Original paper

Multifocal/multicentric breast carcinomas showing intertumoural heterogeneity: a comparison of histological tumour type and Nottingham histological grade of primary tumour and lymph node metastasis

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Our study aimed to compare the histological tumour type and Nottingham histological grade of invasive tumour foci in multifocal/multicentric breast carcinomas with those in corresponding axillary lymph node (LN) metastases.
We reassessed slides from consecutive multiple breast carcinomas surgically treated with axillary LN dissection (2007-2012).
155 (19.23%) of 806 cases had multiple breast cancer, of which 115 (74.19%) cases had identical morphology. Of these, 85 (73.91%) cases had axillary LN metastases morphologically identical to the originating breast tumours. 32 of the 40 (80%) cases with different morphology had axillary LN metastases; in most heterogeneous cases with differences in grade (87.5%), the grade of metastases was identical to the grade of the tumour foci with the highest histological grade, and in 33.33% of cases the grade in LN was concordant with the grade of smaller foci. Among the 18 cases heterogeneous in histological type with axillary metastases, 33.33% presented heterogeneous histological types in LN, and 22.22% of them were only concordant with the histological type of the smaller tumour foci.
The morphological aspects of axillary LN metastases correspond to the highest histological grade and/or histological tumour type with unfavourable prognosis, which does not necessarily appear in the largest tumour focus.

Key words: heterogeneity, lymph node metastases, multiple breast carcinoma.

Introduction

The incidence of multiple breast carcinomas varies considerably in the literature (6-77%) [1,2]. This is due to the implementation of different definitions and selection criteria, as well as to the interpretation of preoperative diagnostic methods [3]. There is a positive correlation between the presence of axillary lymph node metastases and the number of tumour foci [4, 5]. In multiple carcinomas, between 3% and 37.5% of cases may have different histological tumour types and/or histological grades (inter-tumour heterogeneity) [3, 6-10]. This is related to shorter survival and may influence the choice of therapy [6]. There are older studies published in English literature concerning the impact of the morphological/immunohistochemical features of unifocal/multiple tumour foci on the morphological/immunohistochemical features of lymph node metastases [11, 12]. However, as far as we know, no studies have been published on the comparison of histological tumour type and Nottingham histological grade of primary tumour and lymph node metastases in multiple breast carcinomas. The aim of our study was to assess the histological features of axillary lymph node metastases and correlate them with those of the primary

foci in multiple breast carcinomas. We believe that this approach has prognostic and therapeutic value.

Material and methods

This study included a series of consecutive cases diagnosed with breast carcinoma between 2007 and 2012 in Tirgu Mures, Romania, originating in a population that had not been previously screened for breast carcinoma, since a national screening programme concerning this disease is not available in our country. For sampling, we used the MD Anderson, Houston, USA method, consisting in a correlation between preoperative radiologic appearance (ultrasound, mammography, MRI), a radiographic re-examination of the serial sections performed during sampling, a comparison between intraoperative mammography and gross examination and very detailed sampling of all suspected tumour/areas (on conventional small blocks) [13]. Multiple invasive breast carcinoma was defined as at least two histologically confirmed invasive tumour foci separated from each other by uninvolved breast tissue, containing normal tissue, benign lesions and/or in situ carcinoma, regardless of the distance between the foci, in the same or in a different quadrant [14]. Multiple foci were previously identified either by imaging and/or by gross examination. The primary surgical treatment consisted of modified radical mastectomy associated with axillary lymph node dissections. No cases with lumpectomy were accepted in the study and in none of the cases was sentinel lymph node biopsy performed. We excluded all cases treated prior to surgery with chemotherapy and cases of multiple in situ carcinomas. According to the guidelines used by the Oncological Department of Tirgu Mures, patients benefited from adjuvant endocrine therapy in ER and/or PR positive cases, as well as anti-HER2 therapy (trastuzumab) in HER2 positive cases. A high histological grade, a high Ki-67 index, and ER/PR negativity are factors that indicated the use of chemotherapy, for at least 4 cycles over 12-16 weeks [15]. This study was approved by the Ethical Committee of the University of Medicine and Pharmacy of Tirgu Mures, and all the procedures were performed in compliance with relevant laws and institutional guidelines. The patients have submitted their informed consent form for the publication of their case details.

All microscopic slides were reviewed by two pathologists (SS, MB). The histological type of the tumour foci and of the metastases in the lymph nodes was determined using the WHO 2012 criteria [16], while histological grade was assessed according to the Nottingham histological grade (NHG) in all tumour foci (primary tumour – the same grading system was applied in all invasive carcinomas as suggested by most guidelines, not only in No Special Type [NST] ones) and lymph nodes with metastases, regardless of the histological type of the metastases [17]. The mixed type of infiltrating carcinoma was defined as a tumour composed of a non-specialized pattern (NST) representing 10-49% of the tumour, while the rest of the tumour displayed a second recognized special type [16]. In this study we also designated as mixed type the cases in which we encountered a collision or parallel development of 2 different tumour types (excepting the NST type) in one distinct tumour focus. This phenomenon does not represent a mixed tumour type according to WHO 2012, but is a well-described phenomenon in the literature [18]. Also, in every tumour focus diagnosed as NST we looked for the presence of any minor component of a special-type carcinoma associated with the NST type, but we did not find such cases.

In all the cases studied, one tumour focus was larger than the others. We designated the largest tumour focus as the "index" or "1st rank" tumour, and the rest of the foci were designated "2nd to nth rank additional foci" in the descending order of their respective sizes. In multiple carcinomas, we individually reported the histological tumour type and Nottingham histological grade of each tumour focus. We also reported the number of lymph nodes involved by macrometastases (larger than 2 mm) or micrometastases (with a diameter between 2 and 0.2 mm) and the total number of lymph nodes analysed. All the axillary lymph nodes were processed by sectioning them into 2 mm thick samples that were paraffin embedded and stained with haematoxylin and eosin (HE). In each case, we identified and compared the histological type and grade of the lymph node metastases to the histological type and grade of the primary multiple breast tumour foci. A mismatch was defined as at least 1 additional tumour focus displaying differences compared to the largest focus in histological type and/or grade. In cases with more than one metastatic lymph node, we assessed the concordance between the histological appearances and grades of different lymph nodes.

Statistical analysis was performed with MedCalc (MedCalc Software, Ostend, Belgium). Fisher's exact test was used when comparing frequencies between groups. Chi-square test was used to assess the association between the percentages of cases with lymph node metastases in homogeneous tumours versus heterogeneous tumours. A p-value < 0.05 was considered statistically significant.

Results

This study initially included 806 consecutive cases diagnosed with breast carcinomas. After the exclusion criteria were applied, only 155 cases were diagnosed as multiple carcinomas between 2007 and

2012. 117 (75.48%) of the multiple carcinoma cases had axillary lymph node metastases. Out of the 155 multiple carcinomas, 115 (74.19%) cases displayed identical histological type and grade in all foci, while 40 (25.81%) cases showed morphological heterogeneity; of these 40 cases, 11 (7.09%) showed mismatches only between the histological tumour type of the multiple tumour foci, 16 (10.32%) showed mismatches only between histological grade and 13 (8.38%) cases presented with mismatches between histological type and grade (see Table I).

Analysis of cases with identical histological type and grade

Of the cases with identical histological type and grade, we assessed 72 cases with 2 foci, 22 cases with 3 foci and 21 cases with 4 foci or more, with a total of 331 analysed tumour foci. The most frequently encountered histological type was NST (80/115 cases) (69.56%), while special histological subtypes only accounted for 30.43% (35/115 cases), as follows: lobular carcinoma (19 cases), carcinoma with apocrine differentiation (13 cases) and mucinous carcinoma (1 case). Out of the cases with identical histological type and grade, grade G3 was seen in 49 cases (42.6%), G2 in 59 cases (51.3%), and only 6.1% (7/115 cases) displayed grade G1.

73.91% (85 out of 115) of the cases with multiple carcinoma showing identical histological type and grade had axillary lymph node metastases, compared with 80% (32 out of 40) of the cases with mismatches between histological type, grade or both (not statistically significant, $p = 0.525$; OR = 1.415; 95% CI: 0.585-3.403) (see Table I).

Cases with identical histological type and grade foci displayed the same histological type and grade in the metastases involving axillary lymph nodes, regardless of the number of foci, whereas in cases with different histological type and grade of the primary tumour foci lymph node metastases were heterogeneous.

Analysis of cases with histological type and/or grade heterogeneity

The 40 (25.81%) cases with histological type and/or grade heterogeneity had a total of 132 examined tumour foci (19 cases had 2 foci, 9 cases had 3 foci, and 12 cases had 4 foci or more). The predominant histological grade of the tumour foci was G3 (64/132 foci) (48.48%), followed by G2 (61/132 foci) (46.21%), and only 7 foci (5.3%) exhibited grade G1. In these heterogeneous cases (in which mismatches between the histological type and/or grade of the foci were encountered), the most frequent histological types were: NST (78/132 foci) (59.09%), followed by micropapillary type (16/132 foci) (12.12%), lobular and mixed type carcinoma (both types appeared in 11 tumour foci, respectively) (8.33%) (Table II).

Analysis of heterogeneous cases with metastases

32 (80%) of the 40 heterogeneous multiple breast carcinomas determined axillary lymph node metastases, as follows: 14 (87.5%) of 16 cases with grade mismatches, 8 (72.73%) of 11 cases with histological type mismatches and 10 (76.92%) of 13 cases with histological type and grade mismatches.

Of the cases in which only grade mismatches appeared (but which had the same histological type) and which determined axillary lymph node metastases (14/16 cases), the metastases had the same histological features as the multiple breast tumours. The histological grade of the metastases was identical to that of the highest-grade tumour in all cases. In 35.72% (5/14 cases), the grade of the metastases was identical to the grade of a smaller tumour than the index tumour.

Regarding cases in which only histological type mismatches appeared (but which had identical grades) and which had axillary lymph node metastases (8/11 cases), the histological type of the metastases was homogeneous in 4 cases (regardless of the number of metastases), but in the other 4 cases the histological type was heterogeneous (see Table II).

When one of the foci was of mixed type, the mixed aspect was mirrored in the lymph node metastases in 5 of 9 cases (e.g. micropapillary + NST, mucinous + NST, NST + lobular, NST + micropapillary + mucinous) (Figs. 1, 2).

In most (7) of the 10 cases that displayed both histological type and grade heterogeneity and had metastases, the morphological appearance of the lymph node metastases was similar to that of the index tumour. However, in 30% (3/10 cases), the metastasis

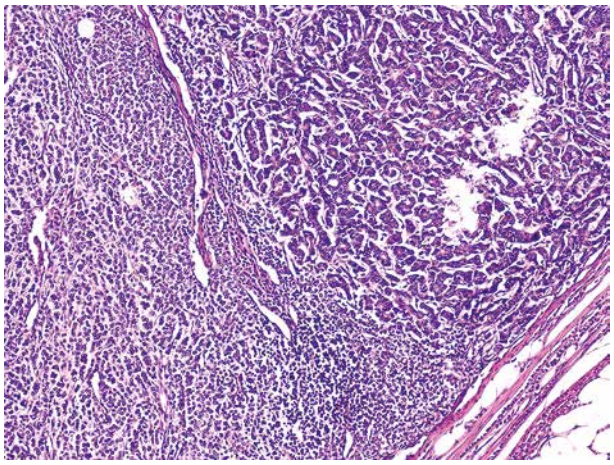

Fig. 1. Axillary lymph node metastasis with mixed histological type (lobular + NST) (also found in the 1st rank tumour); HE, magnification 4×

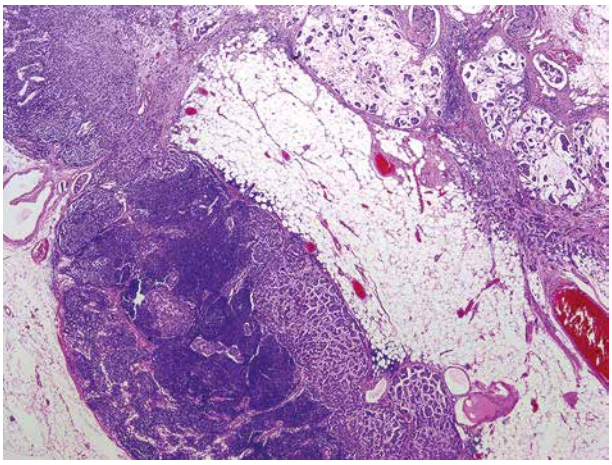

Fig. 2. Axillary lymph node metastasis displaying three different histological types in the metastasis (micropapillary in the lower middle, NST in the upper left and mucinous carcinoma in the upper right of the image); HE, magnification 4×

was most likely determined by additional tumour foci and the metastases in lymph nodes displayed the histological type and grade of these smaller foci; all these multiple metastases had an identical histological type and grade, which was similar to one of the additional foci. The histological grade found in the lymph node metastases was similar to that of the highest-grade tumour focus in 8 of these 10 cases; only in 2 cases did the metastases have a lower grade. Also in this group, the histological type of the axillary lymph node metastases was heterogeneous in 2 cases (20%) (see Table I, II).

The results are summarized in Table III.

Comparison between metastases in heterogeneous tumours

One of the 32 cases analysed had a single lymph node metastasis (micrometastasis). In the 31 cases with macrometastases in which more than one lymph node was involved, we assessed the concordance between the histological appearances of the metastases. In 25 cases (80.64%) all the lymph nodes involved displayed the same histological type, whereas in 6 cases (19.35%) different lymph nodes had different histological types.

Discussion

One of the most important prognostic factors in breast carcinoma is the axillary lymph node status, i.e. the presence or absence of axillary metastases [16, 19]. Disease-free survival and overall survival decrease proportionally with the increase of the number of positive axillary lymph nodes [16]. Most studies reveal an increased rate of metastases in multiple carcinomas when compared to unifocal carcinomas [2-5, 7, 9, 20-22] (Table IV).

A series of factors are known to predict the presence of axillary metastases: larger tumour size, presence of lymphovascular invasion, grade 3 tumour, tumours with lateral or retro-areolar localization, molecular status, as well as the number of tumour foci [15, 16, 24-26]. However, the predictive role of patient age and histological subtype remains controversial [27, 28].

There are histological subtypes with excellent prognosis: tubular carcinoma, cribriform carcinoma, adenoid-cystic carcinoma, pure mucinous carcinoma [16], as well as subtypes associated with a worse prognosis, frequently diagnosed in a metastatic stage: micropapillary carcinoma, inflammatory carcinoma, NST carcinoma, lobular carcinoma [16, 29, 30]. Our study revealed that, when present in association with heterogeneous primary tumours, axillary lymph node metastases may present heterogeneous histological types (in 33.33% of cases). Usually, these metastases display the histological features of the index tumour, but may also display the histological features of the tumour known to have an unfavourable prognosis (such as micropapillary or NST type). In this series, in 4 out of 18 cases with different histological type (22.22%) the histological type of the metastases was only concordant with the histological type of the smaller tumour focus.

Histological grade is a known prognostic factor in breast carcinomas, as numerous studies have proved its significant association with survival [16, 31]. At the same time, it is an important component of the therapeutic decision and has a predictive role in therapy response [15, 32, 33]. In our study, in most heterogeneous cases with differences in grade (21/24) (87.5%), the metastases had identical grade as the tumour with the highest histological grade, usually G3, and in 8 out of 24 (33.33%) cases the grade in LN was concordant with the grade of smaller foci.

Clinical decisions in systemic adjuvant therapy in breast cancer are based on the histological criteria and on the immunohistochemical profile of the largest tumour focus, ignoring those of the smaller simultaneous cancer [15, 32, 33]. In our study, in all 80 cases with axillary lymph node metastases and identical histological type/grade, the lymph nodes displayed identical histology and grade to the primary tumours. However, in 22.2% (4/18) of cases with different histological type, the lymph node metastases had the features (histological type and grade) of the smaller additional tumour and, in 33.33% (8/24) of cases that displayed only grade heterogeneity, the grade of the metastases was similar to the grade of an additional focus. Strictly observing the recommendations of the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagno-

Table I. Clinico-pathological characteristics of 155 multiple breast carcinomas and axillary lymph node metastases

Parameter	Category	Total N (%)	Number of foci			Lymph node status				Histological type and grade in lymph node metastases													
		Total cc with ALNM	2 foci	3 foci	≥ 4 foci	N0	N1	N2	N3	NST G1	NSTG2	NSTG3	MU G1	AP G2	AP G3	LO G2	LO G3	MET G2	MIC G3	NEU	DHG2	DHG3	DH, DG
Total cc		155/117	–	–	–	–	33	25	59	2	35	47	1	2	11	9	1	1	1	1	1	4	1
Number of foci	2 foci	91	–	–	–	–	24	16	26	2	21	21	1	1	9	6	–	1	1	–	1	1	1
	3 foci	32	–	–	–	–	6	6	12	–	7	10	–	1	1	2	–	–	–	1	–	1	–
	≥ 4 foci	32	–	–	–	–	3	3	21	–	7	16	–	–	1	1	1	–	–	–	–	2	–
Lymph node status	N0	38	25	8	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	N1	33	24	6	3	–	–	–	–	–	9	12	1	–	5	4	–	–	–	1	–	1	–
	N2	25	16	6	3	–	–	–	–	2	10	8	–	1	1	1	–	1	–	–	–	1	–
	N3	59	26	12	21	–	–	–	–	–	16	27	–	1	5	4	1	–	1	–	1	2	1
Histological type and grade in tumours	NSTG1	4	2	–	2	3	–	–	–	1	–	–	–	–	–	–		–	–	–	–	–	–
	NSTG2	39	26	7	6	8	8	7	16	–	31	–	–	–	–	–	–	–	–	–	—	–	–
	NSTG3	37	20	9	8	5	8	6	18	–	–	32	–	–	–	–	–	–	–	–	–	–	–
	MUCG1	3	3	–	–	2	1	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–
	APOG2	2	1	1	–	–	–	1	1	–	–	–	–	2	–	–	–	–	–	–	–	–	–
	APOG3	11	9	1	1	2	4	1	4	–	–	–	–	–	9	–	–	–	–	–	–	–	–
	LOBG2	18	11	4	3	10	4	1	3	–	–	–	–	–	–	8	–	–	–	–	–	–	–
	LOBG3	1	–	–	1	–	–	–	1	–	–	–	–	–	–	–	1	–	–	–	–	–	–
	DG	16	8	2	6	2	4	3	7	–	2	10	–	–	–	1	–	1	–	–	–	–	–
	DH	11	5	1	5	3	–	3	5	–	1	2	–	–	1	–	–	–	–	–	1	3	–
	DG and DH	13	6	6	1	3	4	2	4	1	1	3	–	–	1	–	–	–	1	1	–	1	1

n – number of tumour foci; cc – carcinoma; ALNM – axillary lymph node metastasis; DG – different histological grade between tumour foci (grade heterogeneity); DH – different histological type between tumour foci (histological type heterogeneity); G1, G2 and G3 – Nottingham histological grade; NST – Invasive carcinoma of no special type; ILC – invasive lobular carcinoma; MET – metaplastic carcinoma; APO – carcinoma with apocrine differentiation; MIC – invasive micropapillary carcinoma; MIX – 2 different tumour types in one distinct tumour focus; MU – mucinous carcinoma; NEU – carcinoma with neuroendocrine differentiation

Table II. Summary of 40 cases with heterogeneous multiple breast carcinomas, with discordances/mismatches between histological types and grades of multiple tumours and the morphology of lymph nodes

Case no.	No. of foci	Histological type in multiple breast tumours	NHG in multiple tumour foci	N status	Histological type in LNM	NHG in LNM
1	2	MIX/NST	3/1	N2	NST	1
2	2	NST/APO	2/3	N1	APO	3
3	2	MIC/NST	3/2	N2	NST	2
4	2	APO/NST	3/2	N3	APO, NST	3, 2
5	2	ILC/MIC	2/3	N3	MIC	3
6	3	NEU/NST/NST	2/3/2	N1a	NEU	2
7	3	ILC/ILC/NST	2/2/3	N3	NST	3
8	3	MIX/MIC/NST	3/3/2	N1	MIX, NST	3
9	3	NST/MIC/NST	3/3/2	N1	NST	3
10	5	MIX/MIX/ILC/ILC/ILC	3/3/2/2/2	N3	NST	3
11	2	APO/NST	3/1	N0	–	–
12	3	MUC/NST/MUC	2/2/1	N0	–	–
13	3	NST/MET/NST	3/2/3	N0	–	–
14	2	MIX/MUC	3/3	N3	NST, MUC	3
15	2	NST/MIX	2/2	N2	NST	2
16	2	MIX/ILC	2/2	N3	MIX, ILC	2
17	5	APO/NST/NST/NST/NST	3/3/3/3/3	N3	APO, NST	3
18	5	MIX/NST/NST/NST/NST	2/2/2/2/2	N2	NST	3
19	5	APO/MIC/MIC/MIC/APO	3/3/3/3/3	N3	APO	3
20	7	MIX/NST/MIC/MIC/MIC/MIX/MIC	3/3/3/3/3/3/3	N3	NST	3
21	7	MIC/NST/MIC/MIC/MUC/MIC/MIC	3/3/3/3/3/3/3	N2	MIC, NST, MIX	3
22	2	APO/NST	3/3	N0	–	–
23	2	APO/NST	3/3	N0	–	–
24	3	MIX/NST/NST	2/2/2	N0	–	–
25	2	MET	2/3	N2	MET	3
26	2	NST	3/2	N1	NST	3
27	2	NST	2/3	N1	NST	3
28	2	NST	2/3	N1	NST	3
29	2	NST	2/1	N2	NST	2
30	2	ILC	2/3	N3	ILC	3
31	3	NST	3/3/2	N2	NST	3
32	3	NST	3/2/2	N3	NST	3
33	4	NST	3/3/2/3	N3	NST	3
34	4	NST	3/2/3/2	N3	NST	3
35	4	NST	2/1/2/1	N1	NST	2
36	4	NST	3/2/2/2	N3	NST	3
37	6	NST	2/3/2/2/2/2	N3	NST	3
38	11	NST	3/2/2/3/2/2/2/2/2/2/2	N3	NST	3
39	2	ILC	2/3	N0	–	–
40	2	NST	1/2	N0	–	–

11 cases with mismatch in histological type (inter-tumour heterogeneity in histological type) – marked with yellow;
16 cases with mismatch in histological grade between tumoural foci (intertumoural heterogeneity in histological grade) – marked with purple;
13 cases with mismatch in both histological type AND grade – marked with blue
NHG – Nottingham histological grade; LNM – lymph node metastases; NST – invasive carcinoma of no special type; ILC – invasive lobular carcinoma; MET – metaplastic carcinoma; APO – carcinoma with apocrine differentiation; MIC – invasive micropapillary carcinoma; MIX – 2 different tumour types in one distinct tumour focus; MUC – mucinous carcinoma; NEU – carcinoma with neuroendocrine differentiation

Table III. Summary of heterogeneous multiple breast carcinomas and their axillary lymph node metastases

Total	Total (N, %)	ALNM (N, %)	Cases with inter-tumour grade heterogeneity (DG), with ALNM	Cases with grade heterogeneity in which the ALNM is similar in grade with smaller, additional tumours	Cases with histological type heterogeneity with ALNM	Cases in which ALNM display histological type heterogeneity
	155	117 (75.48%)	24	8 (33.33%)	18	6 (33.33%)
Cases with identical histological type and grade	115 (74.19%)	85 (73.91%)	–	–	–	–
Cases with inter-tumour heterogeneity	40 (25.80%)	32 (80%)	24	8 (33.33%)	18	6 (33.33%)
Mismatches between histological grade (DG)	16 (10.32%)	14 (87.5%)	14	5 (35.7%)	–	–
Mismatches between histological type (DH)	11 (7.09%)	8 (72.73%)	–	–	8	4 (50%)
Mismatches between histological type AND grade (DG, DH)	13 (8.38%)	10 (76.92%)	10	3 (30%)	10	2 (20%)

ALNM – axillary lymph node metastases; DG – different histological grade between tumour foci; DH – different histological type between tumour foci

Table IV. Comparative lymph node involvement (LNI) in invasive multiple (M) and unifocal (UF) breast carcinoma (BC)

Authors	Number of cases	LNI in MBC (%)	LNI in UFBC (%)	p-value
Andea *et al.* [7]	570	69.3	54.5	0.0009
Coombs *et al*. [20]	848	52.1	37.5	0.009
Cabioglu *et al.* [5]	1322	58.5	42	< 0.0001
Yerushalmi *et al.* [2]	25.320	48.6	39	< 0.001
Tot [23]	519	53	20	< 0.0005
Weissenbacher *et al*. [21]	576	51.7	41.7	0.0001
Rezo *et al.* [22]	812	49.6	33.7	0.001
Moutafoff *et al*. [9]	1458	59.4	39.3	< 0.0001
Boros *et al*. [3]	418	73.62	58.71	0.01

sis, AJCC (2010) or TNM 2012 regarding multiple tumours, and reporting only the histological tumour type and NHG (Nottingham histological grade) of the index tumour while not taking into consideration the heterogeneous additional tumour foci may limit the patients' opportunity to benefit from appropriate therapy [16, 19, 34].

The aim of the present study was not to prove that particular lymph node metastatic foci originate from a particular tumour focus in multiple breast carcinomas (although it is likely that in these cases more than one tumour focus, including both the additional foci and the index tumour, determined axillary lymph node metastases). This complex problem cannot be solved in some cases even with the use of molecular techniques (since multiple tumour foci may have identical molecular footprints). This paper, however, was aimed at underlining the histological heterogeneity of multiple tumours and their metastases, proving that multiple foci are not as histologically homogeneous as assumed in current practice.

The histological features (type and grade) of axillary lymph node metastases in multiple breast carcinomas correspond to the histological type with unfavourable prognosis and/or the highest histological grade, which is not necessarily of the largest tumour focus. For this reason, we stress the necessity to individually report and assess each tumour focus in multiple breast carcinomas.

The authors declare no conflict of interest.

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