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Predictive factors of invasive component in ductal carcinoma in situ

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Abstract

Introduction: ductal carcinoma in situ (DCIS) is a type of non – invasive breast cancer (1). It can be diagnosed with a core biopsy though the method is known to miss 10 % of the cases of invasive carcinoma (IC), and for that reason operative treatment is indicated for all patients (2–4). The need of sentinel lymph node biopsy (SLNB) depends on factors of invasiveness, which are poorly defined (2,5–8). **Aim:** to establish the incidence of IC in preoperatively diagnosed DCIS and evaluate the factors of invasiveness. **Materials and methods:** medical records of 66 women with preoperatively diagnosed DCIS were analyzed. Patients were assigned to either a DCIS group or an IC group based on surgical specimen histology. Clinical, radiological and pathological factors of invasiveness were compared between the groups. The incidence of SLNB and its necessity based on final histological evaluation was determined. **Results:** there was a significantly higher incidence of IC (28.6 %) in MRI compared to DCIS (0 %) when the tumor was 40 mm and larger, $p = 0.037$. Suspicious lymph nodes in radiological assessment were found in 57.1 % of all IC cases, $p < 0.001$. High grade nuclear polymorphism was significantly higher in the IC group and reached 71.4 % compared to the 44.7 % of cases found in the DCIS group, $p = 0.049$. **Conclusions:** predictive factors for invasiveness are the size of the tumor being ≥ 40 mm on MRI, suspicious lymph nodes on radiological assessment and high grade nuclear polymorphism.

Keywords: ductal carcinoma in situ (DCIS), invasive breast cancer (IC), predictive factors, factors of invasiveness, sentinel lymph node biopsy (SLNB).

Introduction

The incidence of breast cancer and premalignant breast diseases has grown due to an available and more applicable breast cancer screening (9). The most common type of non-invasive breast lesion is ductal carcinoma in situ (DCIS) which accounts for 80 % of non – invasive lesions (1,10). DCIS progresses to invasive cancer in 25 % of the cases and invasive components are already present in 10 % of cases, while 20 % of all DCIS are low grade and have a low possibility of becoming invasive (3,4,10). DCIS is usually diagnosed with a core biopsy, but as it cannot completely exclude invasive components (due to targeting errors and poor tissue acquisition), operative treatment is indicated in both low and high – risk lesions. Consequently, low risk lesions are being overtreated and surgical treatment could be less extensive because SLNB is often unnecessarily done (2–4,10). Undertreatment also occurs in some IC cases as current recommendations for SLNB lack sensitivity (10).

Many researches are investigating the clinical, radiological and histological data that might help conclude the recommendations for clinical practice. Clinical factors associated with invasiveness are palpability of the tumor and younger age (< 50 years), which is associated with genetic predisposition, higher amount of endogenous estrogens and a premenopausal state (7,8,11–13). Factors found on radiological assessment that suggest invasiveness are the larger size of the tumor (threshold ranging from 20 to 40 mm), suspicious lymph nodes, a presence of microcalcifications and a solid tumor, high breast density (6,8,14). Core biopsy results are very important in the histological evaluation – negative estrogen and progesterone receptors, positive HER – 2 receptors, an infiltration of lymphocytes, high grade nuclear polymorphism and comedo type necrosis are possible factors of invasiveness (9,15–18). As literature reports inconsistent results and the thresholds vary greatly, no predictable factors for IC are used in clinical practice (19). The aim of our study is to clarify significant factors that could be used to minimize the unnecessary SLNB and reduce the risk of undertreatment.

Materials and Methods

The single institution retrospective study was carried out in the period of 2017 – 2019. 66 women with preoperatively diagnosed DCIS (based on core biopsy) who underwent surgical treatment were elected out of 680 patients (with the D05 and C50 diagnosis). Women were assigned to either the DCIS group or the IC group based on the surgical specimen histology in the final evaluation. The primary tumor (TNM) and the differentiation grade of the IC group tumors are presented in Table 1. The objects of our study are clinical, radiological and pathological factors of invasiveness which were analyzed and compared between the groups. Clinical information that was analyzed included age (< 50 years) and a presence of a

palpable tumor. Data from mammograms, ultrasonography (US) and magnetic resonance imaging (MRI) was used to evaluate the size of the tumor ($\geq$ 20 mm; $\geq$ 30 mm; $\geq$ 40 mm), microcalcifications, suspicious lymph nodes, high – average breast density. Core biopsy results were reviewed and the incidence and significance of high grade nuclear polymorphism, as well as estrogen and progesterone receptors, were compared in both groups. The rate of SLNB was evaluated and compared between the postoperatively formed DCIS and IC groups. IBM SPSS Statistics 23 was used for the statistical analysis. Significant factors found in the multivariate analysis were evaluated with Pearson's chi-square test, Cramer's V correlation coefficient and the likelihood ratio was established. The difference is statistically significant when $p < 0.05$. The study was ethically approved by Bioethics center of Lithuanian University of Health Sciences, ethical approval code BEC – MF – 17.

Results

65.2 % ($n = 43$) of the women were assigned to the DCIS group and 34.8 % ($n = 23$) were assigned to the IC group based on surgical specimen histology in the final evaluation. The IC group tumors were larger than the DCIS group tumors in the radiological assessment but only a threshold of 40 mm was a specific factor of invasiveness on MRI, $p = 0.035$. Suspicious lymph nodes were also a significant sign with a reliable statistical significance on the radiological assessment ($p < 0.001$). High grade nuclear polymorphism was significantly higher in the IC group and reached 71.4 % while it was found in 44.7 % of cases in the DCIS group, $p = 0.049$ (Table 2). The presence of a palpable tumor, age < 50 years, a presence of microcalcifications and a solid tumor, breast density, estrogen and progesterone receptors were not statistically different between the groups, $p > 0.05$ (Table 3). SLNB was performed in 65.6 % ($n = 42$) of all patients (60 % of pure DCIS cases and 73.9 % upstaged DCIS cases) and an invasion to the SLN was found in 11.9 % ($n = 5$) of the preoperatively diagnosed DCIS cases (Table 4).

Tables

Table 1. Classification of invasive carcinoma tumours

Primary tumor (T)	
T1mic	9.1 %
T1a	50.0 %
T1b	18.2 %
T1c	18.2 %
T2	4.5 %
Differentiation grade (G)	
G1	4.8 %
G2	81.0 %
G3	14.2 %

Table 2. Significant factors of invasiveness

Significant factors of invasiveness	Pearson's Chi square (*p*)	Cramer's V (*r*)	Likelihood ratio
Tumor size on MRI ≥ 40 mm	0.037	0.402 (average correlation)	5.901
High grade nuclear polymorphism	0.049	0.257 (weak correlation)	3.982
Suspicious lymph nodes	< 0.001	0.451 (average correlation)	11.362

Table 3. Incidence and significance of clinical, radiological and histological factors of possible invasiveness.

Factor of invasiveness	DCIS group (*n*=43)	IC group (*n*=23)	*p*
Clinical assessment			
Age < 50	14.0 %	26.1 %	0.223
Presence of palpable tumor	57.1 %	77.3 %	0.111
Radiological assessment			
Tumor size in mammogram ≥ 20 mm	52.6 %	71.4 %	0.390
≥ 30 mm	21.1 %	42.9 %	0.266
≥ 40 mm	21.1 %	42.9 %	0.266
Tumor size in sonography ≥ 20 mm	16.0 %	41.2 %	0.069
≥ 30 mm	8.0 %	5.9 %	0.794
≥ 40 mm	4.0 %	0 %	0.404
Tumor size in MRI ≥ 20 mm	46.2 %	57.1 %	0.568
≥ 30 mm	15.4 %	28.6 %	0.410
≥ 40 mm	0 %	28.6 %	0.037
High / average breast density in US	82.6 %	100 %	0.063
Suspicious lymph nodes	14.3 %	57.1 %	< 0.001
Presence of microcalcifications	17.6 %	33.3 %	0.183
Histological assessment			
Positive estrogen receptors	58.1 %	54.5 %	0.799
Positive progesterone receptors	41.9 %	36.4 %	0.683
High grade nuclear polymorphism	44.7 %	71.4 %	0.049

Table 4. Sentinel lymph node biopsy

	DCIS group (*n*=43)	IC group (*n*=23)
Surgery with SLNB (65.6 %)	58.5 %	41.5 %
Surgery without SLNB (34.4%)	72.7 %	27.3 %

Discussion

Breast cancer screening contributes to an elevated number of the DCIS cases and is associated with a high number of overdiagnosed and overtreated patients (20). As there is a gap of knowledge in distinguishing the DCIS that will never become invasive and the high risk cases, both are treated similarly to invasive cancer (10). Current NCCN recommendations do not recommend routine SLNB and state that it should only be considered when a mastectomy is performed or when the anatomical location of the excision is compromising the performance of a future SLNB. On the other hand, Dutch, English and American guidelines indicate the SLNB in the DCIS patients planning to undergo breast sparing surgery in the presence of a palpable or solid mass, lesions > 25 mm, intermediate or high nuclear grade, extensive calcification in the imaging and age < 55 years (10). National comperhensive cancer network (NCCN) also mentions similar factors as local recurrence indicators which happen to be invasive in 50 % of cases [21]. Many low risk DCIS lesions can also match the criteria, leading to an intervention that is too extensive, while high risk lesions may stay underestimated [10].

The decision to perform SLNB needs to be based on the underlying risk of invasion (17). Currently used methods to evaluate the possible invasiveness have a low sensitivity and specificity. Most studies that analyze such factors have a small sample size and thus report inconsistent results, so no predictable factors for IC are used in clinical practice (11). Exact criteria are needed to prevent both unnecessary extensive interventions for pure DCIS cases and non – radical surgeries for patients with an existing IC component. Our aim was to contribute to the creation of recommendations by evaluating most commonly discussed factors of invasiveness that may help choose a more adequate treatment strategy by determining high and low risk cases of DCIS in clinical practice. The study found that statistically significant factors are tumor size ≥ 40 mm on MRI, high grade nuclear polymorphism and suspicious lymph nodes seen in radiological assessment.

Radiological imaging. Greater tumor size in radiological imaging was mentioned as the most generally accepted risk factor, it was determined that tumor size ≥ 20 mm in ultrasonography showed a higher incidence of DCIS upstaging to IC, while other imaging techniques did not show a significant difference (8). Other study reports that tumor size > 20 mm did not significantly differ in postoperatively diagnosed DCIS and IC groups, $p = 0.663$. The cutoff value of size ranges from 20 to 50 mm in mammography in different studies with bigger size being significantly related to IC (2). Studies analyzing factors of invasiveness on MRI also found that tumor size can be a significant factor: one of the studies mentions diameter > 20 mm to be a predictor of an upgrade to IC, while another retrospective study mentions diameter ≥ 30 mm (22). In our study with 3 different thresholds in US, mammogram and MRI, only size ≥ 40 mm in MRI was determined as a significant predictive factor of IC.

Nuclear polymorphism. Nuclear grade is considered to be an important indicator of the biological behaviour of DCIS. Ponti et al established that high grade nuclear polymorphism determines quicker development from DCIS to IC, while a detected low nuclear grade has no significant value (20). Several studies found that DCIS with a microinvasion usually presents with a high nuclear grade compared with pure DCIS (17). Our results coincided with other scientific publications and high and average nuclear polymorphism was more commonly found in the IC group.

Sentinel lymph node biopsy. SLNB is a minimally invasive procedure, which is used with high risk patients for a lymph node metastasis evaluation. The decision to perform SLNB is based on the underlying risk of invasion, as it expands the radicality of the surgery (17). In a recently published article by James et al SLNB has been performed in 18 % of the DCIS cases. Positive nodal metastases were found in only 0.9 % of the cases, which shows that SLNB is unnecessary in many cases (23). A multicenter study conducted in Denmark found that 25.2 % of preoperatively diagnosed DCIS were upstaged to invasive cancer, 40.2 % SLNB were done unnecessary, while SLNB was not performed and patients were possibly undertreated in 4.5 % of upstaged tumor cases (24). Compared with these studies the number of unnecessary SLNB in our research was even higher (60 %), a higher number of SLNB were not performed when IC was found on the final evaluation as well, meaning that the radicality of the surgery was inappropriate in all those cases.

To conclude our study, possible factors of invasiveness that might be helpful in the future research are the size of the tumor ≥ 40 mm on MRI, suspicious lymph nodes in the radiological assessment and high grade nuclear polymorphism.

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