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Radiologically Unifocal Invasive Breast Carcinomas: Large-Section Histopathology Correlate and Impact on Surgical Management

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Abstract

Background: Most breast carcinomas are morphologically complex, comprising both *in situ* and invasive components that can be unifocal, multifocal, or diffuse. Pre-operative radiological mapping often reveals this complexity, but even in the era of modern multimodality breast imaging lesions may remain undetected.

Methods: We studied the sub gross morphology of tumors in a series of invasive carcinomas determined to be unifocal on pre-operative multimodal radiological imaging. We focused on histological outcome, margin status, and type of surgery. All of the surgical specimens were documented in large-format histological slides.

Results: A total of 44.5% (344/773) of the tumors had separate invasive and/or *in situ* foci in large-format histopathology slides, in addition to the radiologically detected tumor focus. The foci occupied an area ≥ 40 mm in 29.0% (224/773) of the cases, indicating extensive disease. Close/dirty margin upon histological examination was associated with extensive disease (32.1% vs 5.6%, RR 5.6924, $p < 0.0001$), multifocality of the invasive component (26.0% vs 3.3%, RR=7.9755, p=0.0001), and breast conservation (15.4% vs 6.3%, RR=2.4476, p=0.0036), but the differences were found only for extensive tumors. Mastectomy was chosen as the primary or complete intervention in 28.3% (219/773) of cases, mostly in multifocal and extensive tumors.

Conclusion: Our results indicate the presence of extensive disease in a considerable number of breast cancer cases judged pre-operatively as unifocal. Removing the radiologically detectable tumor focus with "no ink on the tumor" may not be sufficient in such cases.

Keywords: Breast; Unifocal tumor; Multifocality; Disease extent; Mastectomy

Introduction

Most breast carcinomas are morphologically complex lesions comprising both *in situ* and invasive components, which can be unifocal, multifocal, or diffuse. This complexity is best evidenced in cases with a detailed systematic radiological-pathological correlation [1] documented in large-format histological slides [2]. Figure 1 illustrates the 17 basic aggregate growth patterns of the *in situ* and invasive tumor components in a series of 1000 breast carcinoma cases and shows that real unifocal lesions represent a minority of breast carcinomas, whereas a considerable proportion of breast cancers are multifocal or diffuses [2].

Modern diagnostic breast imaging methods have high sensitivity and specificity and can accurately map the disease pre-operatively and guide the therapeutic decision making, especially if combined with a multimodal approach [3]. The imaging methods are less sensitive and specific with small invasive tumor foci [4] and non-calcified *in situ* foci [5], although whole breast ultrasound, tomosynthesis, and magnetic resonance imaging (MRI) perform better than mammography in this aspect [4,6,7].

The recent trend of more and more restrictive surgery in breast cancer is based on studies showing the same outcome in patients treated with breast conservation and irradiation as in patients treated with mastectomy. Some studies have indicated no further benefit of margins wider than "no tumor on ink" in terms of local disease control [8], even if the tumors are multifocal [9,10]. On the other hand, studies indicating more unfavorable outcomes in multifocal and extensive carcinomas compared to unifocal carcinomas and those with limited extent have also been published [11-13].

We analyzed the findings of large-format histology slides in cases of breast cancers judged to be unifocal based on pre-operative radiological mapping. We focused on histological outcome, margin status, and type of surgery. In particular, we were interested in the proportion of radiologically occult extensive disease and its impact on surgical management.

Methods

Patient selection

We studied a consecutive series of 1663 invasive breast carcinoma cases diagnosed at the Department of Pathology and Clinical Cytology at County Hospital Dalarna in Falun, Sweden, between January 2008 and June 2015. We excluded all recurrences of tumors diagnosed prior to the study period (n=120) and cases that received any type of neoadjuvant therapy (n=39). Of the remaining 1504 cases, 1403 had complete radiology data in our database. A total of 843 cases were radiologically unifocal based on pre-operative disease mapping, 773 of which had invasive cancer upon postoperative histological examination. Microinvasive tumors (< 1 mm in size) were not included. These 773 patients comprised the study cohort. The study was part of a larger

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project approved by the Regional Ethical Committee Uppsala/Örebro. Written consent was obtained from the patients.

Pre-operative radiological work-up

The pre-operative radiological work-up comprised a clinical examination, mammography, and ultrasound examination in all cases. Magnetic resonance imaging (MRI) was carried out in 75% (581/773) of the cases. The radiologists reported their findings to the pathology department on a data sheath prior to a multidisciplinary tumor board and the data were registered in the pathology research database. The radiological diagnosis was confirmed by core-needle biopsy (754 cases) or fine-needle aspiration biopsy (12 cases) in all but seven cases. All of the cases were discussed at the multidisciplinary tumor board before and after the surgical intervention.

Surgery

Breast conserving surgery (sectorial resection) with sentinel lymph node biopsy was the standard procedure for unifocal breast carcinomas in our institution and carried out in 538 cases in the present series. Modified radical mastectomy was indicated at the patient's request or on the basis of a large tumor size. Axillary lymph node clearance was performed in 55 cases. A total of 481 patients underwent postoperative irradiation.

The completeness of the surgical intervention was assessed by the radiologists based on routine intraoperative specimen radiography. No histopathological examination was carried out intraoperatively with frozen sections or other methods to assess the specimen margins. During the histological evaluation, we followed the recommendations of the regional guidelines of Uppsala/Örebro [14] recommending sectorial resection for tumors < 4 cm with 10 mm minimal macroscopic margin at the beginning of the study period and "no tumor on the ink" at histological evaluation since April 2011. Immediate complete surgery was indicated if a close/dirty margin was seen upon intraoperative radiological analysis of the specimen. Complete mastectomy followed histopathologically established close or dirty margin(s).

Histopathological method and parameters

All specimens were prepared using the large-format histopathology method performed routinely in our laboratory since 1982 and described in detail elsewhere [15]. Sector-resection specimens were sliced into 3 to 4 mm thick tissue slices parallel to the pectoralis fascia and subjected to radiography. One to five of the most representative slices (measuring up to 9 cm × 8 cm) were selected and embedded in large paraffin blocks. Larger slices were bisected and embedded into separate blocks. Mastectomy specimens were sliced perpendicular to the pectoralis fascia to visualize the surgical margin on one histological level. Slices were inked to keep the orientation of the specimen.

The distributions of the invasive and *in situ* components from the same lesion were determined separately using previously published criteria [2,15,16]. Unifocal invasive tumors comprised a single well-delineated focus on the large histology slide. Invasive tumor multifocality was defined as the presence of more than one well-delineated invasive tumor focus with non-malignant tissue or *in situ* tumor in between the foci. Diffuse invasive tumors were identified as tumors dispersed over a large area of the section, similar to a spider web, with no distinct tumor mass. The *in situ* components of the tumors were regarded as "unifocal" if involving a single terminal ductal lobular unit or several neighboring terminal units without uninvolved breast tissue in between, as "multifocal" if involving several distant terminal ductal lobular units with uninvolved breast tissue in between, and as "diffuse" if involving mainly the larger ducts. If a complete surgical intervention was performed in addition to the primary sector resection, an attempt was made to summarize the findings for the entirety of the excised tissue. The aggregate growth patterns of *in situ* and invasive tumor components are illustrated in Figure 1. A typical case is illustrated in Figure 2.

Tumor size was defined as the largest dimension of the largest invasive focus. Disease extent was defined as the tissue area containing all *in situ* and invasive malignant structures and measured in two dimensions. Cases in which the tumor structures occupied an area at

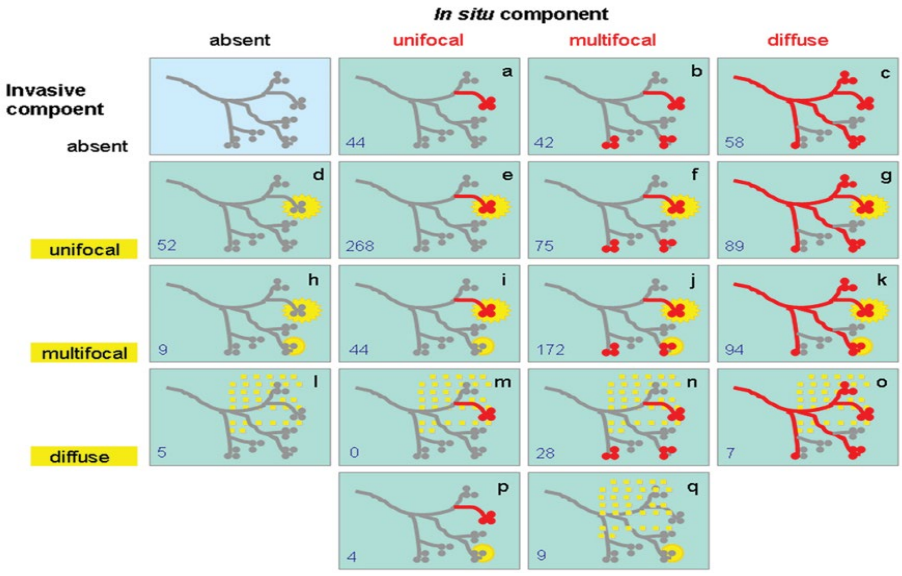

Figure 1: Possible combined growth patterns in breast carcinomas. Tumors with unifocal (d, e, f, g, p), multifocal (h, i, j, k), and diffuse (l, m, n, o, q) invasive component, and with unifocal (a, e, i, m, p), multifocal (b, f, j, n), and diffuse (c, g, k, o) *in situ* component are illustrated. Numbers in the lower left corner of the drawings indicate the number of cases in the series of 1,000 consecutive breast carcinomas belonging to that category (Reprinted from Ref. 2, open access publication).

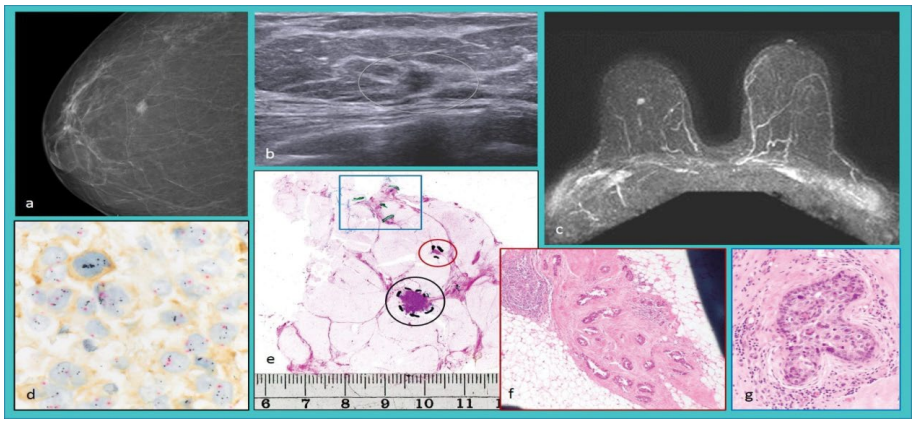

Figure 2: Radiologicallyunifocal invasive breast carcinoma. (a) Radiogram, (b) Sonogram, and (c) Magnetic resonance image. (d) Tricolor bright field in situ hybridization showing HER2 gene amplification. (e) Large-format histology of the surgical specimen shows the radiologically detected invasive tumor focus (black circle), an additional invasive focus (red circle), and structures of the *in situ* carcinoma (blue box). (f) Magnification of the additional invasive focus and (g) *in situ* component stained with hematoxylin and eosin.

least 40 mm in its largest dimension was categorized as extensive and other cases as non-extensive.

Statistical analysis

Comparisons of proportions with the chi-square test and relative risk assessment were carried out using the program MedCalc Statistics for Biomedical Research (MedCalc Software, Belgium). P-values < 0.05 were considered significant.

Results

The radiological tumor size estimated on the basis of mammography and ultrasound measurements was 1-9 mm in 28.7% (222/773) of cases, 10-19 mm in 44.4% (343/773), 20-29 mm in 16.2% (125/773), 30-39 mm in 6.3% (49/773), and 40 mm or larger in 3.6% (28/773). In six cases the radiological size was unknown. The histological size of the radiologically detected tumor focus was 1-9 mm in 16.9% (131/773) of cases, 10-19 mm in 51.9% (401/773), 20-29 mm in 18.6% (144/773), 30-39 mm in 8.0% (62/773), and 40 mm or larger in 4.5% (35/773). All diffuse invasive carcinomas were larger than 20 mm, and 52.0% (14/27) measured ≥ 40 mm.

Of the tumors characterized radiologically as unifocal, 44.5% (344/773) had separate invasive and/or *in situ* foci in large-format histopathology slides. The non-unifocal tumors were categorized as cases with a unifocal invasive focus and multifocal or diffuse *in situ* component, cases with a multifocal invasive component with any *in situ* component, or cases with a diffuse invasive component and any *in situ* component, comprising 22.1% (171/773), 18.9% (146/773), and 3.5% (27/773) of the whole series, respectively. Of the 146 cases with multiple invasive foci, 60 had more than one additional invasive focus. The size of the additional invasive foci was 1-9 mm in 93.2% (136/146) of cases, 10-14 mm in 6.1% (9/146), and > 20 mm in one case. Among unifocal invasive tumors associated with a non-unifocal *in situ* component, the *in situ* component was multifocal in 60.8% (104/171) of cases and diffuses in 39.2% (867/171) of cases. The tumor foci occupied an area ≥ 40 mm in 29.0% (224/773) of the cases, indicating extensive disease (Table 1).

A close/dirty margin upon histological examination was found in 13.3% (103/773) of cases, more often in extensive disease than in non-extensive disease (32.1%, 72/224 vs 5.6%, 31/549; RR=5.6924, p < 0.0001), in cases with a multifocal invasive component compared to those with a unifocal invasive component (26.0%, 38/146 vs 3.3%, 14/429; RR=7.9755, p=0.0001), and in patients who underwent breast conservation compared to those treated with mastectomy (15.4%, 92/598 vs. 6.3%, 11/175; RR=2.4476, p=0.0036). If these results are broken down into morphological subgroups (Table 2), significant differences are seen only in extensive tumors with a multifocal invasive component and in cases with a unifocal invasive and non-unifocal *in situ* component.

Mastectomy was chosen as the primary or complete intervention in 28.3% (219/773) of cases: 47.8% (107/224) of extensive cases and 20.4% (112/549) of non-extensive cases (RR=2.3415, p < 0.0001). As seen in Table 1, significantly different mastectomy rates were found between extensive and non-extensive cases among histologically unifocal tumors ("extensive" in this subgroup was related to tumor size ≥ 40 mm; 66.7%, 12/18 vs 19.2%, 79/411, p < 0.0001) and tumors with histologically verified multiple invasive foci (63.0%, 51/81 vs 23.1%, 15/65, p < 0.0001). No such association was found among tumors with histologically unifocal invasive and non-unifocal *in situ* components (29.2%, 31/106 vs 23.1%, 15/65, p=0.4948) or diffuse invasive breast carcinomas (68.4%, 13/19 vs 37.5%, 3/8, p=0.3081).

Discussion

A recent meta-analysis of studies including more than 10,000 women treated with breast conserving surgery found that 35% of the patients who did not and 19.3% who did undergo postoperative irradiation had local recurrence during a 10-year follow-up period [17]. This high incidence, especially in non-irradiated patients, may be related to tumor foci that remained undetected in the pre-operative radiological examination and were left behind after a seemingly radical surgical intervention. In this study, we focused on tumors judged as unifocal based on pre-operative multimodality breast imaging and analyzed the frequency of additional radiologically occult malignant lesions in large-format histology slides. We paid special attention to how such foci influenced the histological surgical margin status and the performance of complete surgery.

The extent of the disease, defined as the tissue volume containing all *in situ* and invasive malignant structures, was the most important parameter related to the defined outcomes in this study; significant differences were only found in extensive disease. These results are

Surgical Treatment	Extensive disease	Mastectomy rates, extensive disease	Non-extensive disease	Mastectomy rates, non-extensive disease	P value
Unifocal invasive cancer without multifocal or diffuse *in situ* component	4.2% (18/429)	66.7% (12/18)	95.8% (411/429)	19.2% (79/411)	p <0.0001
Unifocal invasive cancer with multifocal or diffuse *in situ* component	62% (106/171)	29.2% (31/106)	38% (65/171)	23.1% (15/65)	p=0.4948
Multifocal invasive cancer, any *in situ* component	55.5% (81/146)	63% (51/81)	44.5% (65/146)	23.1% (15/65)	p <0.0001
Diffuse invasive cancer, any *in situ* component	70% (19/27)	68.4% (13/19)	30% (8/27)	37.5% (3/8)	p=0.3081
Total	29% (224/773)	47.8% (107/224)	71% (549/773)	20.4% (112/549)	p <0.0001

Table 1: Proportions of mastectomy cases by lesion distribution and disease extent, Dalarna 2008-15.

Surgical Treatment	Close/dirty margin, primary mastectomy	Close/dirty margin, breast conservation	P value chi square test	Complete mastectomy	Mastectomy total
Extensive disease					
Unifocal invasive cancer without multifocal or diffuse *in situ* component	0% (0/11)	14.3% (1/7)	p=0.8331	1	66.7% (12/18)
Unifocal invasive cancer with multifocal or diffuse *in situ* component	10.5% (2/19)	43.7% (38/87)	p=0.0154	12	29.2% (31/106)
Multifocal invasive cancer, any *in situ* component	17.1% (6/35)	47.8% (22/46)	p=0.0076	16	63% (51/81)
Diffuse invasive cancer, any *in situ* component	8.3% (1/12)	28.6% (2/7)	p=0.5758	1	68.4% (13/19)
Total	11.7% (9/76)	42.5% (63/148)	p<0.0001	30	47.8% (107/224)
Non-extensive disease					
Unifocal invasive cancer without multifocal or diffuse *in situ* component	1.4% (1/74)	3.6% (12/337)	p=0.3537	5	19.2% (79/411)
Unifocal invasive cancer with multifocal or diffuse *in situ* component	0% (0/11)	14.8% (8/54)	p=0.3831	4	23.1% (15/65)
Multifocal invasive cancer, any *in situ* component	9.1% (1/11)	16.7% (9/54)	p=0.8333	4	23.1% (15/65)
Diffuse invasive cancer, any *in situ* component	0% (0/3)	0% (0/5)	-	0	37.5% (3/8)
Total	2% (2/99)	6.4% (29/450)	p=0.1728	13	20.4% (112/549)

Table 2: Proportion of breast cancer cases with close/dirty margins by lesion distribution, disease extent, and type of surgery.

concordant with the results of some earlier publications [1] and some more recent papers indicating the suitability of breast conserving surgery in multifocal breast carcinomas [10]. Multifocality itself does not distinguish cases suitable for breast conserving surgery from those requiring mastectomy; the tissue volume that the synchronous multiple foci occupy in the breast (disease extent) is more important. Though the involved volume of the breast tissue is three-dimensional and often irregular, it is documented in two-dimensional histological slides and routinely measured in two dimensions. Although this is an obvious limitation, we previously found a 2.75 times higher relative risk of ipsilateral local recurrence in cases with a disease extent ≥ 40 mm in the largest dimension than in cases with a more limited extent [12]. The results of the present study are in line with our previous findings, as differences in the frequency of dirty/close margins and mastectomy rates were much higher in extensive tumors than in non-extensive tumors.

We found significant differences in mastectomy rates between extensive and non-extensive cases among histologically unifocal tumors, in which the large extent was related to a tumor size ≥ 40 mm. This finding was expected because mastectomy is recommended for this tumor size in regional guidelines. Differences in mastectomy rates were also found among tumors with histologically verified multiple invasive foci, but not in tumors with histologically unifocal invasive and non-unifocal *in situ* components. This finding may be explained by the limitation of not distinguishing lobular and ductal *in situ* components and *in situ* components by tumor grade in the present study, though the presence of lobular cancer *in situ* on the margin was not an indication for mastectomy according to the guidelines. Diffuse invasive breast carcinomas comprised a relatively small subgroup of tumors in the present series and were treated with mastectomy in a high proportion of cases. Generally, the mastectomy rates were similar and low in non-extensive cases (with exception of diffuse invasive tumors) and similar and high in extensive cases (with exception of unifocal invasive cancer associated with a non-unifocal invasive component) in the present series.

Both the radiological and histological tumor size reflected the expected range in a population with regular mammography screening, as approximately 70% of the tumors measured < 20 mm. A shift towards the 10-19 mm category was observed in the histological measurements. Most additional invasive tumor foci in multifocal cases measured < 10 mm, which may explain the high proportion of radiologically occult foci in the present series. The other most frequent reason for the discrepancies in the radiological and pathological findings was that the *in situ* components of the tumors were calcified in only about a quarter of the low-grade and half of the high-grade cases (data not shown).

The current trend towards more and more restrictive breast cancer surgery has its background in studies demonstrating a decline in the frequency of local recurrence after breast conserving surgery [18] and a lack of benefit from margins beyond "no ink on invasive tumor or *in situ* cancer" [8,19]. Some studies have indicated that tumor characteristics, such as lobular histology, extensive intraductal component, and molecular phenotype, do not influence the local outcome [20]. In contrast, several studies have indicated a high risk of local recurrence in multifocal invasive breast carcinomas [11], extensive tumors [12], and HER2-positive cancers [21,22], which are associated with an extensive high-grade *in situ* component [23]. Our present study also showed a clear impact of disease extent and multifocality on margin status and mastectomy rates.

Our study has several limitations. The findings are from a regularly

screened population in a single Swedish county. This study was also conducted at a single institution that routinely uses large-format histology slides to evaluate breast surgical specimens; therefore, the results cannot be directly compared to the vast majority of similar series based on conventional histopathology sampling. In addition, the study is purely morphological and does not analyze the impact of individual imaging methods. Furthermore, the findings cannot be related to follow-up results because this study was based on a recent series.

In conclusion, we demonstrated that 44.5% of the tumors judged as unifocal based on the pre-operative multimodal radiology work-up had separate additional invasive and/or *in situ* foci on large-format histopathology slides. These foci occupied an area ≥ 40 mm in 29.0% of cases, indicating extensive disease. Close/dirty margin(s) upon histological examination was associated with extensive disease, multifocality, and breast conservation. Thus, removing the radiologically detectable tumor focus with "no ink on the tumor" may not be sufficient in such cases.

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