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The Role of Sentinel Lymph Node Biopsy in Patients With B5c Breast Cancer Diagnosis

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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.*

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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.

Table I. *Clinical features of 174 patients with B5c breast cancer diagnosis.*

	N	%
Mammographic pattern		
Nodule	46	26.5
Breast architectural distortions	14	8.0
Microcalcifications	114	65.5
Preoperative tumor size		
0-10 mm	60	34.5
11-20 mm	46	26.5
>20 mm	68	39.0
Mammography		
BI-RADS: R3	16	9.2
BI-RADS: R4	113	65.0
BI-RADS: R5	45	25.8
Breast sonography		
U3	15	8.6
U4	118	67.8
U5	41	23.6
Breast MR		
N.A.	153	88.0
MR-3	1	0.6
MR-4	8	4.6
MR-5	12	6.8
Axillary node sonography		
Negative	166	95.4
Positive	8	4.6
Breast surgery		
Breast conserving surgery	137	78.7
Mastectomy	37	21.3
Axillary surgery		
None	163	93.7
Completion axillary dissection	11	6.3
Adjuvant medical treatment		
None	128	73.5
Chemotherapy	20	11.5
Chemo-endocrine therapy	6	3.5
Endocrine therapy	20	11.5
Trastuzumab	12	6.9

N.A.: Not assessed; BI-RADS: Breast Imaging Reporting and Data System; U: ultrasound; MR: magnetic resonance.

Table II. *Pathologic features at definitive histology of 174 patients with B5c breast cancer diagnosis.*

	N	%
pT stage*		
pTis	128	73.5
pT1a	12	6.9
pT1b	15	8.6
pT1c	12	6.9
pT2	7	4.1
pN stage*		
pN0	163	93.7
pN1mi	2	1.1
pN1a	9	5.2
Grading		
G1	19	11.0
G2	94	54.0
G3	61	35.0
Hormone receptor status		
N.A.	75	43.1
ER positive (>10%)	69	39.7
ER negative (<10%)	30	17.2
PgR positive (>10%)	51	29.3
PgR negative (<10%)	50	28.7
Ki67		
N.A.	128	73.5
Low (<15%)	10	5.8
High (>15%)	36	20.7
Vascular and/or lymphatic invasion		
N.A.	128	73.5
No	33	19.0
Yes	13	7.5
C-erb-2		
N.A.	128	73.5
Score 0-2 (negative or mild positive)	34	19.6
Score 3 (highly positive)	12	6.9

N.A.: Not assessed; G: grading; ER: estrogen receptor; PgR: progesterone receptor. *AJCC: American Joint Committee on Cancer - Cancer Staging Manual, eighth edition. The American College of Surgeons (ACS), Chicago, IL, USA.

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

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)	
Mammography				
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.

considered. The study protocol was approved by the Regional Ethics Committee.

Statistical analysis. A descriptive analysis of categorical predictors of B5c was performed, reporting absolute and relative frequency. Univariate analysis was used to correlate clinical and pathologic 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 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		0.046	
0-10 mm	ref.		
11-20 mm	1.75		0.58-5.25
>20 mm	3.19		1.19-8.54
Mammographic pattern		0.112	
Nodule	ref.		
Breast architectural distortion	0.61		0.14-2.67
Microcalcifications	0.39		0.17-0.94
Mammography		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
pT1b	0.19		0.03-1.23
pT1c	5.46		1.35-22.1
pT2	1.00		0.23-4.41
Grading		0.008	
G1	ref.		
G2	6.85		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.

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

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. GZ: Medical treatment and data management. MC: Statistical analysis. DF: Study planning, surgical treatment, manuscript review.

References

1 Lee AHS, Anderson N, Pauline Carder, Julie Cooke, Rahul Deb, Ian O Ellis, Miles Howe, Jacquie A Jenkins, Fiona Knox, Timothy Stephenson, Jyotsna Shrimankar and Robin Wilson: Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening. Royal College of Pathologists – RCPATH June 2016. Available at: https://www.rcpath.org/asset/4B16F19C-F7BD-456C-B212F557F8040F66/

2 Orzalesi L, Casella D, Criscenti V, Gjondedaj U, Bianchi S, Vezzosi V, Nori J, Cecconi L, Meattini I, Livi L and Bernini M: Microinvasive breast cancer: pathological parameters, cancer subtypes distribution, and correlation with axillary lymph nodes invasion. Results of a large single-institution series. Breast Cancer *23(4)*: 640-648, 2016. PMID: 25981971. DOI: 10.1007/s12282-015-0616-9

3 Schnitt SJ: Microinvasive carcinoma of the breast: a diagnosis in search of a definition. Adv Anat Pathol *5*: 367-372, 1998. PMID: 10095878.

4 Mitchell KB and Kuerer H: Ductal Carcinoma In Situ: Treatment Update and Current Trends. Curr Oncol Rep *17(11)*: 48, 2015. PMID: 26373411. DOI: 10.1007/s11912-015-0473-x

5 ACR BI-RADS atlas, 2013. Available at: https://radiologyassistant.nl/breast/bi-rads-for-mammography-and-ultrasound-2013

6 Perry N, Broeders M, de Wolf C, Törnberg S, Holland R and von Karsa L (eds.): European guidelines on quality assurance in breast cancer screening and diagnosis. European Commission, 2006. Available at: https://www.euref.org/downloads?download=24:european-guidelines-for-quality-assurance-in-breast-cancer-screening-and-diagnosis-pdf

7 Lara JF, Young SM, Velilla RE, Santoro EJ and Templeton SF: The relevance of occult axillary micrometastasis in ductal carcinoma *in situ*: a clinic-pathologic study with long-term follow-up. Cancer *98*: 2105-2113, 2003. PMID: 14601079. DOI: 10.1002/cncr.11761

8 Nicholson S, Hanby A, Clements K, Kearins O, Lawrence G, Dodwell D, Bishop H, Thompson A and Sloane Project Steering Group: Variations in the management of the axilla in screen-detected ductal carcinoma *in situ*: Evidence from the UK NHS Breast Screening Programme audit of screen detected DCIS. Eur J Surg Oncol *41*: 86-93, 2015. PMID: 25441934. DOI: 10.1016/j.ejso.2014.09.003

9 Costarelli L, Cianchetti E, Corsi F, Friedman D, Ghilli M, Lacaria M, Menghini L, Murgo R, Ponti A, Rinaldi S, Del Turco MR, Taffurelli M, Tinterri C, Tomatis M and Fortunato L: Microinvasive breast carcinoma: An analysis from ten Senonetwork Italia breast centers. Eur J Surg Oncol *45(2)*: 147-152, 2019. PMID: 30482543. DOI: 10.1016/j.ejso.2018.09.024

10 Lyman GH, Giuliano AE, Somerfield MR, Benson AB III, Bodurka DC, Burstein HJ, Cochran AJ, Cody HS 3rd, Edge SB, Galper S, Hayman JA, Kim TY, Perkins CL, Podoloff DA, Sivasubramaniam VH, Turner RR, Wahl R, Weaver DL, Wolff AC, Winer EP; American Society of Clinical Oncology: American Society of Clinical Oncology Guideline Recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol *23*: 7703-7720, 2005. PMID: 16157938. DOI: 10.1200/JCO.2005.08.001

11 Reimer T, Engel J, Schmidt M, Offersen BV, Smidt ML and Gentilini OD: Is axillary sentinel lymph node biopsy required in patients who undergo primary breast surgery? Breast Care *13*: 324-330, 2018. PMID: 30498416. DOI: 10.1159/000491703

12 Biganzoli L, Marotti L, Hart CD, Cataliotti L, Cutuli B, Kühn T, Mansel RE, Ponti A, Poortmans P, Regitnig P, van der Hage JA, Wengström Y and Rosselli Del Turco M: Quality indicators in breast cancer care: An update from the EUSOMA working group. Eur J Cancer *86*: 59-81, 2017. PMID: 28963914. DOI: 10.1016/j.ejca.2017.08.017

13 Jakub JW, Cox CE, Pippas AW, Gardner M, Pendas S and Reintgen DS: Controversial topics in breast lymphatic mapping. Semin Oncol *31*: 324-332, 2004. DOI: 10.1053/j.seminoncol.2004.03.014

14 Dershaw DD, Morris EA, Liberman L and Abramson AF: Nondiagnostic stereotaxic core breast biopsy: results of re-biopsy. Radiology *198*: 323-325, 1996. DOI: 10.1148/radiology.198.2.8596825

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