

Clinicopathologic, mammographic, and sonographic features in 1,187 patients with pure ductal carcinoma in situ of the breast by estrogen receptor status

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Abstract The clinicopathologic, mammographic, and sonographic findings in patients with pure ductal carcinoma in situ (DCIS) were assessed by estrogen receptor (ER) expression. After institutional review board approval, patients with pure DCIS evaluated from January 1996 to July 2009 with known ER status and available imaging were identified. Images were reviewed as per the ACR BI-RADS® lexicon (4th edition). Clinical, pathologic, and imaging characteristics were analyzed by ER status using *t* test, Chi square test, and Fisher’s exact test. Of 1,219 patients with pure DCIS and known ER status identified, 1,187 with complete data were included. Mammography was performed in all 1,187 patients and sonography in 519

(44 %). There were 972 (82 %) patients with ER-positive and 215 (18 %) with ER-negative disease. ER-negative DCIS was more likely to be high grade (93 vs 44 %, $p < 0.0001$), associated with comedonecrosis (64 vs 29 %, $p < 0.0001$), and multifocal (23 vs 15 %, $p = 0.009$). On sonography, ER-negative DCIS was more likely to be visible (61 vs 46 %, $p = 0.004$), larger (mean size, 2.3 vs 1.6 cm, $p = 0.006$), and show posterior shadowing (53 vs 28 %, $p = 0.006$). Mastectomy was more frequently performed for ER-negative DCIS (47 vs 37 %, $p = 0.008$). Palpable DCIS was visible on sonography in 55 % of cases and mammography in 81 %. Compared with ER-positive palpable DCIS, ER-negative palpable DCIS was larger and more likely to be visible on sonography. Compared with ER-positive noncalcified DCIS, ER-negative noncalcified DCIS was less likely to be visible on mammography. ER-positive and ER-negative pure DCIS have different clinicopathologic and imaging characteristics. ER-negative DCIS is associated with worse prognostic factors than ER-positive DCIS. On sonography, ER-negative DCIS is more frequently visible than ER-positive DCIS, tends to be larger, and more frequently demonstrates posterior shadowing.

Keywords Breast cancer · Biological subtype · Estrogen receptor · DCIS · Mammography · Breast ultrasound

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Introduction

The detection of ductal carcinoma in situ (DCIS) has increased significantly with the widespread use of screening mammography in asymptomatic women. DCIS now accounts for up to 30 % of breast cancers in the screening

population [1–4]. Early diagnosis and management of DCIS are critical in preventing the development of invasive cancer [5–9]. Mammography remains the most valuable technique for the detection of DCIS [10, 11].

Ductal carcinoma is a heterogeneous disease with regard to biology and has histopathologic characteristics similar to those of invasive breast cancer. The malignant potential and behavior of DCIS after treatment are influenced by nuclear grade (low, intermediate, or high), architectural pattern (solid, cribriform, papillary, or micropapillary), and the presence of comedonecrosis. High-nuclear grade and comedonecrosis indicate aggressive biological attributes to DCIS and are associated with a higher rate of local recurrence [2, 5, 11–13].

In recent years, molecular profiling has led to improved understanding of the biology and behavior of invasive breast disease [14]. Within the spectrum of invasive breast cancer, intrinsic biological subtypes exist that have different prognoses and responses to local and systemic therapies [15]. The intrinsic biological subtypes can be approximated with immunohistochemical evaluation of estrogen receptor (ER), progesterone receptor, and HER2-neu expression.

Increasing evidence suggests that biomarker expression in cancer patients influences disease detection, staging, response to treatment, and prognosis after treatment [1, 16]. ER is the best studied biomarker in breast cancer, and the expression or lack of expression of ER defines and differentiates the luminal and basal breast cancer biological subtypes. Several studies have demonstrated a relationship between ER expression and nuclear grade [17–24] and risk of local recurrence of DCIS [25–28]. However, reports focusing on the influence of ER expression on the clinicopathologic and imaging features of DCIS are scarce [29]. The purpose of this retrospective study was to describe the clinicopathologic, mammographic, and sonographic findings in patients with pure DCIS by ER expression.

Materials and methods

Following Institutional Review Board approval, our Breast Cancer Management System database was searched to identify all patients with a diagnosis of pure DCIS and known ER status evaluated and treated between January 1, 1996, and July 31, 2009. Demographic characteristics and clinical, pathologic, mammographic, and sonographic findings were retrospectively analyzed by ER status for all the patients ($n = 1187$) as well as for the subsets of patients with noncalcified lesions ($n = 126$, 11 %) and palpable lesions ($n = 115$, 10 %). Breast magnetic resonance imaging (MRI) findings were not included in this analysis, since MRI was not used routinely during the study period.

Clinicopathologic assessment

The following variables were reviewed: age at diagnosis, menopausal status, use of hormone replacement therapy, bilaterality, presence of contralateral breast cancer (DCIS or invasive breast cancer), initial presenting signs (clinical or radiologic), and type of the first definitive surgery (segmentectomy or mastectomy).

The original pathology slides from biopsy and/or surgery were re-reviewed for this study by a dedicated breast pathologist with 20 years experience. The following parameters were recorded: nuclear grade [well differentiated (grade 1), intermediate (grade 2), or poorly differentiated (grade 3)]; presence of comedonecrosis; architectural pattern (solid, cribriform, papillary, micropapillary, unspecified, or combination); size of the DCIS; and presence of multifocality and multicentricity. ER status was defined as positive if nuclear staining was present in at least 1 % of cells.

Mammography

Each mammogram (standard two-view with additional views as necessary) was originally read by one of 14 dedicated breast radiologists with 6–21 years of experience, and re-read by one of four dedicated breast radiologists with 6–12 years of experience. The American College of Radiology-Breast Imaging Report and Data System (ACR BI-RADS[®]) lexicon, 4th edition [30], was used to classify all the mammographic findings: breast density, masses (shape, margins, density), calcifications (morphology, distribution), architectural distortion, and focal asymmetry. The extent of DCIS was defined as the maximum length for calcifications and maximum diameter for masses. Multifocality was defined as the presence of two or more foci of disease in the same breast quadrant. Multicentricity was defined as the presence of disease in multiple breast quadrants or disease foci separated by more than 5 cm. For cases of multifocality or multicentricity, the size of the largest lesion was recorded.

Sonography

Sonograms were originally read by one of the 14 dedicated breast radiologists with 6–21 years of experience and re-read by one of four dedicated breast radiologists with 6–12 years of experience. Findings were interpreted utilizing the ACR BI-RADS[®] ultrasound lexicon, 4th edition [31], and classified as masses, parenchymal heterogeneity, or calcifications. Parenchymal heterogeneity was defined as an area of breast tissue that appeared distorted with no definable central mass [13, 32, 33]. Multifocality, multicentricity, and size were determined as for mammography.

Statistical methods

T-tests, Chi square tests, and Fisher's exact tests were used to assess univariate association between variables of interest and ER status. Multiple logistic regression was performed to evaluate multivariable associations with ER status. *P* values less than 0.05 were considered statistically significant. No adjustments were performed for multiple comparisons. All the statistical analyses were performed using SAS software, version 9.2, for Windows (SAS Institute Inc., Cary, NC).

Results

Clinicopathologic data

Of the 1,219 patients identified, 32 were excluded because of microinvasion ($n = 8$) or absent imaging ($n = 24$), leaving 1,187 patients for analysis. All 1,187 patients had mammography, and 519 (44 %) had whole-breast sonography. A total of 215 patients (18 %) had ER-negative and 972 (82 %) ER-positive disease. The mean age at diagnosis was 56 years [standard deviation (SD) = 11] for all patients, 57 years (SD = 11) for patients with ER-negative lesions, and 55 years (SD = 11) for patients with ER-positive lesions.

Major clinicopathologic differences between the ER-negative and ER-positive patients are summarized in Table 1. Patients with ER-negative DCIS were slightly older ($p = 0.008$) and more likely to be postmenopausal ($p = 0.003$). ER-negative DCIS was more likely to be high grade ($p < 0.0001$), and to demonstrate comedonecrosis ($p < 0.0001$), multifocality ($p = 0.009$), multicentricity ($p = 0.014$), and solid architectural pattern ($p < 0.0001$). Mastectomy was more common among patients with ER-negative DCIS ($p = 0.008$). Clinical symptoms were present in 165 (14 %) of patients: 119 (10 %) had palpable masses and 46 (4 %) nipple discharge. Patients with ER-negative DCIS were somewhat more likely to present with a clinical abnormality, but this difference did not reach statistical significance (18 vs 13 %, $p = 0.083$).

Of the 115 patients with palpable DCIS, 29 (25 %) had ER-negative and 86 (75 %) ER-positive disease. The mean age of these patients was 49 years (SD = 11), which was significantly younger than the mean age for the rest of the population (56 years, SD = 11, $p < 0.0001$). Mammography and sonography findings were available for 115 patients (100 %) and 78 patients (68 %), respectively. Among patients with palpable DCIS, ER-negative DCIS was more likely than ER-positive DCIS to be high grade ($p < 0.0001$), multifocal ($p = 0.012$), multicentric ($p = 0.023$), and treated by mastectomy ($p = 0.147$).

Among the 126 patients with noncalcified DCIS, mammography and sonography findings were available for 126 patients (100 %) and 110 patients (96 %), respectively. Compared to ER-positive noncalcified DCIS, ER-negative noncalcified DCIS was larger at histopathology ($p = 0.006$) and more likely to be high grade ($p < 0.0001$), multifocal ($p = 0.004$), multicentric ($p = 0.005$), and treated by mastectomy ($p = 0.034$).

Mammography findings

A mammographically detected abnormality was the primary presentation for both ER-negative and ER-positive DCIS (Table 2). In both ER groups, lesions were highly visible on mammography, and calcifications were the dominant mammographic finding. Fine linear and fine pleomorphic calcifications were the most common morphology seen in both ER groups, with increased frequency in high-grade subgroup.

Only 9 % of patients in each ER group presented with a mass. Mass density was distributed differently by ER status ($p = 0.045$): masses were isodense to breast tissue in all eight ER-negative tumors but isodense in 42 (62 %) and high density in 26 (38 %) of the 68 ER-positive tumors with the available data.

In the subset of 115 patients with palpable DCIS, 93 patients (81 %) had a corresponding mammographic abnormality: 69 (75 %) had calcifications only, 13 (14 %) a mass or focal asymmetry, and 10 (11 %) a mass with calcifications. No significant differences were observed in mammographic findings or in mammographic visibility by ER status.

In the subset of 126 patients with noncalcified DCIS, 85 patients (67 %) had a corresponding mammographic abnormality: 52 (61 %) had a mass, 20 (24 %) focal asymmetry, and 13 (15 %) architectural distortion. ER-negative noncalcified DCIS was less likely than ER-positive noncalcified DCIS to be visible on mammography ($p = 0.0335$).

Sonography findings

A sonographic abnormality was seen in 254 patients (49 %); 227 (89 %) of these patients had masses and 27 (11 %) had parenchymal heterogeneity (Table 3). Compared to ER-positive DCIS, ER-negative DCIS was more likely to be visible ($p = 0.004$), was larger ($p = 0.006$) and more frequently demonstrated posterior shadowing ($p = 0.006$).

In the subset of 115 patients with palpable DCIS, 43 patients (55 %) had lesions that were visible on sonography. The most common sonographic finding for both ER-negative and ER-positive palpable DCIS was a hypoechoic

Table 1 Clinicopathologic features in 1,187 patients with pure DCIS by ER status

Feature	All patients	ER-negative DCIS (N = 215)	ER-positive DCIS (N = 972)	p value
Age, years, mean (SD)	56 (11)	57 (11)	55 (11)	0.008
Size at pathology, cm, mean (SD) ^a	2.5 (2.6)	2.8 (2.5)	2.4 (2.7)	0.057
Postmenopausal status ^b	857 (72)	172 (81)	685 (71)	0.003
Hormone replacement therapy	418 (35)	86 (40)	332 (34)	0.105
Presentation ^c				0.083
Clinical symptom	165 (14)	38 (18)	127 (13)	
Radiologic finding	1,016 (86)	177 (82)	839 (87)	
Bilateral cancer	46 (4)	7 (3)	39 (4)	0.603
Type of contralateral breast cancer				0.659
DCIS	36 (77)	5 (71)	31 (78)	
Invasive cancer	11 (23)	2 (29)	9 (23)	
Multifocal ^d	142 (16)	41 (23)	101 (15)	0.009
Multicentric ^e	152 (17)	42 (23)	110 (15)	0.014
Grade ^f				<0.0001
1	104 (9)	4 (2)	100 (10)	
2	450 (38)	11 (5)	439 (45)	
3	629 (53)	199 (93)	430 (44)	
Histology				<0.0001
Solid	239 (20)	85 (40)	154 (16)	
Papillary	22 (2)	1 (0)	21 (2)	
Micropapillary	41 (4)	8 (4)	33 (3)	
Cribriform	133 (11)	7 (3)	126 (13)	
Combination	696 (59)	99 (46)	597 (61)	
Not specified	56 (4)	15 (7)	41 (4)	
Comedonecrosis ^g	398 (36)	134 (64)	264 (29)	<0.0001
Surgery type				0.008
Segmentectomy	724 (61)	114 (53)	610 (63)	
Mastectomy	463 (39)	101 (47)	362 (37)	

Note Unless otherwise indicated, data are numbers of patients (percentages)

Bold values ($p < 0.05$) are statistically significant

^a Not recorded in 211 patients

^b Not recorded in 4 patients

^c Not recorded in 6 patients

^d Not recorded in 316 patients

^e Not recorded in 271 patients

^f Not recorded in 4 patients

^g Not recorded in 70 patients

irregular hypervascular mass, parallel in orientation without posterior features. ER-negative palpable DCIS was larger ($p = 0.008$) and more likely to be visible ($p = 0.079$) on sonography than ER-positive palpable DCIS.

In the subset of 126 patients with noncalcified DCIS, 104 patients (95 %) had lesions that were visible on sonography. The most common sonographic appearance for both ER-negative and ER-positive noncalcified DCIS was a hypoechoic, irregular mass. ER-negative noncalcified DCIS was larger ($p = 0.037$) than ER-positive noncalcified DCIS.

Visibility of DCIS on mammography and sonography

The visibility of DCIS in patients who had both mammography and sonography are summarized in Table 4. ER-positive DCIS was more likely than ER-negative DCIS to

be visible only on mammography, while ER-negative DCIS was more likely than ER-positive DCIS to be visible on both mammography and sonography or on sonography only ($p = 0.032$).

In the subgroup with palpable DCIS, 78 of 115 patients (68 %) had both mammography and sonography; in the subgroup with noncalcified DCIS, 110 of 126 patients (96 %) had both mammography and sonography. There were no differences in visibility on mammography or sonography by ER status in these groups of patients.

Discussion

The National Cancer Institute has identified a need for the investigation and validation of molecular factors that improve risk stratification and facilitate optimal treatment of patients with DCIS [1, 16, 34]. The ER expression rate

Table 2 Mammographic features in 1,187 patients with pure DCIS by ER status

Feature	ER-negative DCIS (N = 215)	ER-positive DCIS (N = 972)	p value
Visible lesion	199 (93)	923 (95)	0.162
Size, cm, mean (SD) ^a	3.2 (2.8)	2.8 (3.0)	0.141
Tissue density			0.054
Fatty	3 (2)	40 (4)	
Scattered fibroglandular	68 (35)	267 (29)	
Heterogeneously dense	116 (59)	550 (59)	
Extremely dense	8 (4)	68 (7)	
Mammographic finding			0.013
Calcifications only	172 (86)	785 (85)	
Mass only	7 (4)	45 (5)	
Architectural distortion	0	13 (1)	
Focal asymmetry	3 (2)	17 (2)	
Mass with calcifications	9 (5)	34 (4)	
Architectural distortion with calcifications	7 (4)	6 (1)	
Focal asymmetry with calcifications	1 (1)	21 (2)	
Mass shape ^b			0.323
Round	0	14 (19)	
Oval	3 (38)	23 (31)	
Lobular	0	11 (15)	
Irregular	5 (63)	26 (35)	
Mass margin ^b			0.624
Circumscribed	2 (25)	17 (23)	
Microlobulated	0	4 (5)	
Obscured	1 (13)	26 (35)	
Indistinct	3 (38)	20 (27)	
Spiculated	2 (25)	11 (15)	
Mass density ^c			0.045
Isodense	8 (100)	42 (62)	
High density	0	26 (38)	
Calcification morphology ^d			0.122
Round	1 (1)	17 (2)	
Amorphous	42 (22)	166 (21)	
Coarse heterogeneous	39 (21)	116 (15)	
Fine pleomorphic	81 (42)	393 (50)	
Fine linear/linear branching	25 (13)	94 (12)	
Calcification distribution ^e			0.287
Diffuse	2 (1)	8 (1)	
Regional	33 (18)	109 (14)	
Segmental	41 (22)	178 (22)	
Linear	5 (3)	47 (6)	
Cluster/group	105 (56)	459 (57)	

Note Unless otherwise indicated, data are numbers of patients (percentages)

Bold values ($p < 0.05$) are statistically significant

^a Not recorded in 190 patients

^b Not recorded in 13 patients

^c Not recorded in 19 patients

^d Not recorded in 61 patients

^e Not recorded in 48 patients

in DCIS ranges from 49 to 97 % (mean, 69 %) [16]. Relationships have been described between ER status and disease recurrence [25–28], nuclear grade [17, 18, 20, 23], indications for adjuvant hormonal therapy [35–38], and presurgical prediction of disease extent [7, 39]. However, information is scarce regarding the influence of ER

expression on clinicopathologic and imaging features of DCIS [29].

Our analysis of 1,187 patients confirmed differences in clinical, pathologic, and imaging features between ER-negative and ER-positive DCIS. Patients with ER-negative DCIS were slightly older and more likely to be

Table 3 Sonographic features in 519 patients with pure DCIS by ER status

Feature	ER-negative DCIS (N = 106)	ER-positive DCIS (N = 413)	p value
Visible lesion	65 (61)	189 (46)	0.004
Size, cm, mean (SD) ^a	2.3 (1.7)	1.6 (1.4)	0.006
Mass shape ^b			0.296
Oval	6 (16)	39 (29)	
Round	2 (5)	7 (5)	
Irregular	29 (78)	87 (65)	
Mass margin ^c			0.284
Circumscribed	3 (9)	14 (10)	
Indistinct	21 (62)	65 (49)	
Angular	3 (9)	15 (11)	
Microlobulated	3 (9)	31 (23)	
Spiculated	4 (12)	9 (7)	
Echogenicity ^d			0.259
Hypoechoic	479 (94)	117 (82)	
Isoechoic/hyperechoic	0	6 (4)	
Complex	3 (6)	19 (13)	
Orientation ^e			0.222
Parallel	18 (58)	89 (70)	
Nonparallel	13 (42)	39 (30)	
Posterior features ^f			0.023
None	14 (44)	72 (57)	
Enhancement	0	13 (10)	
Shadowing	17 (53)	35 (28)	
Combined	1 (3)	6 (5)	
Vascularity ^g	15 (68)	77 (77)	0.385

Note Unless otherwise indicated, data are numbers of patients (percentages)

Bold values ($p < 0.05$) are statistically significant

^a Not recorded in 45 patients

^b Not recorded in 57 patients

^c Not recorded in 59 patients

^d Not recorded in 35 patients

^e Not recorded in 68 patients

^f Not recorded in 69 patients

^g Not recorded in 105 patients

postmenopausal than patients with ER-positive disease. ER-negative tumors were larger on sonography, mammography, and pathologic evaluation, and were more likely to be multifocal and multicentric, explaining the higher frequency of mastectomy in this patient group.

The prognosis of DCIS depends on its histopathologic subtype and nuclear grade. A spectrum of mammographic appearances of DCIS have been described in the literature [10, 12, 13, 40–42]. Calcifications are the most common presentation of DCIS; high-grade lesions present predominantly with fine pleomorphic or fine linear branching

Table 4 Visibility of pure DCIS on mammography and sonography by ER status in 519 patients who had both types of imaging

Visible on	ER-negative DCIS (N = 106)	ER-positive DCIS (N = 413)	p value
Neither mammography or sonography ^a	3 (3)	13 (3)	0.032
Sonography only	11 (10)	30 (7)	
Mammography only	38 (36)	211 (51)	
Both mammography and sonography	54 (51)	159 (39)	

Bold values ($p < 0.05$) are statistically significant

^a Lesions not seen on mammography and sonography were diagnosed as follows: prophylactic mastectomy in high risk patient ($n = 3$); excisional biopsy for palpable finding ($n = 2$), Paget's disease of the nipple ($n = 2$), or nipple discharge ($n = 4$); and MRI diagnosis ($n = 5$)

morphology, while low- and intermediate-grade lesions present predominantly with amorphous or coarse heterogeneous morphology [10–12, 40, 43, 44]. Similarly, in our study, high-grade pure DCIS, independent of ER status, presented predominantly as fine pleomorphic or fine linear branching calcifications.

Analysis of the relationship of nuclear grade with ER status showed that 93 % of ER-negative DCIS lesions and only 44 % of ER-positive DCIS lesions were of high-nuclear grade. ER-negative DCIS was more frequently associated with comedonecrosis (64 %). Both high-nuclear grade and comedonecrosis are associated with higher likelihood of local recurrence and development of invasive cancer [25–28]. Our findings agree with the prior studies showing higher ER expression in well-differentiated lesions than in poorly differentiated lesions [17–24, 45].

The reported sonographic appearance of pure DCIS is a hypoechoic, irregular mass with ductal extension without posterior acoustic shadowing or enhancement [13, 46]. The presence of marked hypoechoogenicity, a spiculated margin, a thick echogenic rim, or posterior acoustic shadowing should prompt concern regarding the presence of DCIS with microinvasion or invasive carcinoma [13, 46, 47].

Our analysis showed that ER-negative DCIS was more likely to be visible on sonography than was ER-positive DCIS, whereas ER-positive DCIS was more likely to be visible on mammography only. On sonography, ER-negative DCIS was larger than ER-positive DCIS and more commonly associated with posterior shadowing. These findings suggest that sonography may have a role in the diagnosis and staging of ER-negative DCIS.

Patients with palpable DCIS, an important subgroup, tended to be younger (mean age, 49 years) than other patients. The most common imaging finding for palpable DCIS, independent of ER status, was calcifications. This explains the high visibility of palpable DCIS on

mammography and the moderate visibility on sonography. On sonography, ER-negative palpable DCIS was significantly larger and was more likely to be detected than ER-positive palpable DCIS.

Another important subgroup was patients with noncalcified lesions, including masses, architectural distortion, and/or focal asymmetry [10, 11]. Interestingly, we found a significant difference in mammographic visibility by ER status in this subgroup: ER-negative noncalcified DCIS was less likely to be visible on mammography than ER-positive noncalcified DCIS. In our study, approximately one-third of noncalcified DCIS lesions were mammographically occult, which is concordant with prior reports [10, 46]. Almost all (95 %) noncalcified DCIS lesions were visible on sonography, and sonographic visibility did not differ by ER status. All ER-negative noncalcified DCIS lesions were visible on sonography, and ER-negative lesions were significantly larger than ER-positive lesions. These findings underscore the role of sonography in the evaluation of patients with DCIS, especially ER-negative DCIS.

The major limitation of our study was its retrospective design. Not all the variables were available for the entire set of patients. Sonography is currently not standard of care for patients with DCIS, which explains why 56 % of the patients in our sample did not have sonography performed.

In summary, compared to ER-positive DCIS, ER-negative DCIS is more likely to be detected at a larger size, to be of high nuclear grade, to demonstrate comedonecrosis, and to be detected in older postmenopausal patients. When ER-negative DCIS presents as a mass, it usually is visible on sonography or both sonography and mammography, shows posterior shadowing on sonography, and is isodense to the breast tissue on mammography. ER-negative DCIS is more likely than ER-positive DCIS to be multifocal or multicentric and is more frequently associated with mastectomy. ER-negative noncalcified DCIS is less likely to be visible on mammography than ER-positive noncalcified DCIS. In patients with palpable DCIS, 55 % of lesions were visible on sonography and 81 % were visible on mammography; ER-negative tumors tended to be larger and were more likely to be visible on sonography.

To our knowledge, this is the first large clinical study describing the clinicopathologic and imaging differences associated with biological subtypes of DCIS—differences that may impact diagnosis, staging, and therapy. Further studies are warranted to evaluate the roles of biological markers in the diagnosis and treatment of DCIS.

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Conflict of interest None.

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