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Radiological and pathological predictors of post-operative upstaging of breast ductal carcinoma in situ (DCIS) to invasive ductal carcinoma and lymph-nodes metastasis; a potential algorithm for node surgical de-escalation☆

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ABSTRACT

Background/aim: Ductal carcinoma in situ is considered a local disease with no metastatic potential, thus sentinel lymph node biopsy (SLNB) may be deemed an overtreatment. SLNB should be reserved for patients with invasive cancer, even though the risk of upstaging rises to 25 %. We aimed to identify clinicopathological predictors of post-operative upstaging in invasive carcinoma.

Methods: We retrospectively analyzed patients with a pre-operative diagnosis of DCIS subjected to breast surgery between January 2017 to December 2021, and evaluated at the Breast Unit of PTV (Policlinico Tor Vergata, Rome).

Results: Out of 267 patients diagnosed with DCIS, 33(12.4 %) received a diagnosis upstaging and 9(3.37 %) patients presented with sentinel lymph node (SLN) metastasis. In multivariate analysis, grade 3 tumor (OR 1.9; 95 % CI 1.2–5.6), dense nodule at mammography (OR 1.3; 95 % CI 1.1–2.6) and presence of a solid nodule at ultrasonography (OR 1.5; 95 % CI 1.2–2.6) were independent upstaging predictors. Differently, the independent predictors for SLNB metastasis were: upstaging (OR 2.1.; 95 % CI 1.2–4.6; $p = 0.0079$) and age between 40 and 60yrs (OR 1.4; 95 % CI 1.4–2.7; $p = 0.027$).

All 9 patients with SLN metastasis received a diagnosis upstaging and were aged between 40 and 60 years old.

Conclusion: We identified pre-operative independent predictors of upstaging to invasive ductal carcinoma. The combined use of different predictors in an algorithm for surgical treatments of DCIS could reduce the numbers of unnecessary SLNB.

1. Introduction

Pure ductal carcinoma in situ (DCIS) is a noninvasive carcinoma of the breast, defined as proliferating malignant breast ductal cells limited to the ducts themselves with no evidence of basement membrane invasion [1]. Theoretically, it is considered a local disease and does not possess a metastatic potential for spread to axillary nodes [1,2].

During the last decades, following the widespread implementation and establishment of breast cancer screening programs and digitalized imaging, detection rates of DCIS increased [3]. Nowadays, DCIS represents 20–25 % of all breast cancer diagnoses [4].

In breast cancer patients, axillary lymph node status remains the

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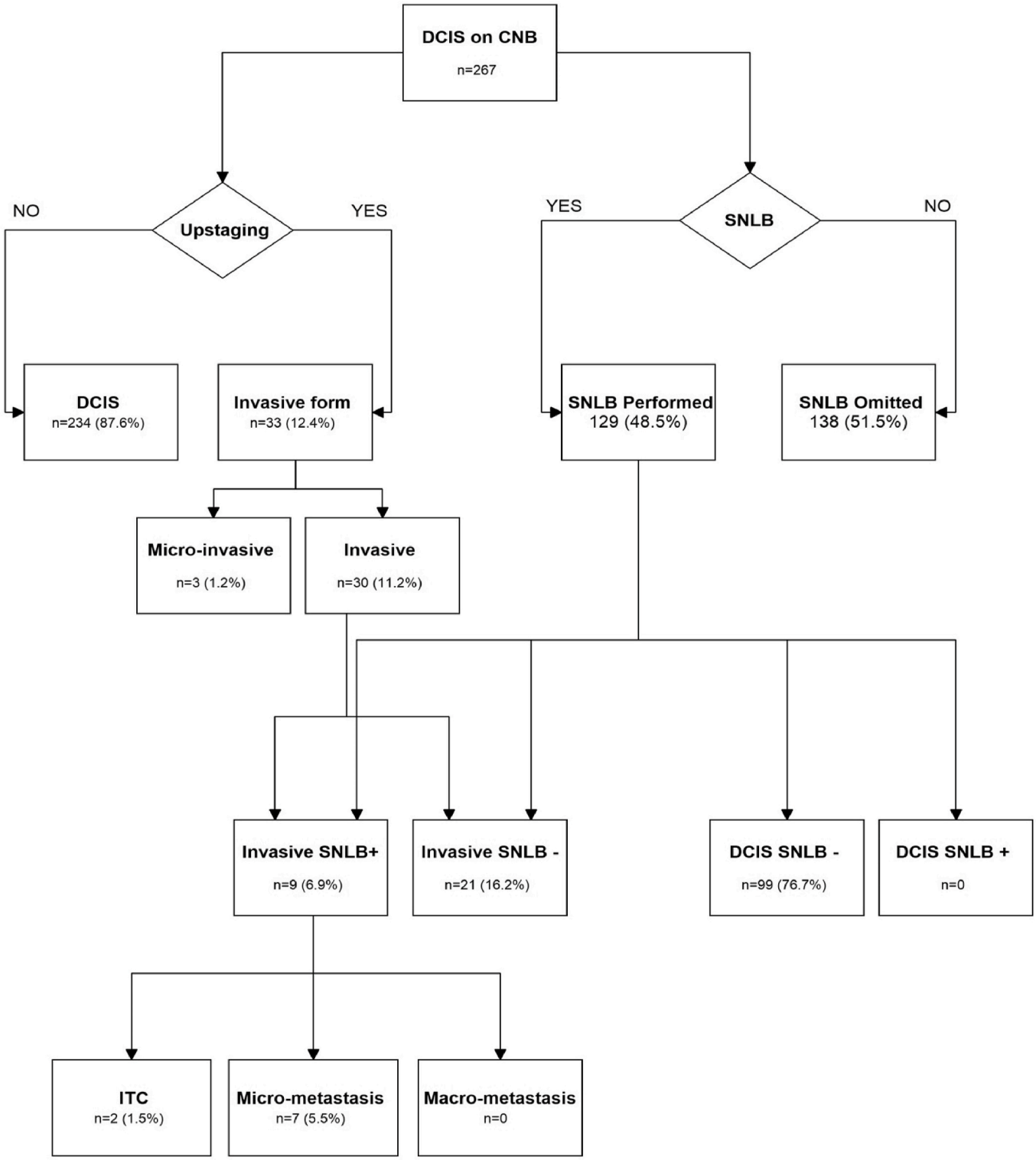

Fig. 1. Overall population, cases of DCIS upstaging end SNlB metastatization.
DCIS: Ductal Carcinoma In Situ, CNB: core needle biopsy, SNLB: sentinel lymph node biopsy SNLB + sentinel lymph node biopsy positive, SNLB- sentinel lymph node biopsy negative, ITC Isolated tumor cells.

strongest prognosticator [5]. Currently, sentinel lymph node biopsy (SLNB) is indicated, for axillary staging, in cases of invasive cancer and clinically node-negative disease, providing non-inferior oncological outcomes to axillary lymph nodes dissection (ALND) [6,7]. Nonetheless, no randomized controlled trials investigating the advantages of carrying out routine SLNB in DCIS patients have been published [2].

According to the best practice guidelines, as reported by the American Society of Oncology and AIOM (Associazione Italiana Di Oncologia Medica), SLNB should be performed in cases requiring mastectomy, extensive disease (greater than 20–50 mm) or when there are physical, radiological, or pathological suspicion of upstaging [8,9]. However, due to sparsity of data supporting these recommendations and the absence of

Table 1
Age, lesion site and characteristics between Upstaging and pure DCIS group.

	Upstaging Group (n = 33)	DCIS group (n = 234)	p value
Age range			0.119
Age<40 y	3(9.1 %)	6 (2.6 %)	
Age 40–60 y	21 (63.6 %)	147 (62.8 %)	
Age>60 y	9 (27.3 %)	81 (34.6 %)	
Tumor position			0.278
Upper outer quadrant UOQ	12 (40 %)	81 (37 %)	
Upper inner quadrant UIQ	3(10 %)	21 (9.6 %)	
Lower outer quadrant LOQ	6 (20 %)	21 (11 %)	
Lower inner quadrant LIQ	3 (10 %)	12 (5.5 %)	
Central Portion	0	3 (1.4 %)	
UOQ-LOQ	3(10 %)	9(4.1 %)	
UOQ-UIQ	3 (10 %)	51 (23.3 %)	
LOQ-LIQ	0	12 (5.5 %)	
LOQ-LIQ	0	6 (2.7 %)	
Tumor dimension ranges			**0.016**
Lesion <15 mm	15(45.5 %)	129 (56.6 %)	
Lesion >15 mm < 40 mm	18 (54.5 %)	75 (32.9 %)	
Lesion >40 mm	0	24 (10.5 %)	
Multifocal lesion	3 (10 %)	36 (16.9 %)	**0.335**
Multicentric lesion	0	21 (9.9 %)	0.071

Values are presented as absolute numbers and percentages. We compared the values according to upstaging of DCIS to invasive or microinvasive ductal carcinoma.

concise criteria for lymph nodes management in DCIS, many patients with such a diagnosis currently undergo unneeded SLNB [2]. Indications for SLNB based on the presence of invasive breast cancer should be dictated by histological evaluations of the resected surgical specimen [2]. Therefore, in patients with a pre-operative diagnosis of DCIS, the rationale of performing routine upfront SLNB in order to avoid a second surgical procedure should be challenged.

Core needle biopsy has become the gold standard procedure for breast cancer diagnosis [10]. However, this diagnostic tool, due to the limited sampling volume, may result in a failure to collect the invasive component of the lesion thus underestimating the disease extent ([10, 11]). Approximately 25 % of DCIS diagnoses are subsequently upstaged to invasive disease [12]. Potential predictive factors of DCIS upstaging could guide surgeons with indications for SLNB and therefore avoid second surgical procedures or avoid unnecessary axillary surgery.

The aim of our study is to evaluate cases with a pre-operative diagnosis of DCIS, detection rates of upstaging, potential pre-operative predictive factors for upstaging and/or SLN metastasis, in order to reduce as much as possible unnecessary node biopsies.

2. Materials and method

All patients with a DCIS diagnosis who were evaluated between January 2017 to December 2021 at the Breast Unit of PTV (Policlinico Tor Vergata, Rome) were retrospectively reviewed. The inclusion criteria were: female patients with a DCIS diagnosis by core needle biopsy who underwent breast surgery. This study was approved by the Ethics Committee (approval number R.S.72.23) of the Policlinico Tor Vergata of Rome.

Ultrasonography and mammography were carried out in all of the patients. MRI was performed according to age, type of diagnosis and presence of microcalcifications. According to our breast unit policy all our patients are subjected to breast ultrasound and bilateral mammography, and in relation to age, the type of diagnosis, the examination of microcalcifications, breast MRI is performed or not. The imaging

Table 2
Radiological findings between Upstaging and pure DCIS group.

	Upstaging Group (n = 33)	DCIS group (n = 234)	p value
Lesion evidence at US	21 (77.7 %)	81 (65.2 %)	**0.036**
US findings			**0.039**
No evidence	6 (22.2 %)	63 (43.8 %)	
Spiculated Margin nodule	3 (11.1 %)	9 (6.3 %)	
Circumscribed margin nodule	12 (44.4 %)	30 (20.8 %)	
Echotexture heterogeneous	6 (22.2 %)	27 (18.8 %)	
Pseudonodular hypoechoic area	0	12 (8.3 %)	
Cystic with vegetations solid wall	0	3 (2.1 %)	
US BI-RADS			0.119
BI-RADS 3	6 (28.6 %)	15 (18.5 %)	
BI-RADS 4a	0	21 (25.9 %)	
BI-RADS 4b	3 (14.1 %)	21 (25.9 %)	
BI-RADS 4c	12 (57.1 %)	15 (18.5 %)	
BI-RADS 5	0	9 (11.1 %)	
Lesion evidence at Mammography	24 (100 %)	186 (98.5)	0.981
Microcalcifications	18 (75 %)	171(90.5 %)	0.114
Mammography findings			**0.013**
No evidence	0	3 (1.6 %)	
Dense speculated lesion	6 (25 %)	15 (7.9 %)	
Cluster Microcalcifications	15 (62.5 %)	138 (73 %)	
Microclcifications and speculated lesion	3 (12.5 %)	33 (17.5 %)	
Mammography BI-RADS			**0.001**
BI-RADS 3	3 (12.5 %)	6 (3.2 %)	
BI-RADS 4a	3 (12.5 %)	54(28.6 %)	
BI-RADS 4b	18 (75 %)	72 (38.1 %)	
BI-RADS 4c	0	42 (22.2 %)	
BI-RADS 5	0	15 (7.9 %)	
Lesion evidence at MRI	3 (50 %)	30 (62.5 %)	
MRI findings			**0.007**
No evidence	3 (50 %)	18 (37.5 %)	
Mass enhancement	3 (50 %)	24 (50 %)	
Non-mass enhancement	0	3 (6.3 %)	
Linear ductal enhancement	0	0	
MRI BI-RADS			**0.030**
BI-RADS 3	0	9 (18.8 %)	
BI-RADS 4	0	15 (31.3 %)	
BI-RADS 5	0	0	
BI-RADS 6	3(50 %)	24 (50 %)	

Values are presented as absolute numbers and percentages. We compared the values according to upstaging of DCIS to invasive or microinvasive ductal carcinoma.

findings were categorized according to the BI-RADS (Breast imaging reporting and data system of the American College of Radiology) and evaluated in the study. Imaging was reviewed by a breast-dedicated radiologist. At ultrasonography, presence of a lesion, its characteristics and maximum diameter were reported. Mammography imaging and reports were reviewed to categorize the patients according to radiological findings (calcification, mass, or architectural distortion). Lesions were reported and categorized according to position within the breast quadrants. Unilateral or bilateral breast involvement was noted. Any multifocal and multicentric disease were reported in the study. All patients underwent core needle biopsy with at least 5 cylinders extractedand the samples were examined by at least two breast -dedicated pathologists. Sonography core needle biopsy was performed when lesion was evident by ultrasound, while mammography stereotactic vacuum for cases with microcalcifications.and Pathological reports were analyzed in order to categorize lesions according to tumor grade, type and subtype, and presence or absence of tumor necrosis.

Lesions were surgically excised and patients were classified according to the type of surgery. The surgical procedure was distinguished between breast conservative surgery, including all procedures with a partial gland removal, and mastectomy which included the complete removal of the glandular tissue with or without sparing the nipple areola

Table 3
Pre-operative pathological findings between Upstaging and pure DCIS group.

	Upstaging Group (n = 33)	DCIS group (n = 234)	p value
Comedonecrosis	12 (50 %)	99 (47.9 %)	0.832
Estrogen Receptor positivity	21 (63.6 %)	147 (62.8 %)	0.512
Progesterone Receptor positivity	9 (27.3 %)	81 (34.6 %)	0.182
Nuclear Grade			**0.001**
Low Grade I	12 (40 %)	81 (37 %)	
Intermediate Grade II	3(10 %)	21 (9.6 %)	
High Grade III	6 (20 %)	21 (11 %)	
Histological classification			0.106
Comedo	12(36.4 %)	75 (32.1 %)	
Solid	9 (27.3 %)	42(17.9 %)	
Micropapillary	0	18 (7.7 %)	
Mixed solid cribriform	3 (9.1 %)	51 (21.8 %)	
Mixed solid micropapillary	0	6 (2.6 %)	
Cribriform	3 (9.1 %)	24 (10.2 %)	
Other	6 (18.2 %)	18 (7.7 %)	

Values are presented as absolute numbers and percentages. We compared the values according to upstaging of DCIS to invasive or microinvasive ductal carcinoma.

Table 4
Final pathological and findings between Upstaging and pure DCIS group.

	Upstaging Group (n = 33)	DCIS group (n = 234)	p value
Diameter maximum mm	9.1 ± 8.8	7.5 ± 7.7	0.377
Estrogen Receptor positivity	33 (100 %)	126 (70 %)	**0.001**
Progesterone Receptor positivity	27 (81.8 %)	102 (56.7 %)	**0.07**
Ki67 Index	19.1 ± 8.2	5 ± 0	0.224
HER2 positivity	6 (22 %)	0	0.592
Nuclear Grade			**0.006**
Low Grade I	0	48 (24.6 %)	
Intermediate Grade II	3 (14.3 %)	45 (23.1 %)	
High Grade III	18 (85.7 %)	96 (49.2 %)	
Nuclear grade comparison			0.171
Nuclear grade up-staging	3 (14.3 %)	24 (12.3 %)	
Nuclear grade down-staging	0	27 (13.8 %)	
Histological classification			0.098
Mixed solid micropapillary	0	6 (2.6 %)	
Cribriform	3 (9.1 %)	24 (10.2 %)	
Other	6 (18.2 %)	18 (7.7 %)	

Values are presented as absolute numbers and percentages. We compared the values according to upstaging of DCIS to invasive or microinvasive ductal carcinoma.

complex. Intraoperative margin status was assessed in all patients who underwent breast conservative surgery. The final pathological characteristics were classified as DCIS, DCIS with microinvasion, or infiltrative breast cancer. Microinvasion was defined as basement membrane invasion not greater than 1 mm. Type of tumor, dimensions, grade, prognostic and predictive factors were recovered from the final pathological examination. Biopsy and final surgical pathological examination were compared in terms of nuclear grade and invasion status in order to identify disease upstaging and downstaging.

Surgical reports were reviewed and divided based on surgical axillary staging and according to whether a SLNB was performed or not. The sentinel lymph node biopsy was performed according to the AIOM guidelines in force during the year [9]. Generally, in case of suspicion of micro-invasive disease (for example: size >1–2 cm and high-grade

Table 5
Age, lesion site and characteristics between SLN positive and negative or omitted group.

	SLN Positive (n = 9)	SLN Negative or omitted (n = 258)	p value
Age range			0.023
Age<40 y	0	90 (34.9 %)	
Age 40–60 y	9 (100 %)	159 (61.6 %)	
Age>60 y	0	9 (3.5 %)	
Tumor position			0.323
Upper outer quadrant UOQ	6 (66.7 %)	87 (36.3 %)	
Upper inner quadrant UIQ	0	24 (10 %)	
Lower outer quadrant LOQ	3 (33.3 %)	27 (11 %)	
Lower inner quadrant LIQ	0	15 (6.3 %)	
Central Portion	0	3 (1.3 %)	
UOQ-LOQ	0	12 (5.0 %)	
UOQ-UIQ	0	54 (22.5 %)	
LOQ-LIQ	0	12 (5.0 %)	
LOQ-LIQ	0	6 (2.5 %)	
Tumor dimension range			0.177
Lesion <15 mm	3 (33.3 %)	141 (56.0 %)	
Lesion >15 mm < 40 mm	5 (55.5 %)	87 (34.5 %)	
Lesion >40 mm	1 (11.1 %)	24 (9.5 %)	
Multifocal lesion	0	39 (16.7 %)	0.362
Multicentric lesion	0	21 (9.0 %)	0.470

Values are presented as absolute numbers and percentages. We compared the values according to the presence of sentinel lymph node metastasis.

DCIS), in case of mastectomy, multiple foci of microcalcifications or DCIS associated with nodular lesion.

Hematoxylin-eosin staining was used for histological assessment of sentinel lymph nodes. A positive sentinel lymph node was defined, as per ASCO guidelines, by presence of metastasis; further differed between isolated tumor cells (single tumor cell, or tumor-cell cluster <0.2 mm), micro-metastasis (>200 cells or >0.2 mm, but <2.0 mm) or macro-metastasis (>2.0 mm) [10].

Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM, Dowsett M. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018 Jul 10; 36 (20):2105–2122. https://doi.org/10.1200/JCO.2018.77.8738. Epub 2018 May 30. PMID: 29846122.

2.1. Statistical analysis

All data were codified into the EXCEL database (Microsoft, Washington, DC, USA).

According to the final pathological examination, clinicopathological variables were compared between DCIS group and the upstaged group using T test for continuous variables. Otherwise, Fisher's exact test was applied in cases of dichotomous variables, and Monte Carlo test in cases of non-dichotomous variables. The same analysis was performed among the DCIS group, with or without sentinel lymph node positive for metastasis. Multivariate logistic regression analysis was performed to identify risk predictors of DCIS upstaging or metastasis to sentinel lymph nodes. P value < 0.05 was considered to be statistically significant. All the statistical analysis was performed in SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

Table 6
Radiological and pre-operative pathological findings between SLN positive and negative or omitted group.

	SLN Positive (n = 9)	SLN Negative or omitted (n = 258)	p value
Lesion evidence at US	9 (100 %)	93 (57.4 %)	**0.012**
US findings			**<0.001**
No evidence	0	69 (42.6 %)	
Spiculated margin nodule	9 (100 %)	12 (7.4 %)	
Circumscribed margin nodule	0	33 (20.4 %)	
Echotexture heterogeneous	0	33 (20.4 %)	
Pseudonodular hypoechoic area	0	12 (7.4 %)	
Cystic with vegetations solid wall	0	3 (1.9 %)	
US BI-RADS			**0.002**
BI-RADS 3	0	21 (22.6 %)	
BI-RADS 4a	0	21 (22.6 %)	
BI-RADS 4b	0	24 (25.8 %)	
BI-RADS 4c	8 (88.9 %)	18 (19.4 %)	
BI-RADS 5	1 (11.1 %)	9 (9.7 %)	
Lesion evidence at Mammography	9 (100 %)	201 (100 %)	1.000
Microcalcifications	9 (100 %)	186 (91.2 %)	0.352
Mammography findings			**<0.001**
No evidence	0	3 (1.5 %)	
Dense speculated lesion	6 (66.7 %)	15 (7.4 %)	
Cluster Microcalcifications	3 (33.3 %)	150 (73.5 %)	
Microclcifications and speculated lesion	0	36 (17.6 %)	
Mammography BI-RADS			**0.001**
BI-RADS 3	0	6 (3.0 %)	
BI-RADS 4a	3 (33.3 %)	57 (27.9 %)	
BI-RADS 4b	1 (11.1 %)	84 (41.2 %)	
BI-RADS 4c	6 (66.7 %)	42 (20.6 %)	
BI-RADS 5	1 (11.1 %)	15 (7.4 %)	
CORE NEEDLE BIOPSY			
Comedonecrosis	6 (66.7 %)	108 (46.8 %)	0.105
Estrogen Receptor positivity	5 (55.5 %)	171 (66.5 %)	0.895
Progesterone Receptor positivity	4 (44.4 %)	93 (36.0 %)	0.723
Nuclear Grade			**0.007**
Low Grade I	0	63 (29.2 %)	
Intermediate Grade II	6 (66.7 %)	45 (20.8 %)	
High Grade III	3 (33.3 %)	108 (50 %)	
Histological classification			0.106
Comedo	2 (22.2 %)	84 (32.6 %)	
Solid	3 (33.3 %)	51 (19.8 %)	
Micropapillary	0	18 (7.0 %)	
Mixed solid cribriform	2 (22.2 %)	51 (19.8 %)	
Mixed solid micropapillary	0	6 (2.3 %)	
Cribriform	2 (22.2 %)	44 (17.1 %)	

Values are presented as absolute numbers and percentages. We compared the values according to the presence of sentinel lymph node metastasis.

3. Results

From January 2017 to December 2021, 267 women with pre-operative diagnosis of DCIS by core needle biopsy and subsequently subjected to surgery were evaluated at our Breast Unit (Policlinico Tor Vergata, Rome). Mean age was 56.67 ± 12.21 years and mean BMI was 24,89 ± 4.26. Comedonecrosis was noted in 111 (45.6 %) cases at pathological examination of specimens from core needle biopsy. Radiological lesions smaller than 15 mm were reported in 144 (55.5 %) cases, 93 (35.6 %) were between 16 mm and 40 mm while 24 cases (9.2 %) exhibited lesions larger than 40 mm. Nuclear grading was 3 (high grade) in 111 (49.3 %) cases, whereas 51 (22.7 %) and 63 (28 %) cases showed grades 2 and 1, respectively. Mastectomy was performed in 60 patients (22.5 %) while the remaining 207 (77.5 %) underwent a breast conservative surgery (Fig. 1). Out of 267 patients, 33 (12.4 %) received a diagnosis upstaging (30 from DCIS to invasive ductal carcinoma and 3 to micro-invasive ductal carcinoma) at final pathological examination

Table 7
Final pathological and findings between SLN positive and negative or omitted group.

	SLN Positive (n = 9)	SLN Negative or ommitted (n = 258)	p value
Diameter maximum mm	16.7 ± 5.1	18.7 ± 8.6	0.981
Estrogen Receptor positivity	9 (100 %)	150 (73.5 %)	0.116
Progesterone Receptor positivity	9 (100 %)	120 (58.8 %)	**0.013**
Ki67 Index %	12.5 ± 2.7	19.6 ± 8.8	0.224
HER2 positivity	6 (22 %)	0	0.302
Nuclear Grade			0.326
Low Grade I	0	54 (26.2 %)	
Intermediate Grade II	3 (33.3 %)	45 (21.7 %)	
High Grade III	6 (66.7 %)	108 (52.2 %)	
Nuclear grade comparison			0.120
Nuclear grade up-staging	3 (33.3 %)	24 (11.6 %)	
Nuclear grade down-staging	0	27 (13.0 %)	

Values are presented as absolute numbers and percentages. We compared the values according to the presence of sentinel lymph node metastasis.

(Fig. 1). Nuclear grade upstaging was observed in 27 (12.5 %) cases and 27 (12.5 %) presented a nuclear grade downstaging. 129 (48.3 %) underwent SLNB according to current guidelines and local policy (Fig. 1). About 129 patients who underwent SLNB, 9 (6.97 %) presented SLN metastasis. No cases of macro-metastasis were reported, 7 (77.7 %) of the positive SLNB revealed micro-metastasis and 2 (22.3 %) showed isolated tumor cells (Fig. 1).

3.1. Upstaging

Comparing the group that presented upstaging from DCIS to invasive breast cancer with patients that not received diagnosis upstage, no differences were recorded in terms of age, BMI, pre-operative tumor dimensions and tumor diameter at final pathological examination; relative *p* values were 0.762, 0.879, 0.311 and 0.377, respectively. Age distribution and relative p values are resumed in Table 1. Further, lesion sites did not show significant statistical differences between the groups, as reported in Table 1. Even though pre-operative absolute tumor dimension was not significantly different, we reported a difference in terms of size distribution. In the Upstaging group, 15 (45.5 %) patients had a lesion <15 mm, 18 (54.3 %9) had a lesion with a maximal diameter between 16 mm and 40 mm and no cases of lesions greater than 40 mm. Differently, in the DCIS group, 129 (56.6 %) patients presented with lesions <15 mm, 75 (32.9 %) between 16 mm and 40 mm, and 24 (10.5 %) larger than 40 mm, showing a statistically significant difference at Monte Carlo Test with a *p* value of 0.016 (Table 1). Cases of multifocal or multicentric breast cancer were comparable between the two groups and *p* values were, respectively, 0.335 and 0.071(Table 1). Among the different radiological exams there is evidence to say that the presence of nodules at US is associated with higher rate of upstaging. Radiological findings of the lesions, relative Bi-RADS score and relative *p* values between groups are resumed in Table 2.

Pre-operative histopathological characteristics and hormone expression did not show any significant difference in the two groups. Nuclear grading at pre-operative examination showed a significant statistical difference with a *p* value of 0.001. All data from pre-operative pathological examination of core needle biopsy and relative *p* values are resumed in Table 3.

30 (90.9 %) SLNBs were performed in the upstaging group, versus 99 (42.3 %) in the pure DCIS group, showing a significant difference between groups, $p < 0.001$. Out of 129 SLNB performed in the upstaging group, in 9 (27.3 %) cases lymph nodes were sites of metastasis: 7 (21.2 %) micro-metastasis and 2 (6.15 %) isolated tumor cells. In the pure

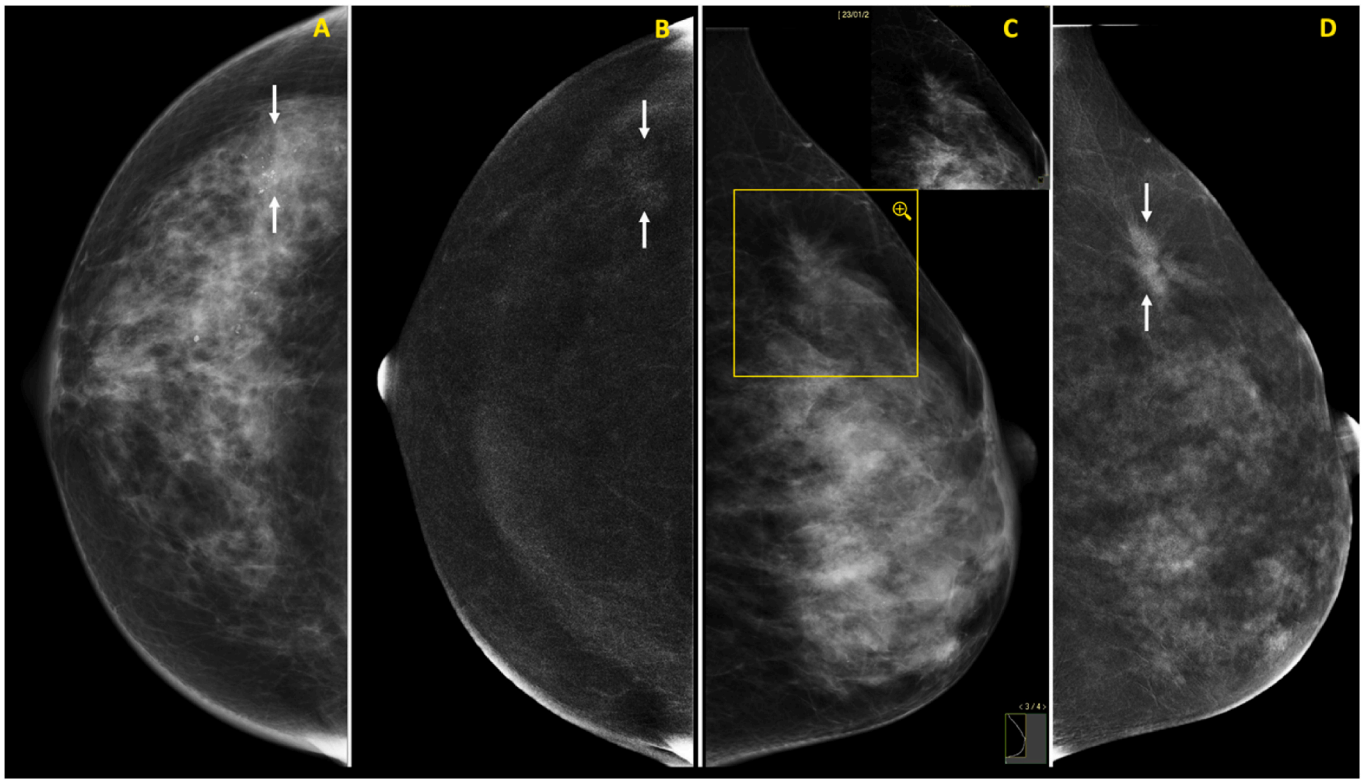

Fig. 2. Different mammographic pattern between DCIS and invasive ductal carcinoma
a) 2D Digital Mammography RCC with cluster of pleomorphic microcalcification in the upper external quadrant of left breast (arrows) (DCIS)
b) Contrast Enhancement Spectral Mammography RCC with non mass enhancement in the site of microcalcification (arrows) (DCIS)
c) 2D Digital Mammography LML with irregular nodular opacity with high density in the superior quadrant (Invasive Ductal Carcinoma)
d) Contrast Enhancement Spectral Mammography LML with mass enhancement in the site of opacity (arrows) (Invasive Ductal Carcinoma).

DCIS group, no cases of SLN metastasis were reported, exhibiting a statistically significant difference with a p value < 0.001.

Differences in final pathological examination between the upstaging group and pure DCIS group, and relative p values are resumed in Table 4.

In multivariate analysis, a high nuclear grade at core needle biopsy specimen (odds ratio 1.9; 95 % confidence interval 1.2–5.6; $p = 0.0013$), presence of a dense nodule at mammography (odds ratio 1.3; 95 % confidence interval 1.1–2.6; $p = 0.039$), and presence of a solid nodule at ultrasonography (odds ratio 1.5; 95 % confidence interval 1.2–2.6; $p = 0.0079$) remained as independent predictive factors for DCIS upstaging. MRI parameters were not evaluated in the multivariate analysis due to the small sample of patients with DCIS upstaging that were subjected to magnetic resonance imaging. Among 33 patients, without any of these predictors, the probability of post-operative DCIS upstaging to invasive ductal carcinoma was 9.1 % (3 out 33).

3.2. Sentinel lymph node metastasis

We performed our analysis taking into account the whole population comparing patients with positive lymph node with the omitted or negative SLNB. Patients who presented with positive SLN were significantly younger, with a mean age of 45 ± 1.86, versus 57.1 ± 6.4 in the control group; relative p value was 0.007. No differences were noted between the groups in terms of BMI, pre-operative tumor dimensions and tumor diameters at final pathological examination; relative p values were, respectively, 0.578, 0.317, and 0.981. Patients with lymph node involvement were all within the age range of 40–60 *years old*. Age distribution showed a statistically significant difference between the groups; age distribution is reported in Table 3. Sites of primary lesions did not show any statistically significant difference between the groups, with or without SLN metastasis, as resumed in Table 5 ($p = 0.323$). Additionally, tumor dimensions were not significantly different in the SLN positive group, and p value was 0.177 (Table 5). No cases of multifocal or multicentric breast cancer were reported in the group with positive SLN, as reported in Table 5.

In the SLN positive group, a significantly higher incidence of spiculated margin nodules at breast sonography was reported. Additional sonographic and mammographic findings and relative BI-RADS scores are resumed in Table 6.

At pathological examination of core needle biopsy specimen, type of tumor, comedonecrosis, and hormone receptors did not show any statistically significant differences between the groups. Conversely, patients with positive SLN presented with significantly higher nuclear grade. All data from pathological examination of core needle biopsy specimens are reported in Table 6 with relative p values.

There was a significantly higher rate of mastectomies performed in patients with positive SLN; 5 (55.5 %), versus 54 (21.2 %) in the control group, $p = 0.0291$.

Upon pathological examination of the definitive surgical specimen, all patients with SLN positive for cancer received an upstaging diagnosis. Out of 9 patients with an upstaged diagnosis, 3 (33.3 %) had micro-invasive ductal carcinoma and 6 (66.7 %) invasive ductal carcinoma.

Definitive pathological examination comparison between groups and relative p values are reported in Table 7. No differences were recorded in terms of histological classification of the tumors; $p = 0.063$.

The upstaging from DCIS to invasive or micro-invasive ductal carcinoma (odds ratio 2.1.; 95 % confidence interval 1.2–4.6; $p = 0.0011$), and an age between 40 and 60 *years old* (odds ratio 1.4; 95 % confidence interval 1.4–2.7; $p = 0.027$) were the independent predictors for SLN metastasis at multivariate analysis.

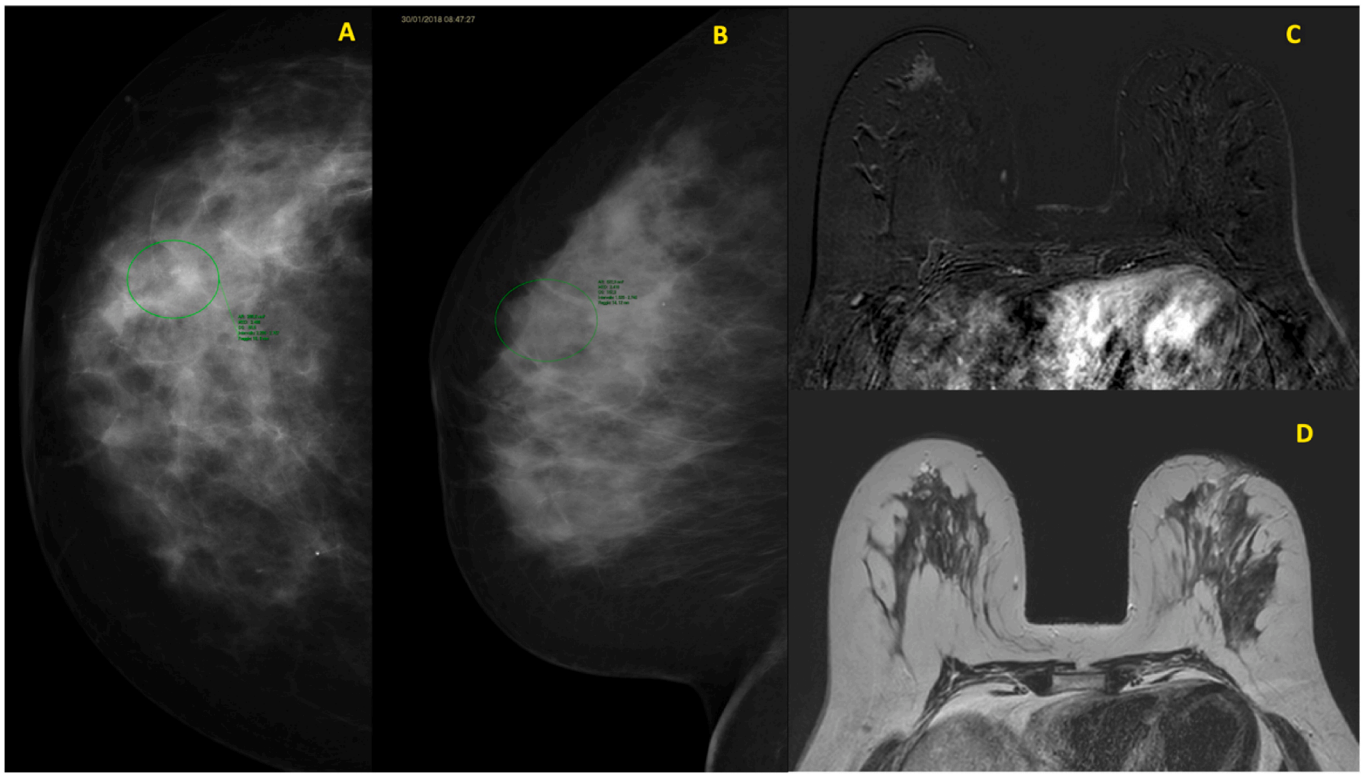

Fig. 3. CESM and MRI for DCIS
a + b) 2D Digital Mammography RCC (a) and RML (b) with cluster of pleomorphic microcalcification in the upper quadrant of right breast (ROI)
c + d) Breast MRI of a woman with CDIS with a non mass enhancement (arrows) in the right breast (b: axial T1w post intravenous contrast medium images) with no nodular mass in the morphological images (c: axial T2w images).

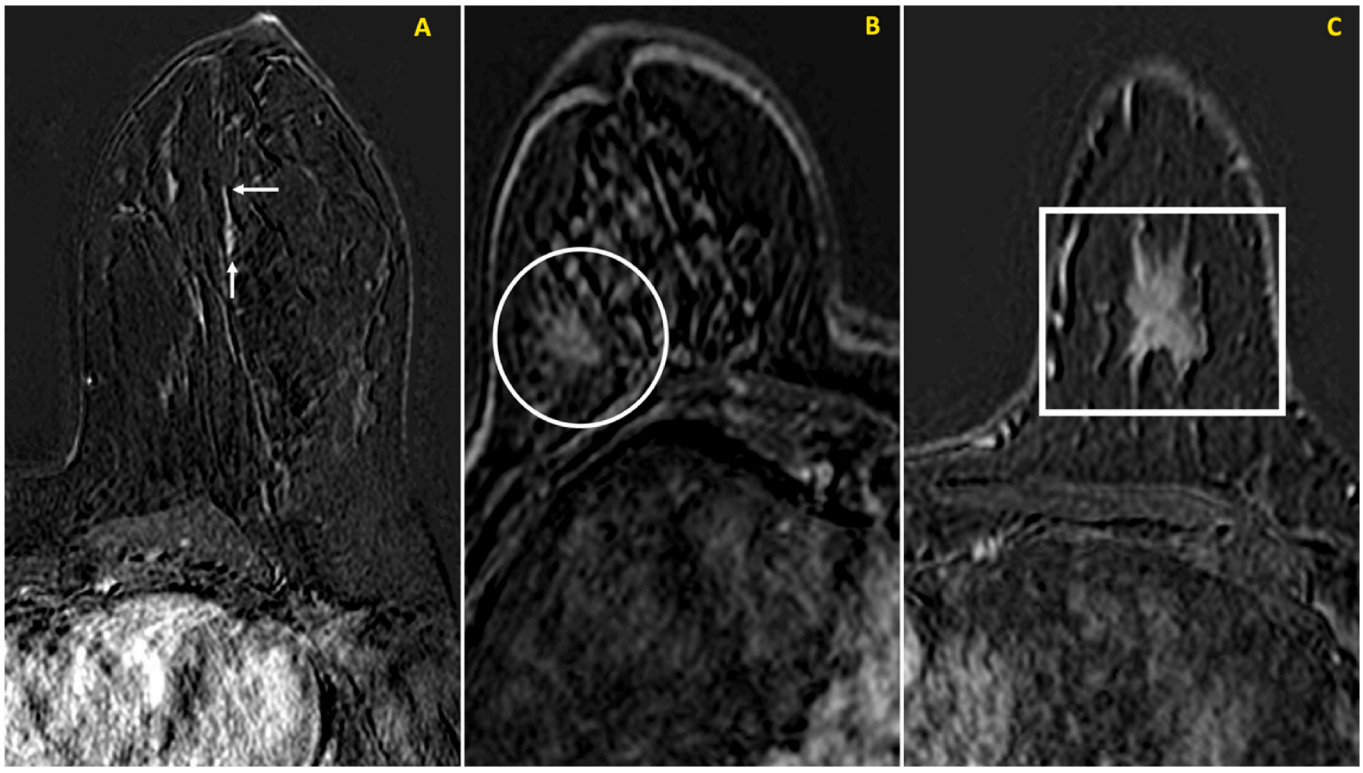

Fig. 4. MRI Patterns
Breast MRI axial T1w post intravenous contrast medium images with (a) linear contrast enhancement (arrows) (DCIS) (b) segmental non mass enhancement (ROI) (DCIS) (c) nodular mass enhancement (square) (Invasive Ductal Carcinoma).

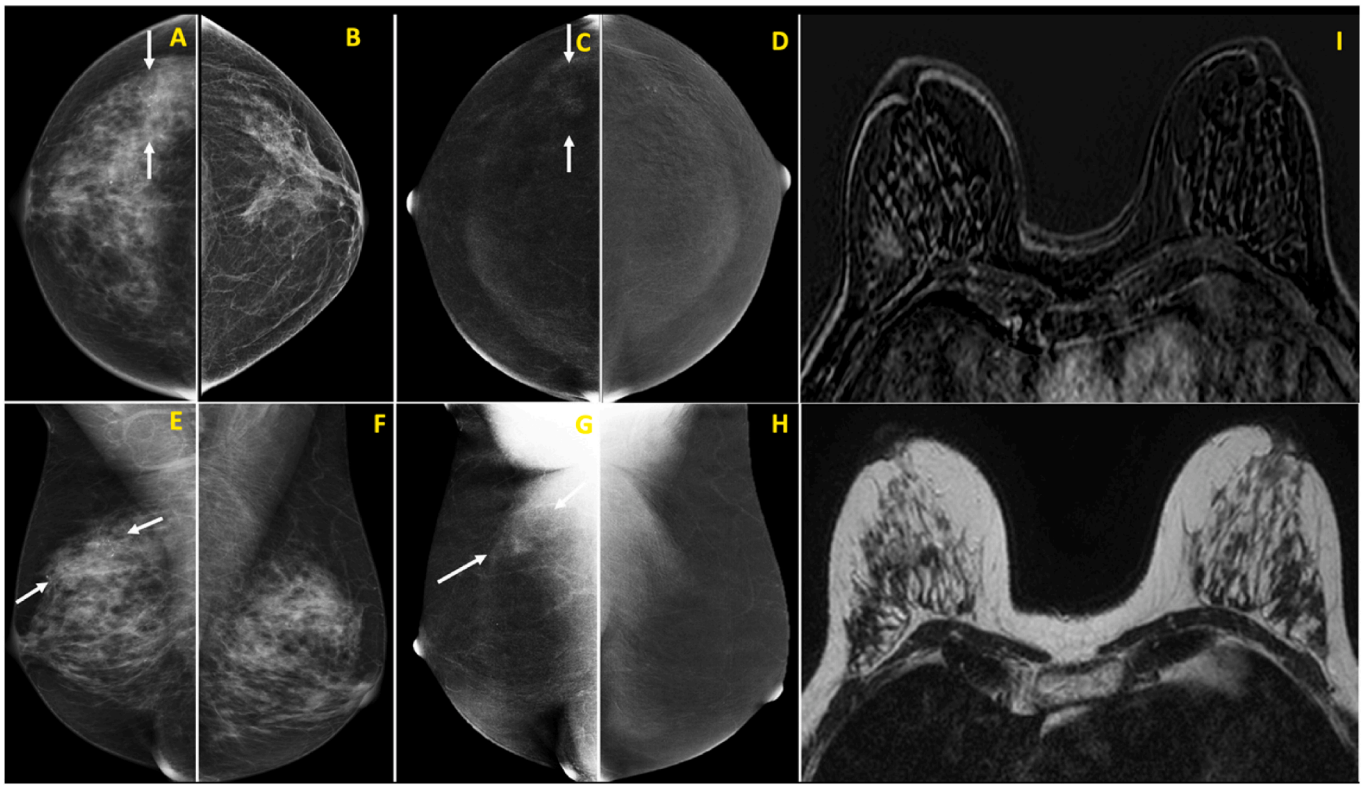

Fig. 5. DCIS radiological pattern
a + b) 2D Digital Mammography RCC (a), LCC (b) with cluster of pleomorphic microcalcification in the upper external quadrant of right breast (arrows)
c + d) Contrast Enhancement Spectral Mammography RCC (c), LCC (d) with non mass enhancement in the site of microcalcification (arrows)
e + f) 2D Digital Mammography RMLO (e), LMLO (f) with cluster of pleomorphic microcalcification in the upper external quadrant of right breast (arrows)
g + h) Contrast Enhancement Spectral Mammography RLML (g), LMLO (h) with mass enhancement in the site of microcalcification (arrows)
i + l) Breast MRI of a woman with CDIS with a non mass enhancement (arrows) in the right breast (i: axial T1w post intravenous contrast medium images) with no nodular mass in the morphological images (l: axial T2w images).

4. Discussion

In our study, 12.41 % of patientis with preoperative diagnosis of DCIS presented upstaging at final pathological examination. Significant predictive factors of upstaging are high grade and solid tumors at US and mammography. In addition, among patients who underwent SLNB, 27.30 % presented tumor involvement, of which 2 (6.15 %) ITC and 7 (21.2 %) micrometastases and no cases of macrometastasis and no one need further treatment due to involved lymph nodes and predictive factors for nodal metastatization are age and upstaging.

Ductal carcinoma in situ is a proliferating malignancy of breast ductal cells with no evidence of basement membrane invasion [1]. Nowadays, DCIS constitutes approximately a quarter of all breast cancer diagnoses, with a continuous rise in detection rate by virtue of screening programs implementation and imaging digitalization [3,4]. In principle, DCIS does not hold a metastatic potential, systemic or lymphatic [1,2]; therefore surgical staging of axillary nodes could be avoided [2].

Core needle biopsy has become the gold standard tool to achieve pre-operative diagnosis of breast cancer [10]. However, despite the observed increase in sensitivity and specificity of this diagnostic tool, due to the volume limitations of the sample and the potential failure of harvest the invasive component of the lesion, it is possible to underestimate the extent of the disease [10,11]. According to the analyses reported in literature, a pure DCIS diagnosis holds between 8 % and 56 % to be upstaged into invasive or microinvasive carcinoma at final pathological examination [15]. In our retrospective study, 33 (12.4 %) of the 267 patients with a pre-operative diagnosis of DCIS were upstaged to invasive or micro-invasive ductal carcinoma. Our results were in accordance with ranges reported in previous studies published in the literature [16,17]. Differently, a meta-analysis reported a higher incidence of DCIS upstaging compared to our result [12,18]. These improved rates could be associated with the recent development of our multidisciplinary breast unit along with a long-term experience and improvement of imaging.

Tumor dimensions ranged between 15 mm and 40 mm (score 2 according the Van Nuys prognostic index) was significantly higher in the upstaging group [19,20]. This is the range where a lesion has the higher probability of being palpable independently of the breast volume. As reported in other studies, the presence of a palpable mass is a clinical predictor of upstaging to invasive ductal carcinoma [21,22]. Unfortunately, due to the retrospective design of the study, we do not have these data regarding our patients. DCIS lesions with dimension greater than 40 mm are usually non-mass lesions, a frequent presentation for pure DCIS [19]. The presence of a palpable lesion larger than 40 mm is fortunately rare nowadays and often associated to other disease. This category could probably correspond to palpable lesions reported in older analyses.

The presence of a nodule, both on breast ultrasonography and mammography, was significantly higher in the upstaging group at univariate analysis (Figs. 2 and 3). A DCIS with a dense nodule at mammography and/or a solid nodule at sonography were affirmed at multivariate analysis as independent factors for DCIS upstaging (Figs. 2 and 3). In a previous analysis, Jakub et al. validated a nomogram that considers the presence of a nodule as a predictor for upstaging DCIS to invasive disease [23]. In concordance with our result, many authors demonstrated the association between DCIS upstaging and the presence of a nodular lesion in pre-operative imaging [20,23,24]. Moreover, the presence of a nodule is strongly correlated with the possible presence of

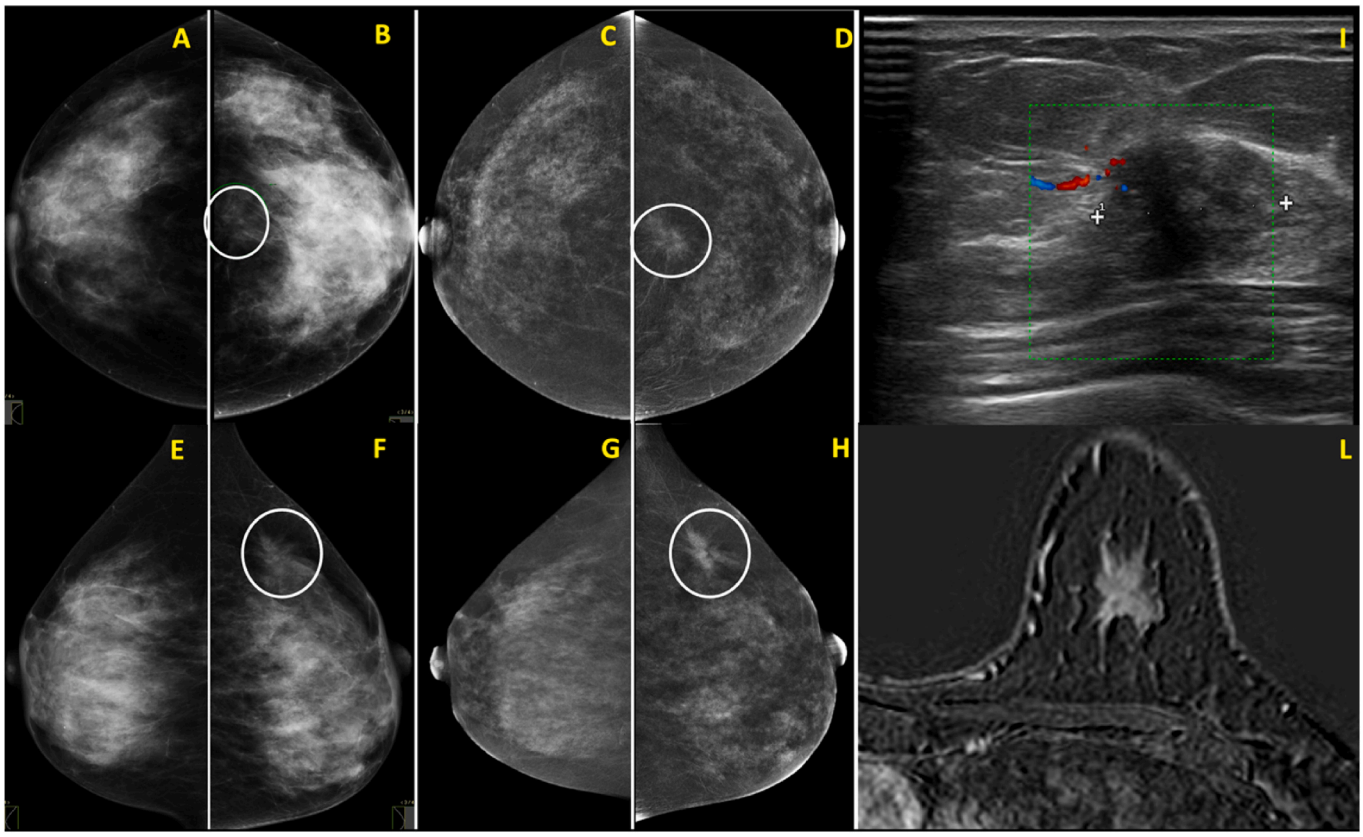

Fig. 6. Invasive ductal carcinoma radiological pattern
a + b) 2D Digital Mammography RCC (a), LCC (b) with irregular nodular opacity in the superior quadrant of the left breast (ROI)
c + d) Contrast Enhancement Spectral Mammography RCC (c), LCC (d) with mass enhancement in the site of opacity in the left breast (ROI)
e + f) 2D Digital Mammography RML (e), LML (f) with irregular nodular opacity in the superior quadrant of the left breast (ROI)
g + h) Contrast Enhancement Spectral Mammography RML (g), LML (h) with mass enhancement in the site of opacity in the left breast (ROI)
i)Breast US with a hypoechoic nodular lesion with irregular margins and internal vascularization
l) Breast MRI axial T1w post intravenous contrast medium images with mass enhancement at the left breast.

a palpable lesion. This hypothesis could be linked to the correlation between palpable lesions and the risk of DCIS upstaging [21]. In our study, 33 patients (12.4 %) presented upstaging. Main predictive values are tumor grade 3, solid tumors at US and mammography.

Tanaka et al. considered in their analysis a tumor size >20 mm at MRI or an MRI mass as predictive factors for DCIS upstaging [21,22]. Notwithstanding the significant difference between the groups, DCIS with or without upstaging, in terms of MRI and BI-RADS, we preferred not to consider MRI findings as independent factors of upstaging to invasive ductal carcinoma by reason of the small number of patients that underwent magnetic resonance,.

DCIS presentation is varying and in most mammography images intraductal lesion exhibits microcalcifications. A smaller portion of DCIS appear as architectural distortion and cases with masses are usually associated with an infiltrative component [25,26] (Figs. 2 and 3). Ultrasound examination can increase the specificity evaluating masses or an area with calcification detected in the mammogram [25] (Fig. 6). The noncalcified area and presence of nodule may represent the invasive component of the ductal lesion [27] (Figs. 2 and 3). Recently and increasingly often, magnetic resonance of the breast is being used as complement to the standard mammography (Fig. 5). MRI is helpful in the assessment of the detection of DCIS and the associated invasive carcinoma as reported in our analysis, despite the small number of MRI performed, and previous analyses [25,26,28,29]. Pure DCIS shows non-nodular lesions in roughly 86 % of cases [30] (Fig. 4). Similar results are reported by Rosen et al., where 76 % of invasive lesions presented with a nodule enhancement [31] (Figs. 4–6). Despite, the superior sensitivity and specificity of MRI compared to breast ultrasound and mammography, the higher cost and limited availability of the exam remain the main causes of MRI not being routinely performed in all DCIS cases [32]. Contrast-enhanced spectral mammograms were reported as useful in reducing DCIS undestraging and in identifying possible invasive lesions pre-operatively [33] (Figs. 2 and 3). Even though both of these contrast-enhanced imaging modalities have demonstrated increased sensitivity and specificity in detecting invasive lesions allowing to reduce overtreatment and undertreatment, they are still not routinely used [33]. Moreover, MRI and contrast-enhanced mammography could play a fundamental role with the advent of artificial intelligence [34,35]. Usually, DCIS do not present as a nodular lesion as showed in the figures, while invasive lesions are more frequently associated with nodular lesions or mass enhancements (Figs. 2 and 3).

The best practice guidelines for management of DCIS suggest to preform SLNB in patients with DCIS and a high nuclear grade [8,9]. The rationale of such indications stems from the greater risk of upstaging to invasive ductal carcinoma [36]. Many studies reported high nuclear grades as predictive factors of DCIS upstaging [21]. Upon investigation at multivariate analysis, higher nuclear grade at pathological examination by core needle biopsy was indeed an independent predictor for upstaging to micro-invasive or invasive ductal carcinoma. This result was consistent with those reported in the literature ([37,38]).

Comedonecrosis at pre-operative biopsy examination is considered an indication for SLNB in many practice guidelines [8]. According to this indication, many authors considered the presence of comedonecrosis as a potential risk for diagnosis upstaging in patients with DCIS [35,36]. In

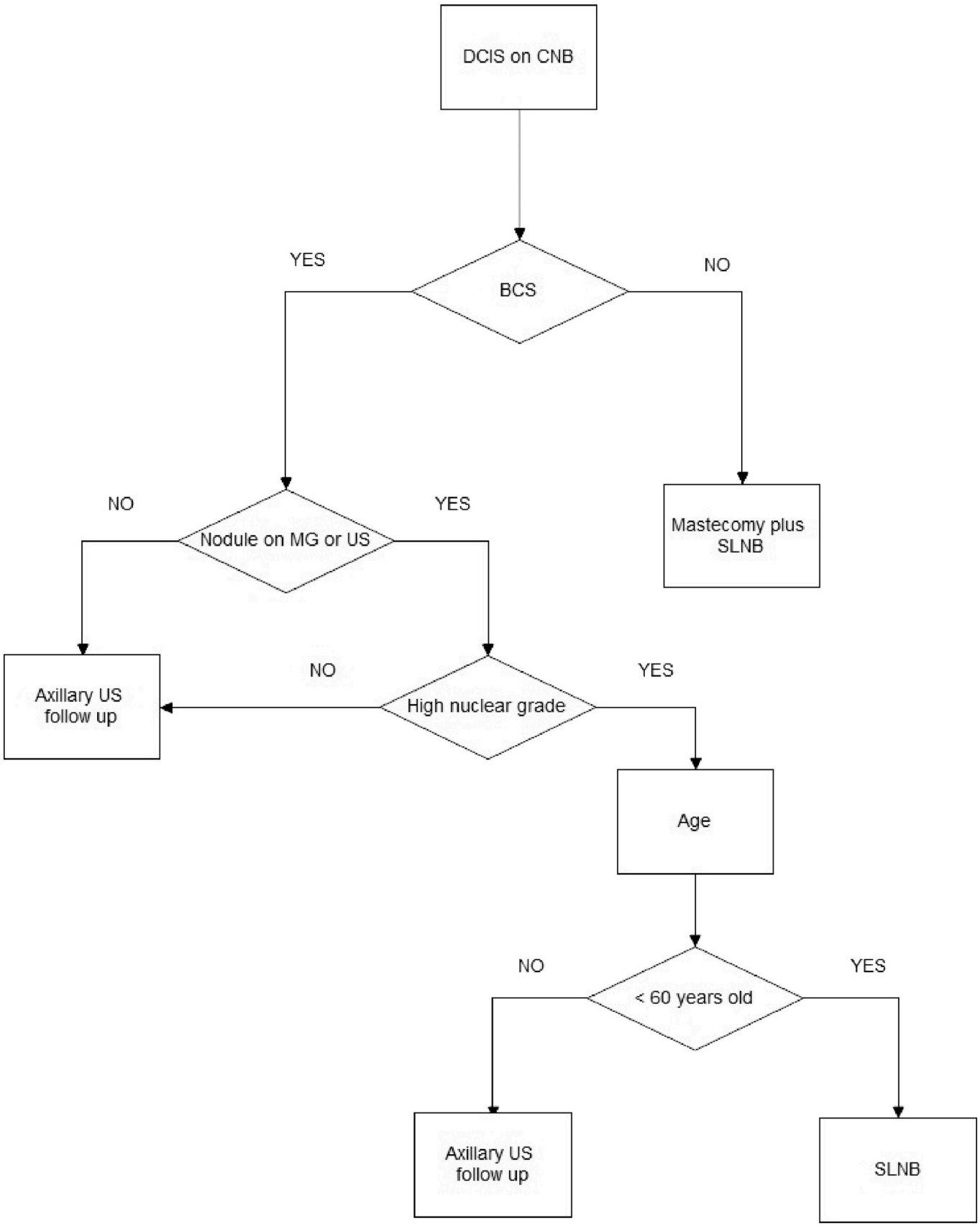

Fig. 7. Algorithm of surgical treatments for DCIS.
DCIS: Ductal Carcinoma In Situ, CNB: core needle biopsy, BCS: breast conserving surgery; MG: mammography, US: ultrasound, SNLB: sentinel lymph node biopsy.

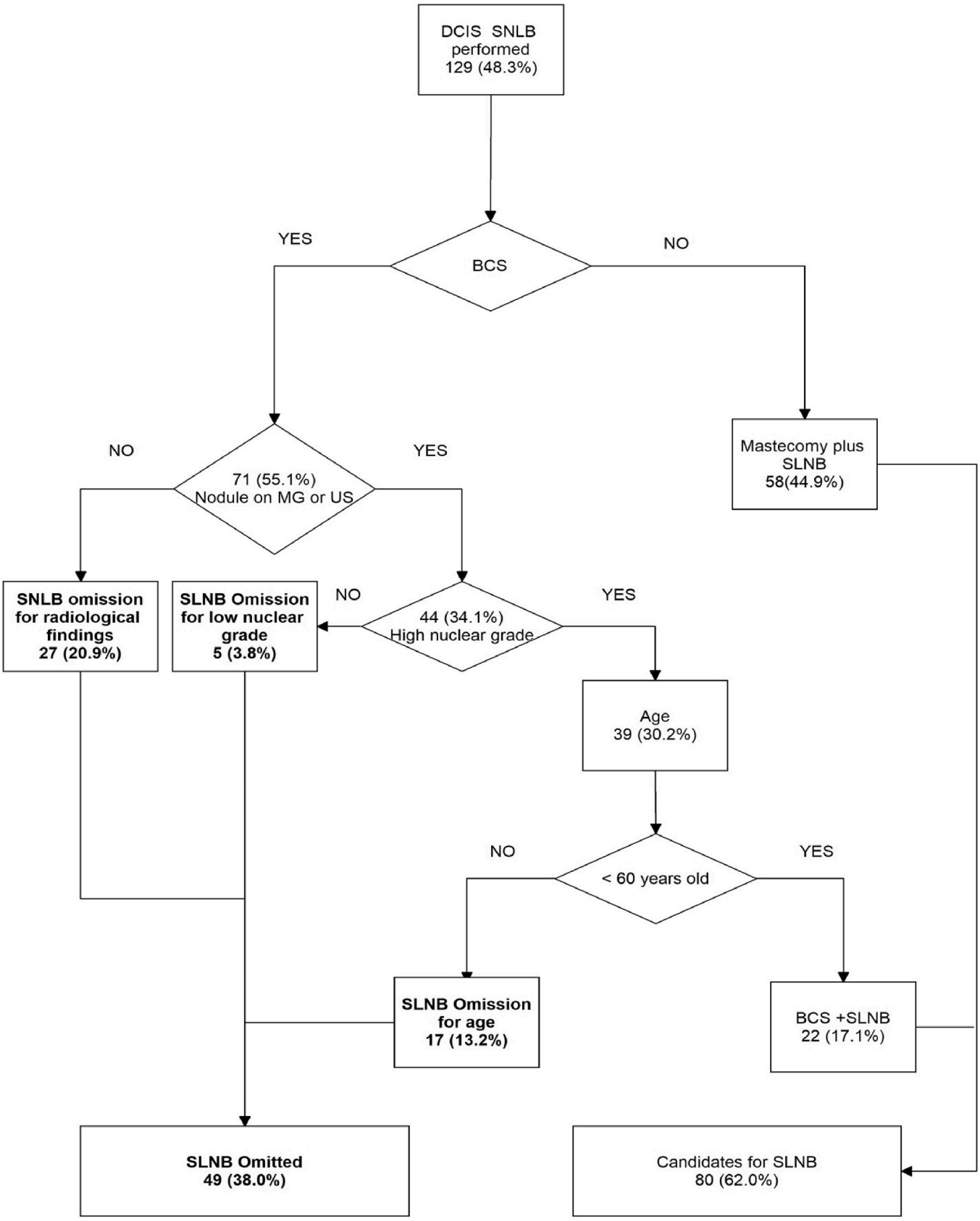

Fig. 8. Potential SNLB omittend in our sample according to the algorithm of surgical treatments for DCIS.
DCIS: Ductal Carcinoma In Situ, CNB: core needle biopsy, BCS: breast conserving surgery; MG: mammography, US: ultrasound, SNLB: sentinel lymph node biopsy.

our research, this pathological finding seemed not to be associated with an upstaging risk. A similar result was reported in a previous analysis of 587 cases by Goyal et al. [41].

An indication to carry out a SLNB is often driven by physician's concern of a potential second surgical procedure following the DCIS surgical treatment. This is partly justified by the sparsity of data concerning SLNB recommendations and the absence of consensus regarding criteria for management of lymph nodes in DCIS [2–42]. Regarding the rate of SLN metastasis in patients with a pure diagnosis of DCIS, our results (3.4 %) were in line with rates reported in previous studies; ranging from 2.5 to 6.8 % [43,44]. Among 129 patients who underwent SLNB, 9 presented tumor involvement of which 2 ITC and 7 micrometastasis. Predictive factors for SL involvement are age and upstaging.

In recent years, surgical biopsy of lymph nodes can be omitted in many cases with a pre-operative diagnosis of a pure DCIS [21]. In our series, 48.3 % of patients with a pre-operative DCIS diagnosis underwent SLNB. Cases in which this surgical strategy was withheld included patients with low risk of DCIS upstaging. Out of 129 patients, 9 (6.97 %) presented micro-metastasis or isolated tumor cells while no cases of macro metastasis were observed, and no patient was subjected to axillary lymphadenectomy and/or adjuvant chemotherapy. All patients with SLN metastasis presented with an invasive ductal carcinoma at definitive pathological examination. The ACOSOG Z0011 trial, demonstrating the possibility of avoiding ALND in cases of limited metastatic disease in invasive breast cancer, led to the development of this approach [7–45]. Recent data showed no difference in oncological outcomes among patients with positive SNLB, whether were subjected to ALND or not, raising doubts about the role of SNLB in invasive breast carcinoma [47]. Based on these doubts, Gentilini et al. proposed the concept of abandoning SNLB in early breast cancer [47]. According to these innovative results, omitting SLNB would probably have caused no effect in the 9 patients of our population. Significant differences between groups with or without SLN metastasis were similar to the predictors of risk detected for upstaging, as reported in our result.

Interestingly, all the patients with SLN metastasis in our analysis were aged between 40 and 60 years old and were significantly younger than cases with negative or omitted SLN. Correlation to age was reported in the literature [48,49]. Moreover, Ramzi et al. described in their retrospective analysis the relation between the upstaging risk and the consequential risk of SLN metastasis [50]. Ramzi et al., although suggested to avoid routine omission of SLNB, concluded that a discriminative approach based on age should be considered.

Despite the various predictive factors reported in many studies, there is no consensus in the literature regarding predictive factors which constitute a diagnosis upstaging of DCIS lesions into ductal invasive cancer [8,9]. Pre-operative identification of SLN metastasis is difficult and axillary surgical management could be challenging for breast physicians.

Routine SLNB in DCIS lesions could be considered an overtreatment, especially in the era of breast surgical de-escalation. Postponing an eventual SNLB to after the final pathological examination could encompass many disadvantages. A second procedure to perform surgical axillary staging could impair patients' quality of life and increase health costs [51,52-53]. Contrarily, omitting SLNB could represent an undertreatment according to currently guidelines, as about 30 % of DCIS cases are upstaged into invasive breast cancer [54]. In our opinion, as confirmed by our results, the SLN metastasis risk in patients with a pre-operative diagnosis of DCIS and an upstaging to invasive cancer is low. Supported by the preliminary results of SOUND study, a trial for abandoning SLNB in early invasive breast cancer, we strongly believe in axillary surgical de-escalation in DCIS patients [47]. Upon our data we could have avoided SLNB in 49 cases (38 %).

While waiting for international consensus for abandoning SLNB in DCIS lesions, we adopted a potential algorithm of surgical treatments for DCIS in order to reduce SNLB in DCIS patients and minimize as much as possible overtreatment and undertreatment (Fig. 7). In Fig. 8 are shown number of possible SNLB omitted, according to our flowchart, in out sample (Fig. 8). This flowchart in clinical practice could lead to reducing axillary surgery and reducing related side effects. Main limitations of our study are the retrospective nature of it that lead to some missing data, and the small size of the sample. Our result should be confirmed in our ongoing prospective study to achieve a surgical de-escalation also in DCIS.

5. Conclusion

In the era of minimizing invasive surgical procedures for breast cancer, supported by the findings of the axillary surgical de-escalation trials, routine SLNB must be avoided in patients with a pre-operative diagnosis of DCIS.

While the literature is rich in predictors of underestimation of invasive breast cancer, in our opinion there is an absence of consensus regarding parameters associated with upstaging. Additional prospective randomized trial studies are required to corroborate our result. Moreover, an international consensus to establish independent factors for risk of DCIS upstaging with the possibility of abandoning SNLB in patients with a pre-operative diagnosis of DCIS is essential. Awaiting an international consensus, along with the progress of artificial intelligence to predict invasive component in DCIS, our algorithm could help the breast oncological physicians to manage DCIS in order to minimize possible overtreatment and undertreatment.

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None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This study was approved by the Ethics Committee of the Policlinico Tor Vergata of Rome (approval number R.S.72.23).

CRediT authorship contribution statement

Gianluca Vanni: Resources, Conceptualization. **Marco Pellicciaro:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **Marco Materazzo:** Formal analysis, Data curation. **Massimiliano Berretta:** Supervision, Investigation. **Rosaria Meucci:** Visualization, Data curation. **Tommaso Perretta:** Data curation. **Ilaria Portarena:** Resources, Data curation. **Chiara Adriana Pistolese:** Validation, Supervision. **Oreste Claudio Buonomo:** Visualization, Validation, Supervision, Resources, Funding acquisition.

Declaration of competing interest

All the authors declare that they have no potential conflict of interest.

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