Abstract. Background/Aim: The histopathological assessment of the B5c category may sometimes be hampered by simple artifacts that may lead to over- or underestimation of that particular breast cancer so that its management is still controversial, especially with regard to the decision to proceed immediately to sentinel lymph node (SLN) biopsy. Hence, a retrospective study was performed in 174 patients undergoing breast-conserving surgery with a preoperative diagnosis of B5c in order to assess the usefulness of axillary node staging by means of SLN biopsy. Patients and Methods: Pre- and post-operative parameters including imaging data, histology of the primary tumor and SLN biopsy, biological prognostic factors, type of operation, and adjuvant regimens were computed. Results: Invasive carcinoma and carcinoma in situ were diagnosed in 46 (26.5%) and 128 patients (73.5%), respectively. Preoperative tumor size was significantly related to post-operative diagnosis of invasive carcinoma (p=0.020), retaining its predictive value at logistic regression analysis (p=0.046). Post-operative predictive factors of invasion were represented by tumor stage (p=0.008) and grading (p=0.008). Conclusion: B5c preoperative diagnosis in patients undergoing breast conservative surgery would suggest an immediate wide local excision avoiding any further preoperative histologic assessment. Conversely, one-stage SLN biopsy might be suggested for patients eligible to mastectomy, similar to patients with carcinoma in situ, although its impact on the therapeutic and prognostic assessment seems negligible.

The Royal College of Pathologists (RCPath) has released a series of national guidelines regarding non-operative diagnostic procedures and pathological reporting in breast cancer patients. This dataset allows pathologists and clinicians to define the stage and grade of the disease in order to optimize the clinical decision-making and to guarantee a high standard of care (1). With regard to diagnostic biopsy, five categories (from B1 to B5) are currently used, especially in core-needle biopsy. B5c represents a particular subgroup of the B5 category that is used when the histological differentiation between in situ (B5a) and invasive neoplasia (B5b) cannot be defined (1).

The histopathological assessment of the B5c category, although relevant, may sometimes be hampered by simple artifacts, such as paucity of available tissue and/or less than optimal reading of the immunohistochemical evaluation (IHC), thus, leading to over- or underestimation of that particular breast cancer (2-4). For instance, in the case of large ducts with large fragments of carcinoma without surrounding stroma that may have been lost during specimen processing, many histological techniques, i.e., IHC, cannot be properly used for the differential diagnosis (1). B5c category is rarely used both in Europe and in the USA, due to paucity of data from large multicenter studies, so that, in most instances of equivocal diagnosis, the core biopsy is preferably repeated rather than giving a doubtful diagnosis of B5c.

Due to these reasons, the management of B5c is still controversial, especially with regard to the decision to proceed immediately to sentinel lymph node (SLN) biopsy.
According to current guidelines, SLN biopsy should not be performed in patients with carcinoma in situ of the breast undergoing conservative treatment but only in patients with a definitive diagnosis of invasive carcinoma or in patients with carcinoma in situ undergoing total mastectomy (1, 3, 5, 6-12). Here, we performed a retrospective study in patients undergoing breast-conserving surgery with a preoperative diagnosis of B5c was undertaken in order to assess the usefulness of axillary node staging by means of SLN biopsy.

**Patients and Methods**

A retrospective analysis of 174 patients with a pathological B5c diagnosis of breast cancer undergoing SLN biopsy between 2004 and 2018 at the Breast Unit of San Martino University Hospital in Genoa was performed. All clinical, imaging, and pathological data were included into a specific database. Preoperative parameters included: i) mammographic pattern (i.e., nodule, distortion, microcalcification), ii) tumor size, iii) BI-RADS score according to the American College of Radiology (5), iv) breast magnetic resonance (RM) and v) sonography (US), including axillary node US assessment (5). Peri- and post-operative parameters included: i) number and type of operations, ii) assessment of SLN biopsy specimen, iii) definitive histopathology of the primary tumor and SLB biopsy, and iv) biologic prognostic factors (i.e., primary tumor histotype, hormone receptor status, proliferation rate, and c-erb-2 mutation) according to the European Guideline of Quality Assurance in Breast Cancer Screening and Diagnosis (European Commission) (6). Moreover, adjuvant treatments, such as: i) post-operative chemo- and/or endocrine treatment, ii) biologic therapy with Trastuzumab, and iii) regional radiation therapy were...
Conservative surgery and mastectomy were performed in 137 (78.7%) and 37 (21.3%) patients, respectively, while SLN sonography was negative in 166 patients (95.4%) and distortions (BI-RADS R4-R5) were observed in 46 and 14 patients (65.5%) and grading factors in patients with or without invasion by means of Fisher’s exact test. A Cox proportional hazard regression model was used to assess the independent significance of variables.

### Results

The clinical and pathologic features of 174 patients with B5c breast cancer diagnosis are reported in Tables I and II. Concerning the mammographic pattern, microcalcifications were the most frequent finding (114 out of 174 patients; 65.52%), whereas nodular and/or breast architectural distortions (BI-RADS R4-R5) were observed in 46 and 14 patients, respectively (54.6%). Moreover, axillary node sonography was negative in 166 patients (95.4%) and suspicious/positive in the remaining 8 patients (4.6%). With regard to the management of the primary tumor site, conservative surgery and mastectomy were performed in 137 (78.7%) and 37 (21.3%) patients, respectively, while SLN definitive histology detected macro- and micrometastases (<2 mm) in 9 and 2 patients, respectively. Completion axillary lymph-node dissection was always performed in these patients but no residual nodal disease was detected.

Definitive tumor histology diagnosed invasive carcinoma in 46 out of 174 patients (26.5%), with ductal carcinoma and lobular carcinoma in 43 (24.7%) and 3 (1.8%) patients, respectively. Carcinoma in situ was diagnosed in the remaining 128 patients (73.5%), with ductal carcinoma and lobular carcinoma in 118 (67.8%) and 10 patients (5.7%), respectively. At univariate analysis of preoperative clinical and pathologic parameters, only preoperative tumor size from imaging was significantly related to post-operative diagnosis of invasive carcinoma (p=0.020; Fisher’s exact test), retaining its predictive value at the logistic regression analysis (p=0.046) (Tables III and IV). With regard to the logistic regression analysis of post-operative predictive factors of invasion, tumor stage (p=0.008) and grading (p=0.008) were significantly related to invasive carcinoma (Table V).

Concerning adjuvant treatment, patients undergoing conservative treatment always underwent post-operative radiotherapy of residual breast. Moreover, 46 patients had post-operative medical treatment: i) 20 had chemotherapy, ii) 6 had chemo-endocrine treatment, and iii) 20 had endocrine

| Table III | Univariate analysis of preoperative clinical and pathologic features of 174 patients with B5c breast cancer diagnosis stratified by definitive histology (carcinoma in situ vs invasive carcinoma). |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      | Carcinoma in situ N (%) | Invasive carcinoma N (%) | Total N (%) | p-Value |
| Mammographic pattern                  |                           |                           |             |
| Nodule                                | 28 (21.9)                 | 18 (39.1)                 | 46 (26.5)   | 0.232   |
| Breast architectural distortion       | 11 (8.6)                  | 3 (6.5)                   | 14 (8.0)    |          |
| Microcalcifications                   | 89 (69.5)                 | 25 (54.4)                 | 114 (65.5)  |          |
| Preoperative tumor size               |                           |                           |             |
| 0-10 mm                               | 52 (40.6)                 | 8 (17.4)                  | 60 (34.5)   | 0.020   |
| 11-20 mm                              | 36 (28.1)                 | 10 (21.7)                 | 46 (26.5)   |          |
| >20 mm                                | 40 (31.2)                 | 28 (60.8)                 | 68 (39.0)   |          |
| Mammmography                          |                           |                           |             |
| BI-RADS: R3                           | 9 (7.0)                   | 7 (15.2)                  | 16 (9.2)    | 0.282   |
| BI-RADS: R4                           | 88 (68.8)                 | 25 (54.4)                 | 113 (65.0)  |          |
| BI-RADS: R5                           | 31 (24.2)                 | 14 (30.5)                 | 45 (25.8)   |          |
| Breast sonography                     |                           |                           |             |
| U3                                     | 11 (8.6)                  | 4 (8.7)                   | 15 (8.6)    | 0.328   |
| U4                                     | 95 (74.2)                 | 23 (50.0)                 | 118 (67.8)  |          |
| U5                                     | 22 (17.2)                 | 19 (41.3)                 | 41 (23.6)   |          |
| Axillary node sonography              |                           |                           |             |
| Negative                               | 123 (96.0)                | 43 (93.5)                 | 166 (95.4)  | 0.980   |
| Positive                               | 5 (4.0)                   | 3 (6.5)                   | 8 (4.6)     |          |
| Grading                                |                           |                           |             |
| G1                                     | 10 (7.8)                  | 9 (19.6)                  | 19 (11.0)   | 0.103   |
| G2                                     | 70 (54.7)                 | 24 (52.2)                 | 94 (54.0)   |          |
| G3                                     | 48 (37.5)                 | 13 (28.2)                 | 61 (35.0)   |          |

N.A.: Not assessed; BI-RADS: Breast Imaging Reporting and Data System; U: ultrasound; G: grading.
treatment alone, with 12 C-erb-2 Score3 positive patients receiving in addition Trastuzumab.

Notably, in order to assess the prognostic role of the SLN pathologic status with regard to the clinical decision making of the adjuvant post-operative treatment, the most relevant tumor prognostic factors used for selecting patients eligible to medical treatment: i) T stage, ii) grading, iii) Ki67, iv) lymphatic and v) vascular invasion, were computed in the 11 patients with the SLN metastasis. Interestingly, this information did not modify the adjuvant therapeutic planning because all these patients were eligible for medical treatment notwithstanding SLN positivity.

Discussion

B5c is a relatively novel entity in the breast cancer categories panorama. In this view, standardized indications as well as treatment planning are necessary to achieve a high standard of care and reduce over-diagnosis (1). One of the most relevant questions regarding the management of the axilla is the therapeutic and prognostic implications of SLN biopsy in this specific subset of patients.

A definitive histologic diagnosis of B5a (carcinoma in situ) was reported in 128 out of 174 patients (73.5%); hence, in this specific cohort of patients most of who went through breast conserving surgery (78.7%), SLN biopsy would have not been recommended according to current guidelines (4). As a matter of fact, carcinoma in situ is a precancerous lesion without the involvement of the basal membrane and, consequently, it cannot metastasize to regional lymph nodes or systemically (8-10). Moreover, notwithstanding the diagnosis of invasive cancer in 46 out of 174 patients (26.5%) with positive SLN in 11 of them (23.9%), the completion axillary lymph-node dissection did not identify any additional positive nodes; hence, even in this specific subset of patients with a positive SLN, the therapeutic benefit of SLN biopsy should be excluded. This agrees with recent literature data suggesting that axillary surgery, including SLN biopsy, may have at most a marginal role into the management of early-stage breast cancer patients (7, 13). Moreover, the morbidity rate of SLN biopsy and its negative impact on the quality of life of approximately 23% of patients should be included into a cost/benefit ratio, which should also consider the risk to postpone the adjuvant treatment due to SLN-related morbidity (11). Actually, avoiding SLN biopsy represents a good quality indicator of best practice in breast cancer treatment established by EUSOMA (12). Moreover, even from a prognostic standpoint, SLN biopsy was not specifically predictive concerning the need of adjuvant medical treatment because patients with a positive SLN would have undergone adjuvant therapy based, per se, on the biologic prognostic factors of the primary tumor.

Certainly, there is a need to preoperatively define at best the histologic diagnosis of B5c both for proper patient information and therapeutic planning. In this view, preoperative tumor size at imaging was the only predictive factor of invasion in this specific subset of patients so that women with a tumor size over 1 cm are at a significant risk of harboring invasive carcinoma. Patients with smaller lesions might undergo a repeated needle biopsy based on

Table IV. Logistic regression analysis of preoperative predictive factors of invasion in 174 patients with B5c breast cancer diagnosis.

| Preoperative predictive factor | Odds ratio* | p-Value | 95% CI |
|-------------------------------|-------------|---------|--------|
| Preoperative tumor size       |             |         |        |
| 0-10 mm                       | 1.75        | 0.58-5.25 | 1.19-8.54 |
| 11-20 mm                      | 3.19        |          |        |
| >20 mm                        |             | 0.112    |        |
| Mammmographic pattern         |             |          |        |
| Nodule                        | ref.        |          |        |
| Breast architectural distortion | 0.61     | 0.14-2.67 | 0.17-0.94 |
| Microcalifications            | 0.39        |          |        |
| Mammmography                  | 0.124       |          |        |
| BI-RADS: R3                   | ref.        |          |        |
| BI-RADS: R4                   | 3.68        | 1.13-12.0 |        |
| BI-RADS: R5                   | 1.19        | 0.43-3.30 |        |

BI-RADS: Breast Imaging Reporting and Data System; 95% CI: 95% confidence interval. *Adjusted by age and other variables included in the logistic model. Odds ratio >1 is related to invasive carcinoma.

Table V. Logistic regression analysis of post-operative predictive factors of invasion in 174 patients with B5c breast cancer diagnosis.

| Post-operative predictive factor | Odds ratio* | p-Value | 95% CI |
|----------------------------------|-------------|---------|--------|
| pT stage**                       |             | 0.008   |        |
| pTis                             | ref.        |          |        |
| pT1a                             | 0.08        | 0.01-0.92 | 0.03-1.23 |
| pT1b                             | 0.19        |          |        |
| pT1c                             | 5.46        | 1.35-22.1 |        |
| pT2                              | 1.00        | 0.23-4.41 |        |
| Grading                          | 0.008       |          |        |
| G1                               | ref.        |          |        |
| G2                               | 2.65        | 1.79-26.2 |        |
| G3                               | 0.73        | 0.31-1.74 |        |
| Hormone receptor status          | 0.307       |          |        |
| ER positive (>10%)               | ref.        |          |        |
| ER negative (<10%)               | 3.36        | 0.72-15.80 |        |
| Hormone receptor status          | 0.404       |          |        |
| PgR positive (>10%)              | ref.        |          |        |
| PgR negative (<10%)              | 2.67        | 0.64-11.20 |        |

95% CI: 95% Confidence interval; G: grading; ER: estrogen receptor; PgR: progesterone receptor. *Adjusted by age and other variables included in the logistic model. Odds ratio >1 is related to invasive carcinoma. **AJCC Cancer Staging Manual, eighth edition. The American College of Surgeons (ACS), Chicago, IL, USA.
current literature data suggesting an accuracy of a second needle biopsy in B3 (doubtful) lesions of approximately 60% (14). Repeated needle biopsy might be proposed for selecting patients eligible for one-stage SLN biopsy, however, this happens provided there is proof of its prognostic and therapeutic benefit in patients with a B5c diagnosis, which was not the case in our clinical experience.

Taken together, patients with B5c preoperative needle biopsy diagnosis undergoing breast conservative surgery should be preferably treated with an immediate wide local excision and intraoperative margin assessment without performing any other histologic assessment. Conversely, one-stage SLN biopsy might be suggested for patients eligible for mastectomy, similar to patients with carcinoma in situ, even though its impact on the therapeutic and prognostic assessment seems negligible.

Conflicts of Interest

This study received no grant and each Author declares that they have no conflicts of interest to declare.

Authors’ Contributions

PF and MG: Study planning, surgical treatment, manuscript editing.
RD, RDR, FD: Follow-up and data management.
FP: Pathological evaluation.
IB: surgical treatment and data management.
MC: Statistical analysis.
DF: Study planning, surgical treatment, manuscript review.

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Received October 25, 2019
Revised November 4, 2019
Accepted November 15, 2019