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Surgical Treatments for Ductal Carcinoma *In Situ* (DCIS) in Elderly Patients

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Abstract. *Background/Aim: Despite an aging population, there is no consensus regarding ductal carcinoma in situ (DCIS) treatment for elderly women. Breast surgery can be well tolerated even in elderly patients. The aim of this study is to evaluate the surgical management of DCIS in elderly patients. Patients and Methods: We retrospectively analyzed patients with DCIS from 2016 to 2022 at our Breast Unit and divided our population according to age. Results: Out of 231 patients with DCIS, 45 (19.5%) were elderly. The Charlson comorbidity index and American Society of Anesthesiology (ASA) score was significantly higher in the elderly (p<0.001 for both). Among the elderly, 10 (22.2%) patients received upstaging diagnoses, versus 18 (9.7%) in the control (p=0.048). Twelve (26.7%) of the elderly patients underwent sentinel lymph node biopsy, versus 93 (50%) in the control group (p=0.005). No difference was reported between groups in terms of breast conserving surgeries performed. A higher incidence of surgeries performed using local anesthesia was reported in the elderly group (p=0.041). Thirty-day surgical complications, according to Clavien-Dindo, did not show significant differences. Conclusion: Despite higher comorbidity and ASA score, breast surgery is safe and feasible in elderly patients. Due to the higher risk of upstaging to invasive ductal carcinoma, surgery should be performed but sentinel lymph node biopsy should be omitted, owing to the low risk of lymph node metastasis and lower use of adjuvant treatments.*

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The widespread breast cancer screening and implementation of digital mammography led to an increase in the detection of ductal carcinoma *in situ* (DCIS) (1). This condition is considered the earliest detectable breast cancer (stage 0) and is probably underdiagnosed prior to breast cancer screening (2). Pure DCIS is defined as proliferating malignant breast cells without evidence of basement membrane invasion (3). Theoretically, DCIS does not possess metastatic potential, yet it could represent an underdiagnosis of invasive breast cancer, or progress to it (4). The risk of progression to invasive cancer ranges from 14% to 50 % (4, 5).

According to the current guidelines, over 95% of women diagnosed with DCIS will chose to receive a combination of surgery and adjuvant treatments (radiation and/or endocrine therapy) (6). Lymph node evaluation for stage 0 breast cancer is controversial, and sentinel lymph node biopsy (SNLB) should be reserved for invasive cancer (4). Due to the risk of upstaging to invasive breast cancer and in order to avoid a potential second surgical procedure, a large proportion of women with a DCIS diagnosis undergo unnecessary SLNB (7). Despite DCIS often receiving similar treatments as ductal invasive cancer, all these measures have not been shown to reduce overall mortality in large observational studies (8). According to these studies, surgery may not be the optimal treatment choice, especially for elderly patients with high levels of comorbidity and a DCIS diagnosis whose disease course differs significantly from that of invasive breast cancer (9).

Active surveillance as an alternative to surgery could be an option, and has been investigated in many studies, but due to the lack of analysis of long-term results and different outcomes within these, it has not been validated by routine guidelines (10). Progression risk, health cost and long-term outcomes in patients with DCIS subjected to active surveillance is yet to be assessed (10). Notwithstanding this newly proposed strategy, minimally invasive breast surgery remains the gold standard of treatment, even for elderly patients without compromised performance status (11, 12). Further, surgical excision allowing a complete sampling of the lesion prevents potential downstaging (10). The aim of this retrospective study is to evaluate the surgical management of DCIS in elderly patients and the short-term outcomes in our breast unit.

Patients and Methods

Patients. All patients with a DCIS diagnosis who underwent breast surgery between January 2016 to March 2022 at the Breast Unit of PTV (Policlinico Tor Vergata, Rome) were retrospectively reviewed and considered for the study. All female patients with a diagnosis of DCIS by core needle biopsy who underwent breast surgery were included in the study. Exclusion criteria were male patients, age <45 years old and patients who received diagnoses in different institutions, due to the lack of information and absence of potential revision of core needle specimen pathological examination.

Pre-operative findings. The patients' performance status was evaluated using the Charlson comorbidity index (CCI) and the American society of anesthesiologists (ASA) classification, both retrieved from preoperative evaluation of the patients (13, 14).
Report or imaging of the lesion investigated with ultrasonography, mammography, or magnetic resonance imaging (MRI) according to the clinical characteristics was reported and for each type of imaging, the Breast imaging reporting and data system of the American College of Radiology (BI-RADS) score was evaluated in the study. Radiological parameters were reported following imaging revision by a breast-dedicated radiologist.

At breast ultrasonography, evidence or not of a lesion, maximum diameter and lesion features were reported. Mammography findings such as calcification, mass, or architectural distortion were retrieved and analyzed. Breast quadrants involved by the lesions were reported. Multifocal and multicentric disease, as the bilaterality of the tumor, were reported in the study. According to the inclusion criteria, all patients underwent a core needle biopsy, and the samples were analyzed by at least two breast-cancer dedicated pathologists. Pathological examination reports of biopsy specimen were reviewed in order to categorize lesions according to tumor features.

Surgical procedure and outcome. All patients evaluated in the study underwent surgical excision of the lesion and were classified according to the type of surgery as breast conservative surgery or mastectomy. Breast conservative surgery included all procedures with partial gland removal, while mastectomy included the complete removal of the glandular tissue with or without sparing the skin or nipple areola complex.

The final pathological exam was reported, and tumors were classified as DCIS, DCIS with microinvasion or invasive breast cancer. Microinvasion was defined as basement membrane invasion no greater than 1 mm. Type of tumor, dimensions, grade, prognostic, and predictive factors were retrieved from the final pathological examination of the surgical specimen and compared to preoperative exam in order to detect cases of upstaging to microinvasive or invasive ductal carcinoma.

Patients subjected to SNLB were identified from surgical notes and reported along with the histological assessment from pathological examination. A positive sentinel lymph node was defined by the presence of breast cancer metastasis; categorized as 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).

Anesthetic strategies adopted to perform surgery were retrieved from clinical notes and reported. All procedures performed with administration of local anesthetics or regional anesthesia without mechanical ventilation were considered awake breast surgery. Length of hospitalization was reported in days, considered from the date of admission until discharge to home and calculated from clinical notes.

Thirty-day surgical complication scoring, according to Clavien-Dindo, was retrieved from clinical notes and analyzed in the study (15). Female patients aged ≥70 years old were considered in the Elderly DCIS group while the DCIS control group, consisting of patients aged between 45 and 69 years old.

Statistical analysis. All data were collected into an EXCEL database (Microsoft, Washington, DC, USA). According to patients' age, clinicopathological variables were compared between the elderly DCIS group and the control group using the *t*-test for continuous variables. Otherwise, for dichotomous variables, the Fisher's exact test was applied, or the Monte Carlo test in cases of non-dichotomous variables to compare the two age-based groups. *p*-Values <0.05 were considered to be statistically significant. All the statistical analyses were performed using SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

From January 2016 to March 2022, 231 patients aged >45 years old received a diagnosis of DCIS by core needle biopsy and subsequently underwent surgery at the Breast Unit of PTV (Policlinico Tor Vergata, Rome). The mean age was 59.1±11.2 years and BMI was equal to 25.8±3.2. One hundred and twenty-nine (56.5%) patients presented lesions smaller than 15 mm, 78 (34.2%) cases with diameter between 16 mm to 40 mm while 22 cases (9.2%) exhibited lesions greater than 40 mm. High nuclear grade (grade 3) was reported in 99 (50.8%) preoperative biopsies, whereas 42 (21.5%) and 54 (27.7%) cases showed intermediate (grade 2) and low nuclear grade (grade 1), respectively. Comedonecrosis was reported in 102 (44.2%) cases at pathological examination of a core needle biopsy specimen.

Out of 231 patients, 45 (19.5%) underwent mastectomy while 186 (80.5%) underwent a breast conservative surgery. One hundred and five (45.5%) patients were subjected to SNLB. Out of 105 women subjected to axillary surgical

Table I. *Pre-operative and baseline patients' Charlson comorbidity index (CCI), anesthetic risk using the American Society of Anesthesiology score (ASA) and pre-operative tumor characteristics between the elderly and the ductal carcinoma in situ (DCIS) control group.*

	Elderly DCIS group (n=45)	DCIS control group (n=186)	*p*-Value
ASA risk			<0.001
ASA I	4 (%)	136 (%)	
ASA II	26 (%)	45 (%)	
ASA III	12 (%)	4 (%)	
ASA IV	3 (%)	1 (%)	
Charlson Comorbidity Index	5 (3-11)	1 [0-4]	<0.001
Tumor dimension range			0.613
Lesion <15 mm	24 (53.3%)	105 (57.4%)	
Lesion >15 mm <40 mm	18 (40%)	60 (32.8%)	
Lesion >40 mm	3 (6.7%)	18 (9.8%)	
Multifocal lesion	3 (7.7%)	30 (17.5%)	0.150
Multicentric lesion	0	15 (8.8%)	0.079
Comedonecrosis	24 (53.3%)	78 (49.1%)	0.736
Nuclear grade			0.001
Low grade I	18 (50%)	36 (22.6%)	
Intermediate grade II	9 (25%)	33 (20.9%)	
High grade III	9 (25%)	90 (56.6%)	

Table II. *Radiological findings at breast ultrasonography (US) and mammography with relative breast imaging reporting and data system (BI-RADS) between the elderly and the ductal carcinoma in situ (DCIS) control group.*

	Elderly DCIS group (n=45)	DCIS control group (n=186)	*p*-Value
Lesion evidence at US	3 (9.1%)	63 (55.3%)	0.001
US findings			0.001
No evidence	3 (9.1%)	63 (55.3%)	
Spiculated margin nodule	3 (9.1%)	6 (5.3%)	
Circumscribed margin nodule	15 (45.5%)	24 (21.1%)	
Echotexture heterogeneous	6 (18.2%)	15 (13.2%)	
Pseudonodular hypoechoic area	6 (18.2%)	3 (2.6%)	
Cystic with vegetations solid wall	0	3 (2.6%)	
US BI-RADS			0.203
BI-RADS 3	6 (20%)	12 (23.5%)	
BI-RADS 4a	9 (30%)	9 (17.6%)	
BI-RADS 4b	9 (30%)	9 (17.6%)	
BI-RADS 4c	3 (10%)	15 (29.4%)	
BI-RADS 5	3 (10%)	6 (11.8%)	
Lesion evidence at Mammography	42 (88.9%)	186 (100%)	0.028
Microcalcifications	18 (66.7%)	150 (94.3%)	0.001
Mammography findings			0.001
No evidence	3 (11.1%)	0	
Dense speculated lesion	6 (22.2%)	15 (9.4%)	
Cluster microcalcifications	12 (44.4%)	114 (71.7%)	
Microcalcifications and speculated lesion	6 (22.2%)	30 (18.9%)	
Mammography BI-RADS			0.001
BI-RADS 3	3 (11.1%)	0	
BI-RADS 4a	9 (33.3%)	36 (23.6%)	
BI-RADS 4b	9 (33.3%)	75 (47.2%)	
BI-RADS 4c	3 (11.1%)	33 (20.8%)	
BI-RADS 5	0	15 (9.4%)	

staging, six (5.7%) patients presented with sentinel lymph nodes (SNL) metastasis (all of which presented micro-metastasis, while no cases of macro-metastasis were reported).

Twenty-eight (12.1%) patients received a diagnosis upstaging (26 from DCIS to invasive ductal carcinoma and two to micro-invasive ductal carcinoma) at final pathological examination. All six patients with a SNL site of micro-metastasis received an upstaging diagnosis at final pathological examination.

Out of 231 women with a pre-operative diagnosis of DCIS, 45 (19.5%) patients were older than 70 years old and considered in the elderly DCIS group, and 186 (80.5%) patients aged between 45 and 69 years old were considered as the control group. No differences were reported in terms of BMI between the groups (p=0.786). Charlson comorbidity index and ASA score were significantly higher in the elderly: 5 (3-11) *vs*. 1 (0-4), (p<0.001 for both); the score of anesthetic risk (ASA) and the median of CCI are summarized in Table I.

Preoperative tumor dimensions were comparable between groups: in the elderly DCIS group, 24 (53.3%) lesions had a diameter <15 mm, 18 (40%) ranged between 15 mm and 40 mm, and three (7.7%) were greater than 40 mm, *versus* 105 (57.4%), 60 (32.8%) and 18 (9.8%) in the control group, respectively (p=0.613, Table I). No cases of multicentric lesions were reported in the older population, *versus* 15 (8.8%) in the younger patients, showing no statistically significant differences between the groups (p=0.079). Additionally, the incidence of multifocal lesion did not show any significant statistical differences (p=0.150), with three (7.7%) cases in the elderly DCIS group *versus* 30 (17.5%) in the control group (Table I).

In the elderly DCIS group, 24 (53.3%) patients presented comedonecrosis at pathological examination, *versus* 78 (49.1%) in the younger group (p=0.736). Nuclear grade was significantly lower in elderly patients representing a statistically significant difference (p=0.001). Grade distribution between groups is shown in Table I.

Pre-operative radiological imaging in the elderly patients was different compared to the control group, and imaging features with relative p-values are summarized in Table II. Ultra-sonography findings showed a statistically significant difference between the elderly and the control group. A higher incidence of nodular lesions was reported in older patients: 45.5% *versus* 21.1%, and the overall ultra-sonography findings p-value was less than 0.001, as shown in Table II. Differently, the presence of microcalcification, reported at mammography, was lower in

Table III. *Surgical procedure performed and outcome: pathological examination of sentinel lymph node biopsy (SNLB), cases of upstaging to invasive or microinvasive breast cancer and surgical complications between the elderly and the ductal carcinoma in situ (DCIS) control group.*

	Elderly DCIS group (n=45)	DCIS control group (n=186)	*p*-Value
Breast conserving surgery	39 (86.7%)	147 (79%)	0.298
SNLB	12 (26.7%)	93 (50%)	0.005
SNL pathological examination			0.612
Negative	12 (100%)	87 (93.5%)	
Isolates tumor cells	0	0	
Micro-metastasis	0	6 (6.5%)	
Macro-metastasis	0	0	
DCIS upstaging			0.041
To micro-invasive DC	0	2 (1.1%)	
To invasive DC	10 (22.2%)	16 (8.6%)	
Total case of DCIS upstaging	10 (22.2%)	18 (9.7%)	
Awake surgery	16 (35.5%)	38 (20.4%)	0.048
Hospital stays median days	1 [0-5]	1 [0-3]	0.288
Surgical complications	10 (22.2%)	28 (%)	0.377
No complications	35 (77.7%)	158 (84.9%)	
Clavien-Dindo grade I	5 (11.1%)	18 (9.6%)	
Clavien-Dindo grade II	4 (8.8%)	8 (4.3%)	
Clavien-Dindo grade IIIa	1 (2.2%)	2 (1.1%)	
Clavien-Dindo grade IIIb	0	0	

elderly patients; 18 (66.7%) *versus* 150 (94.3%) in the control group (p-value <0.001). Other mammography features and BI-RADS scores are summarized in Table II.

In the elderly DCIS group, 39 (86.7%) patients underwent breast conservative surgery, *versus* 147 (79%) in the younger group, without a statistically significant difference (p=0.298). Contrastingly, a higher percentage of younger patients underwent SNLB: 93 (50%), *versus* 12 (26.7%) in elderly group. This difference is statistically significant (p=0.005). Out of 93 patients subjected to SNLB, six (6.4%) presented micro-metastasis at pathological examination of the removed lymph node, *versus* no cases in the elderly group (p=0.612). As summarized in Table III, no cases of isolated tumor cells or macro-metastasis were reported in both groups.

Elderly patients presented with a significantly higher incidence of DCIS upstaging to micro-invasive/invasive ductal carcinoma. Cases of DCIS upstaging were 10 (22.2%) in the elderly patients *versus* 28 (9.7%) in the control (p=0.041). Out of 10 elderly patients, no cases were upstaged in micro-invasive ductal carcinoma *versus* two (1.1%) in the control group. Rates of upstaging to invasive or microinvasive ductal carcinoma are summarized in Table III.

Out of 45 patients, 16 (35.5%) underwent awake breast surgery in the elderly DCIS group *vs.* 38 (20.4%) in the control group, showing a significant difference between the groups (p=0.048). Despite this difference, the median of hospital stay was comparable between the two groups (p=0.288): one (range=0-5) day in the elderly and one (range=0-3) in the younger patient group. Thirty days surgical complication incidence according to Clavien-Dindo did not show significant differences between groups (p=0.377). Complication grades are summarized in Table III.

Discussion

The majority of breast cancer surgeons during the last decades would agree that optimal treatment of DCIS has yet to be defined (10). Despite the publication of several randomized, prospective, and retrospective studies, documenting outcomes data on DCIS, its management is still a matter of controversy (10-16, 19). Recent epidemiological data have shown a dramatic increase of elderly woman with DCIS (20). This increase can be attributed to many factors such as enlarging pool of older women, the higher prevalence of breast cancer in older women, increased detection rate of DCIS secondary to digital mammography implementation and greater availability and accessibility to breast cancer screening programs (21, 22).

Selecting the appropriate treatments for DCIS is a clinical quandary, especially in older patients where comorbidities could play a cardinal role in guiding physicians, although these treatments do not impact survival (20). On the other hand, multiple randomized trials demonstrated an improvement in disease free survival among DCIS patients subjected to adjuvant radiation following conservative breast surgery (16-19). Proper data collection and analysis can reliably identify a population whose risk of recurrence is low (20). Nonetheless, nowadays, not enough is known regarding the clinical, pathological, and other factors to predict recurrence after DCIS (20). We strongly believe that molecular evaluation of DCIS could better predict recurrence in those patients but is not currently routinely validated.

DCIS is defined as proliferating malignant breast cells and is considered a pre-invasive neoplastic lesion (23). Due to the absence of basement membrane invasion, theoretically, DCIS does not possess a lymph nodes and distant metastatic potential (3).

Active surveillance as an alternative to surgery followed by adjuvant treatments could be a strategy in which treatment decisions are based on watchful waiting and observation of disease progression (9). This strategy could reduce the potential for overtreatment; however, it could increase cases of DCIS upstaging requiring more invasive treatments. In our study, all patients underwent breast surgery followed by adjuvant treatments: with hormone therapy according to biological characteristics of the tumor, or radiation according to patient's comorbidity and surgical treatments. Active surveillance was not chosen, due to the lack of data supporting this non-operative management and

due to patients' desire, who strongly believe that excision would resolve the disease. Moreover, the natural history of this pre-invasive neoplasia is not known and predicting its evolution could be challenging (23).

Currently, core needle biopsy has become the gold standard for diagnosis of breast cancer (24). It plays a key role in the decision-making process of correct breast cancer treatments (25). However, the limitations in sampling of cancer tissue carry the risk of missing the invasive component and thus underestimating the disease (25, 26). Accordingly, micro-invasive or invasive ductal carcinoma could be underdiagnosed in DCIS patients, and consequently this pre-neoplastic lesion upstaged to invasive cancer at pathological examination of the whole lesion (25). Approximately 15-25% of patients with a pre-operative diagnosis of DCIS are later upstaged to invasive ductal disease (26). In our study, DCIS upstaging stood roughly at 12%. This percentage was significantly higher in the elderly women with a peak of 23% in older DCIS patients (26, 27). According to the higher risk of breast cancer diagnosis underestimation, we believe that a pathological examination of the whole lesion should also be performed in elderly patients. Furthermore, healthcare compliance of elderly patients may be low, and lack of surveillance in underdiagnosed invasive cancer or progressing DCIS may lead to the need for more invasive treatments and higher national healthcare costs due to the delay in surgical treatments (28-31).

The analysis of hormone receptor expression still remains the evaluation criterion for carrying out adjuvant hormonal treatment in patients with DICIS (32-35). Analysis of hormone receptors in breast cancer is increasingly being conducted in preoperative core needle biopsies but the concordance with the excisional biopsy is debated (36, 37). In our analysis, we did not evaluate this concordance as it deviates from the aim of the study; but evaluation of breast cancer predictive factors in the whole lesion is indeed more accurate and useful for the decision of a possible adjuvant hormonal treatment.

When performed, genomic assay scores supported omission of adjuvant treatments for over 75% of cases (37). In this study, according to clinical guidelines, no patients with DCIS were subjected to genomic assays, yet we strongly believe in its potential to predict the recurrence risk and the feasibility of non-operative management.

Although we do not have tools capable of predicting the risk of recurrence with certainty, many factors are reported in the current literature as predictors of DCIS upstaging to invasive cancer (39, 40). Both pre-operative radiological features, histological characteristics are reported as predictive factors of DCIS upstaging (40-43). In our analysis, we reported an increased incidence of nodular lesions in the elderly patients. Nodular lesions are among the most predictive factors of DCIS upstaging to invasive cancer, and this correlation is further confirmed in our study (40). Differently, microcalcification alone, typical of pure DCIS was reported with higher frequency in the younger women in our analysis (44). This radiological association was confirmed in our study.

SNLB should be reserved for patients with invasive breast cancer. Nonetheless, in order to avoid a potential second surgical procedure, it should also be carried out in patients with DCIS diagnosis and increased risk for upstaging as well as in patients planned for mastectomy as SNL cannot be subsequently identified (45, 46). Due to lack of well-defined guidelines, a large portion of women with DCIS diagnosis underwent unnecessary SNLB (47). In our analysis, despite the increased risk of upstaging to invasive cancer in older patients, the number of patients subjected to SNLB was significantly lower in the elderly DCIS group. Out of these, no patients older than 70 years presented lymph nodes metastasis. Moreover, out of these 6 cases with positive lymph nodes reported in the younger group, all presented micro-metastasis, and none required further surgical procedure or adjuvant chemotherapy. Increased incidence of SNLB omitting in elderly DCIS, despite the increased risk of upstaging to invasive cancer, could be correlated to the fact that even in the case of SNL metastasis no further treatments are adopted, especially in older frail women (48-50).

Regardless, the higher incidence of comorbidity and anesthetic risk, evaluated with the ASA score in elderly patients' surgical procedures, were comparable between the groups. This result could be explained by the fact that the surgical strategy is guided by tumor and breast characteristics. Moreover, we have a long experience with awake breast surgery allowing avoidance of general anesthesia, especially for frail patients (11-12). Thus, in our study, the mini-invasive approach was the largely adopted strategy in elderly patients.

Conclusion

In elderly patients, the risk of DCIS upstaging to invasive cancer is higher than in younger women with similar pre-operative diagnosis. Despite a higher ASA score and comorbidities, breast surgery is safe and feasible in older patients providing a complete sample size for pathological examination of the tumor, thus reducing cases of upstaged breast cancer and without increased incidence of surgical complications. Pending standardized genetic testing to predict DCIS cases that will progress or are at high risk of recurrence, breast surgery still plays a key role in the treatment of DCIS even in elderly patients. SNLB in elderly patients diagnosed with DCIS, despite the increased risk of upstaging to invasive cancer, should be omitted due to the low risk of lymph node metastases and the fact that no further treatments are being adopted, particularly in this category.

Conflicts of Interest

All the Authors declare that they have no potential conflicts of interest.

Authors' Contributions

OCB and MP: conceptualization, methodology, formal analysis, and design of the study; equally contributed to the manuscript. MP and GV: writing original draft. MM and MP: statistical analysis. SB RM, TP, IP, and PEG: data collection. JC: writing review. OCB, MD, CAP and GV: supervision. All the Authors reviewed and approved the final version to be published.

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