vs. others	0.006	4.68	1.56-14.02			

OS: Overall survival; MRM: Modified radical mastectomy; BCS: Breast conserving surgery; VNPI: Van Nuys prognostic index; CI: Confidence interval.

**TABLE 5: Univariate and multivariate analysis for DFS.**

Univariate analysis for DFS				Multivariate analysis for DFS		
Categorical variables	p	Hazard ratio	CI 95%	p	Hazard ratio	CI 95%
Diagnostic age						
≤60 years	0.61	0.6	0.15-3.00			
>60 years						
Menopausal status						
Premenopausal	0.03	0.3	0.11-0.94			
Postmenopausal						
Smoking history						
Current	0.82	1.18	0.27-5.19			
Past						
Surgical method						
MRM	0.55	0.74	0.28-1.94			
BCS						
Radiotherapy						
Yes	0.86	1.08	0.41-2.82			
No						
Endocrine therapy						
Yes	0.22	1.84	0.68-4.99			
No						
VNPI score	<0.001	8.88	3.62-21.76			
Low vs. Intermediate vs. high	0.04 <0.001	8.18	1.08-61.86	<0.001	8.8	3.62-21.76
Low vs. others		14.5	5.29-39.92			
High vs. others						
DFS: Disease free survival; MRM: Modified radical mastectomy; BCS: Breast conserving surgery; VNPI: Van Nuys prognostic index; CI: Confidence interval.						

DFS: Disease free survival; MRM: Modified radical mastectomy; BCS: Breast conserving surgery; VNPI: Van Nuys prognostic index; CI: Confidence interval.

**TABLE 6: Contribution of radiotherapy and endocrine therapy according to VNPI score in the subgroup of patients undergoing breast conserving surgery.**

VNPI score	Radiotherapy		P	Endocrine therapy		p
	Yes	No	0.5	Yes	No	0.2
Low	15	4		17	2	

in patients undergoing BCS, the addition of radiotherapy did not show a statistically significant contribution to DFS.

Tamoxifen (20 mg) or anastrozole (1 mg) can be used in adjuvant endocrine therapy for ER-positive DCIS. Randomized prospective studies have shown that both drugs reduce the frequency of ipsilateral and/or contralateral invasive and non-invasive recurrences. However, their effects on OS have not been demonstrated.<sup>20-23</sup> In a study comparing low-dose tamoxifen (5 mg/day) with the standard dose (20 mg/day), no significant difference was found in recurrence rates between the two doses.<sup>24</sup> In our study, receiving adjuvant endocrine therapy contributed to DFS, although this was not statistically significant.

As screening mammography becomes more widespread, the number of patients diagnosed with DCIS has increased. There remains uncertainty regarding the optimal treatment

approach for DCIS, as consensus on the best strategy is still lacking. While our study has limitations due to its retrospective nature and small sample size, it offers valuable insights into the role of VNPI in predicting survival outcomes in DCIS.

## CONCLUSION

In conclusion, the VNPI score may play a decisive role in the treatment of DCIS. Local excision alone could be sufficient, particularly in the low-risk VNPI group. We believe that the VNPI score can be valuable in identifying the patient group for which radiotherapy can be omitted.

## Ethics

**Ethics Committee Approval:** The Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital approved the study (date: September 30, 2023, approval number: 2023/514/260/17).

**Informed Consent:** Retrospective study.



## Footnotes

### Authorship Contributions

Surgical and Medical Practices: Ö.N.S., T.B., Ş.K., H.O., Concept: Ö.N.S., T.B., H.O., Design: Ö.N.S., H.O., Data Collection or Processing: Ö.N.S., T.B., Ş.K., Analysis or Interpretation: T.B., Literature Search: Ö.N.S., Writing: Ö.N.S., T.B., Ş.K., H.O.

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

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