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The role of sentinel lymph biopsy in patients with microinvasive breast cancer: A multicentric study

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ABSTRACT

Microinvasive breast cancer (MIBC) is a rare tumor. Despite of its good prognosis, which is similar to in situ breast cancer, its management is still similar to invasive tumors. The aim of this study is to assess the prognostic implications of SNLB in MIBC patients and to evaluate the possibility for surgical de-escalation in these patients.
Methods: A multicentric retrospective study including all patients with MIBC diagnosis who underwent surgery from 2012 to 2022 is carried on. Seven different Italian Breast Units contributed to the study. Preoperative, intraoperative and post operative data were taken into account, including final histological report with tumor staging and oncological outcomes.
Results: 261 patients were included. The metastatic rate of sentinel lymph node biopsy (SLNB) was 9.2 % (2.3 % macrometastasis, 6.9 % micrometastasis or isolated tumors cells). Multifocal lesions (p-value: 0.045; OR:1.730), and the absence of hormone receptors (p-value: 0.018; OR:3.658) are all predictors of sentinel lymph node metastasis, while a Ki67 proliferation index <20 % associates with a low risk of nodal metastasis (p-value: 0.035; OR:0.289). Five-years loco-regional recurrence in patients with metastatic sentinel lymph node was comparable to the non-metastatic ones (95.7 % vs 94.1 %; p-value: 0.951). Cox Regression analysis identifies age at diagnosis as a predictive factor of locoregional recurrence at five years (OR 0.831 95%CI: 0.721–0957, p-value: 0.010).
Conclusion: MIBC has a favorable prognosis and very low macrometastatic sentinel lymph node rates. The omission of SNLB in patients with MIBC provides a similar overall survival rate, therefore SNLB should be reserved to younger patient with preoperative radiological or clinical suspicion of metastatic lymph nodes.

1. Introduction

Microinvasive cancer is a rare breast cancer, accounting for

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Abbreviations

MIBC	Microinvasive Breast Cancer
SNLB	Sentinel lymph node biopsy
SNL:	Sentinel lymph node
OR	Odds Ratio
DCIS	Ductal carcinoma in situ
CBS	Conserving breast surgery
ALND	Axillary lymph nodes dissections

approximately 1 % of all breast oncological neoplasms [1]. Its definition has varied over time [2]. The current definition is given according to the latest ACJCC staging manual, which defines MIBC as any tumor with an extension of breast cancer cells beyond the basement membrane with a focus of ≤ 1 mm in dimension [3]. MIBC usually arises in the setting of ductal carcinoma in situ (DCIS) and, likewise, it has been reported to be associated with a good overall clinical outcome and with a low rate of distant metastasis and favorable overall survival [4].

Although the prognosis is more comparable to DCIS than ductal invasive breast cancer, the treatment for MIBC patients is still similar to invasive cancer. According to the current global consensus, axillary staging in DCIS is reserved to patients with an elevated risk of invasive cancer or to those undergoing mastectomy; however, its need remains controversial in patients with MIBC [2,5,6]. Probably due to the rarity of MIBC, guidelines regarding the role of SLNB in those patients have not been defined yet [7,8]. A recent meta-analys reported a significatively shorter disease-free survival in patients with MIBC compared to those with DCIS [7]. According to these reasons, for many authors MIBC could be considered more similar to invasive ductal carcinoma than DCIS [9]. The literature reports a 0–20 % rate of lymph node metastasis in MIBC [7–9], this large spectrum could be explained by the different definitions given to MIBC within past years. Due to its rare entity, the prognostic role of metastatic sentinel lymph node is unclear and still debated.

The aim of this study is to assess the prognostic implications of SNLB in MIBC patients and to evaluate the possibility of surgical de-escalation for these patients.

2. Materials and methods

The study was approved by the institutional review board of Policlinico Tor Vergata (approval number 72.23). Seven Italian Breast Units contributed to a common multicentric database of patients who underwent oncological breast surgery from 2012 to 2022. Breast units involved were: Policlinico Tor Vergata (Rome), Umberto I Hospital (Rome), Sant'Andrea hospital (Rome), Cottolegno Hospital (Turin), Cattinara hospital (Trieste), Ospedale Maggiore Policlinico (Milan) and Ospedali Riuniti (Foggia). All patients with a definitive diagnosis of microinvasive breast cancer were identified and included in the study, all other patients' diagnosis were excluded. MIBC was considered as a tumor with an extension of breast cancer cells beyond the basement membrane with a focus of ≤ 1 mm in dimension [3]. The sample was divided in two groups according to either the presence or absence of sentinel lymph node metastasis, p-N≥1 group and p-N = 0 group respectively.

Sentinel lymph node identification was performed using a radiocolloid technique. The intraoperative sentinel lymph node histopathological evaluation, when deemed necessary, was conducted using hematoxylin and eosin-stained sections. Axillary lymph node metastases were defined as follow: isolated tumor cells $N1_{ITC}$ (single tumor cell, or tumor-cell cluster <0.2 mm), $N1_{mi}$ micro-metastasis (>200 cells or >0.2 mm, but <2.0 mm) or $N1_{M}$ macro-metastasis (>2.0 mm). All data regarding axillary staging was reported in the study [3].

The breast surgical procedures were categorized into demolitive surgery and conserving breast surgery (CBS). Final pathological examination and relative breast cancer predictive and prognostic factors were retrieved from clinical note and reported in the study. Data from surgical specimens were included in the study. Estrogen receptor (ER), Progesterone receptor (PR) and Ki67 indexes were expressed as percentage of positive cells found in the specimen studied through immunohistochemistry (IHC). Overexpression of Her2 gene (HER2+) was identified by IHC or by FISH, as indicated by the recommendations of the 2018 ASCO/CAP and reported as a score [3].

The adjuvant systemic treatments (Hormone therapy, Chemotherapy) and local treatment (breast radiation) were evaluated. Cancer recurrences, either local or distant recurrences, as well as mortality rates were retrieved from follow-up data and analyzed in the study. Patients' follow-up was scheduled according to routine clinical practice and performed by breast physician. Local recurrence was defined as the reappearance of the tumor in the ipsilateral breast, chest, or ipsilateral axillary lymph nodes and confirmed at pathological examination.

2.1. Statistical analysis

All data analyzed were recorded using a Microsoft EXCEL®. For the statistical analysis the software used was SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL). The study sample's demographics, types of surgery and clinical characteristics were analyzed using descriptive statistics.

Quantitative variables were reported as median value and interquartile range. The Mann-Whitney *U* test was used to compare two different groups. Categorial variables were presented as absolute numbers and percentages, and they were analyzed using the Chi-squared test (Fisher's exact test). For no-dichotomous variables Monte Carlo test was adopted. All variables with a p-value <0.05 were considered statistically significant. The Kaplan–Meier method was used to generate survival and? recurrence curves. In case of comparations between group Log-Rank was considered as p-value.??

Multivariate logistic regression analysis was used to assess the effect of SLN metastases, independently of potential confounders. Multivariate cox regression analysis was used to assess the effect of loco-regional recurrence, independently of potential confounders.

3. Results

261 patients underwent breast surgery due to microinvasive ductal carcinoma between 2012 and 2022. Median age was 56 ± 12.1 years old [34; 90].

237 patients (90.8 %) did not present sentinel lymph node metastasis at the final histopathological evaluation (pN = 0 group); 24 patients (9.2 %) had one or more metastatic sentinel lymph nodes (pN ≥ 1 group).

Out of 24 patients with metastatic lymph nodes, 6 (2.3 %) patients presented macrometastasis, 10 (3.8 %) micrometastasis and 8 (3.1 %) isolated tumor cells. Axillary lymph node dissection (ALND) was performed in 12 out of 24 women presenting metastatic sentinel lymph node. Out of the 12 patients subjected to ALND:6 (50 %) SNL macrometastasis, 4 (33.3 %) micrometastasis, 2 (16.6 %) clinically positive lymph nodes. In women subjected to ALND, 1 (8.4 %) presents negative lymph node (pN0), 4 (33.3 %) one metastatic or micro-metastatic lymph node, 3 (25 %) two lymph nodes, 1 (8.4 %) three lymph nodes (pN1a), 2 (16.6 %) patients presented respectively 4 and 7 metastatic lymph nodes (pN2a) and 1 (8.4 %) missing data regarding the number of positive lymph nodes. Out of 261 patients 226 (86.6 %) MIBC were associated with DCIS, 23 (8.8 %) DCIS were not reported in the pathological report and in 12 (4.6 %) data were missing.

Among the 261 patients, 179 (68.6 %) underwent breast conserving surgery and 82 (31.4 %) were subjected to mastectomy. Hormone therapy was administered for at least five years to 159 (64.9 %), chemotherapy to 29 (11.1 %) and target therapy to 9 (5.9 %). Radiation

therapy was omitted in 49 (18 %) patients. Out of 132 (50.5 %) patients subjected to radiation therapy, 130 underwent breast irradiation and 2 underwent axillary irradiations due to metastatic lymph nodes (pN2a).

Median follow-up was 5.2 years [1.7:11.8]. Five years overall disease free-survival was 97.7 %. 6 patients (2.3 %) died; out of the 6 patients 2 of them (0.8 %) had distance recurrence and the cause of death was the disease progression. Five years free-locoregional recurrence was 95.4 %.

In pN = 0 group the mean of age was 58.4 ± 12.7 years versus the 55.6 ± 11.6 years in the pN0 group. Patients over 70 years old were 63 (26.5 %) in the pN0 group and 3 (12.5 %) in the pN ≥ 1 group, p = 0.147.

Out of 237 patients, 70 (29.4 %) patients with negative sentinel lymph node (pN = 0 group) underwent mastectomy while in the pN ≥ 1 group there were 12 (50 %) and the relative p value was 0.025. In the pN = 0 group: 32 cases (13.6 %) were multifocal lesions versus 6 (28.6 %) in the metastatic lymph nodes group, p-value = 0.063. Histological tumor grading was comparable between groups and relative p-value was 0.954: 39 (17.3 %) low grade, 62 (27.4 %) intermediate grade and 125 (55.3 %) high nuclear grade in the pN = 0, while 4 (18.2 %), 5 (22.7 %) and 13 (59.1 %) respectively in the control group. In patients with negative sentinel lymph node (pN = 0 group), 207 (87.3 %) MIBC were associated with DCIS and only 19 (79.2 %) in the pN ≥ 1 group, the relative p value was 0.339.

Out of 24 patients with metastatic sentinel lymph node (pN ≥ 1) 10 patients (41.7 %) did not express hormone receptors at the final histopathological exam. Differently, in the pN = 0 group 94 tumors resulted hormone-negative at the final histopathological exam, showing no statiscal significant difference between the compared groups, with a relative p-value of 0.424. In the pN = 0 group, 93 (39.3 %) cases were HER2+ versus 7 (29.2 %) in the pN ≥ 1 group and relative p value was 0.384. Ki67 proliferation index was >20 % in 70 (29.5 %) cases in the pN = 0 group and in 11 (45.8 %) in the pN ≥ 1 and relative p value was 0.109.

No differences were reported in terms of adjuvant treatment and lymph nodal status. Adjuvant radiation therapy was comparable between the two groups: with 11 cases (45.8 %) vs 122 (51.5 %) respectively in the pN ≥ 1 and pN = 0 group, p-value:0.670. Likewise, adjuvant chemotherapy was comparable, with p = 0.699: women subjected to this treatment were 2 (8.3 %) in the pN ≥ 1 group versus 27 (11.3 %) in the p-N = 0 group. In p-N≥1 group 41.6 % (n:10) patients were subjected to adjuvant hormone therapy versus 62.8 % (n:149) in the pN = 0 group and relative p-value was 0.050.

Multifocal lesions and lack of hormone receptors are both predictors of metastatic lymph nodes with a relative p-value of 0.045 (95%CI: 0.086–0.973) and 0.018 (95%CI: 1.093–12.0239) and OR of 1.73 and 3.658 respectively. Ki67 < 20 % associates with a low risk of nodal metastasis (p-value: 0.035; OR: 0.289 95%CI: 0.028–0.717)[Table 1].

Five years loco-regional recurrence was comparable between groups. Five years locoregional recurrence-free survival was 95.7 % in the pN ≥ 1 group versus 94.1 % in the pN = 0 group and relative p-value was 0.951 (Fig. 1a). The comparison between patients with macrometastatic sentinel lymph node and patients with negative, micrometastatic or ITC SNLB showed a significant difference in the locoregional recurrence-free survival (p-value: 0.036): 83.3 % in the macrometastatic patients versus 95.7 % in the no-macro metastatic SNLB group (Fig. 1b). Comparison of five years loco-regional recurrence according to axillary nodal status did not show any statistically significant difference and relative Log Rang was 0.166.

By Cox Regression analysis age at diagnosis >70yo is a protective factor for LRR at five years (OR 0.831 95%CI: 0.721–0.957, p = 0.010). Other factors analyzed in the multivariate analysis did not show any statistical significance (Table 2).

Table 1
Binary logistic regression used to identify predictive factors for lymph node metastasis.

Multivariate			
Variables	**OR**	**95%CI**	**p value**
Multifocal Lesion	1.731	0.086–0.973	**0.045**
Tumor Grade	1.029	0.462–2.968	0.289
Nodular Lesion	2.580	0.811–8.203	0.108
Hormone Receptors Negative	3.658	1.093–12.0239	**0.018**
Ki67 Proliferation Index<20 %	0.289	0.028–0.717	**0.035**
Older Age at Diagnosis (>70yo)	0.978	0.935–1.023	0.329

OR: Odds Ratio, CI: Confidence Interval.

4. Discussion

This observational multicentric retrospective study was based on data from seven Italian Breast Units and it is one the largest current studies on MIBC reported.

In our analysis, the incidence of SLNB metastasis (considering macro/micro metastasis and ITC) in patients with diagnosis of MIBC was 9.2 %. This incidence falls within the range reported in literature: from 0 % to 13 % in the contemporary series [10,11]. The rate of nodes macrometastasis was low (2.3 %) and similar to the range reported in published series [12,13]. The interest of our analysis in this context is justified by the knowledge that lymph nodes metastasis represent the most important breast cancer prognostic factor [14]. Despite the importance of axillary staging: only macrometastasis impact adjuvant treatment decision and its incidence is low in MIBC. Several randomized clinical trials demonstrated that disease local control can be achieved also without axillary lymph node dissection, even in the presence of minimal to moderate nodal involvement and could be omitted in selected cases of invasive cancer [15]. Given the decreased prognostic value of axillary staging, over the last decades, and in the era of "SOUND" results, SLNB could be safely omitted in patients with MIBC. Incidence of nodes macrometastasis was lower compared to the "SOUND" study (2.3 % VS 8.6 %), this difference is associated to the fact that Gentilini and his colleagues considered in their analysis invasive breast cancer and not the MIBC as done in our study [15]. In our population, five-year locoregional recurrence incidence was 4.6 %. Due to the retrospective nature of the study, we do not have data stating if the recurrence is in lymph-nodes or in the breast. In the "SOUND" trial, locoregional relapse was about 1.7 % [15]. This higher locoregional rate, compared to that observed in the SOUND study, in our opinion, could be explained by the fact that microinvasive breast cancer usually arises in the context of DCIS, about 80 % in our series. Higher locoregional recurrence rates have been reported for patients with DCIS, probably also due to the characteristic skip lesions; or the presence of more extensive disease not assessable by imaging [16]. Furthermore, a recent meta-analysis revealed that DFS was significantly shorter for DCIS associated with a microinvasive component compared to the one of pure DCIS [7].

According to these findings, this study indicates that SLNB may not be useful in MIBC owing to the low risk of lymph node metastasis and adjuvant treatments. In our study, out of six patients with macrometastasis, only one (0.4 %) presented more than four metastatic lymph nodes and therefore required axillary irradiation and could benefit from cyclin-dependent kinase inhibitors therapy [17]. The majority of patients with metastatic sentinel lymph node met the American College of Surgeons Oncology Group Z0011 criteria: this also supports the conclusion that SLNB in microinvasive DCIS is not useful and it could be considered an overtreatment, especially in the era of "SOUND" randomized clinical trial results [15].

After a multivariate analysis, biological characteristics of the cancer are predictive factors for metastatic sentinel lymph node. Low Ki67 proliferation index, inferior than 20 %, reduces the risk of nodes metastatization. Differently, the lack of hormone receptor expression in tumoral cells is a predictive factor for metastatic lymph node. Both higher Ki67 proliferation and negative hormone receptors expression are

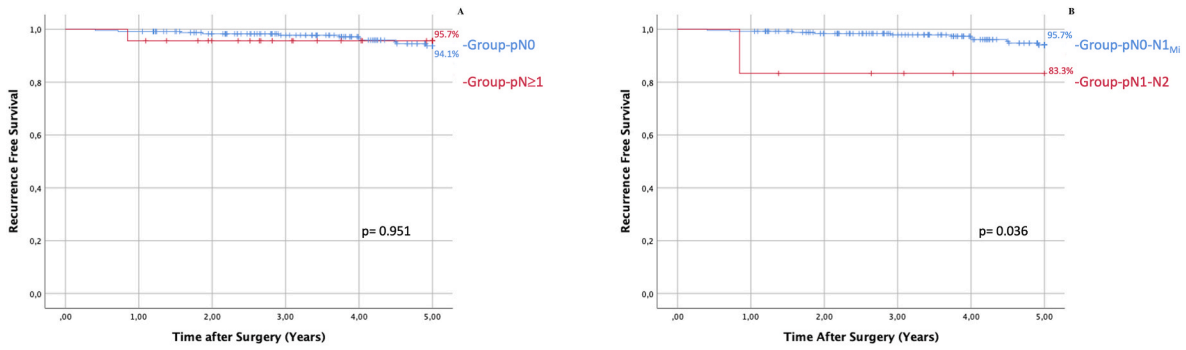

Fig. 1. Comparison of five years loco-regional recurrence according to sentinel lymph node status.
Fig. 1a comparison between groups with or without metastatic sentinel lymph nodes. Fig. 1b comparison between groups with negative, ITC (isolated tumor cells) or micrometastatic sentinel lymph nodes versus macrometastatic and or > N1?? Sia and che or o è solo and?

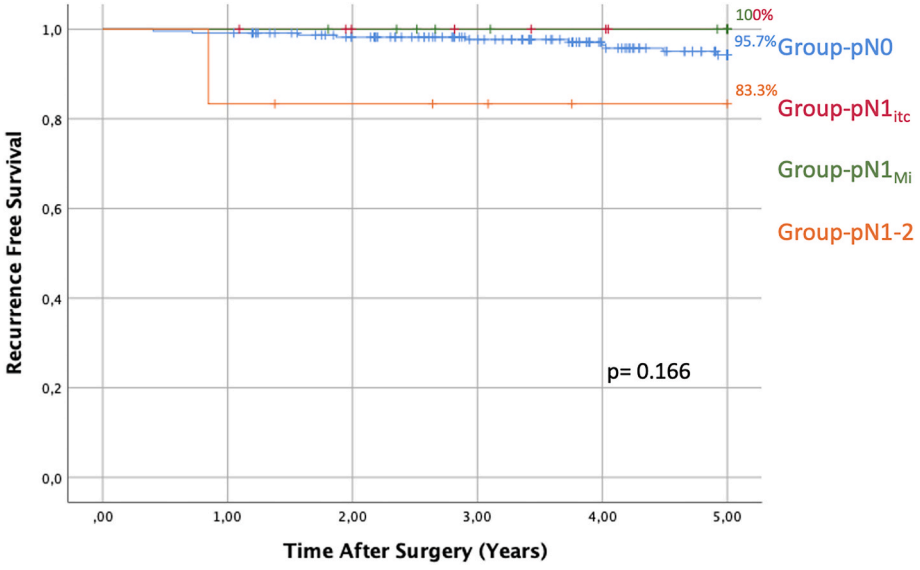

Fig. 2. Comparison of five years loco-regional recurrence according to axillary nodal status.
Fig. 2 comparison between axillary staging groups. ITC (isolated tumor cells) and MI (micrometastatic).

Table 2
Cox regression was used to identify predictive factors for recurrence risk.

Multivariate			
Variables	OR	95%CI	p value
Multifocality	1.539	0.105–22.619	0.753
Tumor Grade	0.643	0.086–4.817	0.808
Breast Conserving Surgery	1.185	0.072–0.957	0.906
Hormone Receptors Negative	2.193	0.221–21.772	0.502
Ki67 Proliferation Index<20 %	0.978	0.935–1.023	0.329
Older Age at Diagnosis (>70yo)	0.831	0.721–0.957	**0.010**
Adjuvant Hormone Therapy	0.356	0.027–4.756	0.435
Adjuvant Chemotherapy	0.229	0.009–5.849	0.373
Adjuvant Radiation Therapy	1.175	0.128–17.211	0.752
Metastatic Sentinel Lymph Node	2.140	0.511–7.291	0.098

OR: Odds Ratio, CI: Confidence Interval.

typical of triple negative breast cancer, which is more aggressive and more frequently associated with metastatic lymph nodes [18]. In these patients adjuvant treatments are tailored based on tumor's intrinsic subtype rather than axillary status [18,19]. Fan et al., in a previous analysis reported similar results [20]. Our study highlights how the presence of multifocal lesions could be associated with a higher risk of metastatic sentinel lymph node. Typically, the first surgical choice in patients with multifocal lesions is mastectomy. In these patients for many years the lymph node biopsy could not be omitted due to the impossibility of performing it once finding out the presence of an invasive tumor at the definitive pathological examination. This problem has been partially overcome thanks to delayed sentinel lymph node dissection technique, through preoperative injection of super-paramagnetic iron oxide nanoparticles [21]. This technique is not available and used in all centers, but it could certainly play a fundamental role in this type of patients having an upstaging, allowing them to undergo the biopsy at a later time.

A relevant number of studies have investigated histopathological characteristics and risks of metastatic lymph nodes in patients with MIBC but the biological behavior remains controversial [22–24]. This study confirms that the lack of hormone receptors and high Ki67 proliferation index, typical of triple negative breast cancer, are associated with a higher risk of metastatic lymph node. However, they do not seem to have a worse impact on oncological outcome. Such results could be explained with a higher incidence of adjuvant treatment administered to these patients. In our study, consistent with findings reported in the literature, metastatic lymph node do not appear to have an influence on adjuvant treatments [25–27].

MIBC has a favorable prognosis with an overall disease-free survival of 95.4 %, congruent with other analysis reported in literature, which have shown disease-free survival rate between 90 and 97 % [28,29].

We found no correlation between metastatic sentinel lymph node

and regional recurrence. In a previous Italian study performed at "Istituto Oncologico Europeo", authors reported higher rate of regional recurrence in patients with MIBC and negative sentinel lymph node [4]. We believe that these interesting results reported by Mangoni et al. are more correlated with the higher incidence of patients with MIBC and negative SNLB [4].

In our study, axillary lymph nodes dissection is not correlated with overall survival and recurrence risk. In a recent study of more than 11000 patients from the Surveillance Epidemiology and End Results database between 2003 and 2015 authors reported that ANLD did not demonstrated survival benefit in patients with MIBC [27]. Differently from our results, Chen et al. demonstrated that metastatic lymph node was the best survival predictor. Due to the short follow-up of our study, we cannot confirm such results. According to our findings, lymph node stages did not influence adjuvant treatments or disease recurrence. ALND has been widely demonstrated to be associated with an increased risk of surgical complications and a worse outcome in terms of quality of life [30,31]. Also, sentinel lymph node biopsy is associated with a worst quality of life for breast cancer patients and its omission could reduce surgical impairment [32,33]. While waiting for the results of the SOUND trial study assessing the quality of life, omitting SNLB in those patients still reduces surgical impairment and a better quality of life.

In our study, age seems to be related to the risk of recurrence. Younger patients more frequently present aggressive breast cancer [25]. In MIBC, the presence of metastatic sentinel lymph node is rare even in younger patients. Adjuvant treatments are influenced by histopathological characteristics and age rather than axillary staging [25–27]. This study supports the evidence that omission of SNLB combined with adequate presurgical study could be performed also in younger patients.

There were several pitfalls in the study. Firstly, it was a retrospective study which could carry selection bias. All the patients considered were subjected to SLNB and had a histological diagnosis of microinvasive carcinoma at the final pathological examination. Due to the retrospective nature of the study and since data were taken from seven different Breast Units, it was not possible to obtain pre-operative histological diagnosis data from all centers and evaluate the incidence of diagnosis upstaging, therefore it was not considered in the analysis. Moreover, the size of the MIBC lesion and the percentage of in situ component could not be obtained, therefore it was not considered in the analysis. It would be interesting for further prospective studies to evaluate those parameters and their relative impact. Moreover, the follow-up was relatively short and despite this being one of the largest ongoing studies on this topic and its multicentricity, the patient's sample is still too small.

5. Conclusion

MIBC is a rare breast carcinoma and it is usually associated with DCIS. As DCIS, it has a favorable prognosis and very low macrometastatic sentinel lymph node rates. In these patients, ALND does not improve oncological outcomes and the presence of metastatic nodes do not influence the choice of adjuvant treatments. In our opinion, omission of SNLB in patients with MIBC and no preoperative clinical or histological suspicious lymph nodes, provides similar levels of overall survival with a better quality of life. SNLB should be reserved for patients with pre-surgical suspicion of metastatic lymph nodes, especially if are younger patients, in order to better decide on adjuvant treatments.

CRediT authorship contribution statement

Gianluca Vanni: Conceptualization, writing and editing manuscript, equally contribute to the manuscript, Methodology, Review & Editing. **Marco Pellicciaro:** Conceptualization, writing and editing manuscript, equally contribute to the manuscript, Methodology, Review & Editing. **Marco Materazzo:** Methodology, Review & Editing. **Silvia Petrucci:** Data collection. **Riccardo Affaniti:** Data collection. **Sara Pepe:** Data collection. **Maria Rosaria Mastrangeli:** Data collection. **Maria Ludovica Costanzo:** Data collection. **Pietro Vita:** Data collection. **Luca Despini:** Data revision. **Riccardo Penazzi:** Data revision. **Valeria Vitale:** Data revision. **Annamaria Ruggieri:** Data revision. **Dorelsa Buccilli:** Data revision. **Natalia Zhurakivska:** Data revision. **Marcello Di Millo:** Supervision. **Marina Bortul:** Supervision. **Augusto Lombardi:** Supervision. **Maria Ida Amabile:** Supervision. **Gretha Grilz:** Supervision. **Massimo Giroda:** Supervision. **Oreste Claudio Buonomo:** Supervision.

Ethics statements

The studies involving humans were approved by the Ethics Committee of the Policlinico Tor Vergata (Approval number 72/23). No potentially identifiable images or data are presented in this study. All procedures performed in the studies involving human participants were conducted in accordance with ethical standards (1964 Helsinki declaration). Due to the retrospective nature of the study, formal consent is not required.

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Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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