Is Mammographic Spiculation an Independent, Good Prognostic Factor in Screening-Detected Invasive Breast Cancer?

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OBJECTIVE. The aim of this study was to review the prognostic significance of pathologic and radiologic factors for screening-detected invasive breast cancers of any size.

MATERIALS AND METHODS. The patient group was a consecutive series of 470 screening-detected invasive breast cancers that were diagnosed between 1988 and 1998. Data regarding tumor type, grade, maximum invasive diameter, lymph node status, and the presence or absence of vascular invasion were recorded, as were the mammographic features of the lesion. Survival was ascertained from hospital records and a cancer registry. Differences in survival were assessed using Kaplan-Meier survival curves with a log-rank test for difference. The significance of any correlations was assessed using the chi-square test and the chi-square test for trend. Multivariate analysis used a Cox proportional hazards model.

RESULTS. At univariate analysis, large invasive size, the presence of definite vascular invasion, high histologic grade, and nodal involvement were associated with poorer breast-cancer-specific survival. Mammographic spiculation (the presence of either a spiculated mass or distortion) was associated with more prolonged breast-cancer-specific survival. The presence or absence of mammographic comedo calcification did not influence breast-cancer-specific survival. In a Cox multivariate analysis that included those factors significant in univariate analysis, size, grade, nodal stage, and mammographic spiculation maintained their prognostic significance.

CONCLUSION. Mammographic spiculation is an independent, good prognostic factor for screening-detected invasive breast cancer. The mechanism of how mammographic spiculation confers a beneficial prognostic effect is not clear.

The established prognostic factors for invasive breast cancer are lymph node stage [1], histologic grade [2], and histologic invasive size [3]. Other pathologic factors known to influence prognosis include vascular invasion status [4] and histologic tumor type [5]. A number of groups have combined a variety of these factors to form a prognostic index [6]. Such indexes, however, have been derived and validated in women with symptomatic breast cancer [7]. In addition, recent work has suggested that vascular invasion, although associated with nodal status, may add important prognostic information, especially in patients with node-negative disease [8, 9].

Interest has been increasing in prognostic factors for screening-detected invasive cancers. Although the traditional pathologic factors of grade, nodal stage, and size are known to provide valid prognostic information for screening-detected cancer, their prognostic strength decreases with increased length of follow-up [10]. In addition, the individual importance of factors may potentially vary in different patient groups. For example, a number of studies have suggested that histologic grade ceases to have prognostic value in tumors smaller than 10 mm [11].

Some studies have suggested that radiologic features provide prognostic information. Tabar et al. [12, 13] have suggested that the presence of mammographic comedo calcification is a poor prognostic factor in small screening-detected invasive cancers, although others have found conflicting results [14–16]. Tabar et al. [13] have also shown that malignant stellate (spiculated) lesions detected at mammographic screening have an excellent outcome.

Tumor-associated fibrosis may influence the radiologic appearance of tumors, perhaps by causing spiculation. However, the formation of fibrotic foci in tumors is associated with poor prognostic features such as nodal positivity and angiogenesis [17, 18].

Keywords: breast cancer, breast imaging, mammography, oncology, screening, spiculation

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TABLE 1: Pathological Features of 470 Women with Screening-Detected Breast Cancer

Pathologic Feature	Incidence Screening (*n* = 209)	Prevalence Screening (*n* = 261)	Total (*n* = 470)
Grade 1	56 (27)	106 (41)	162 (34)
Grade 2	79 (38)	103 (39)	182 (39)
Grade 3	74 (35)	52 (19)	126 (27)
Node-negative	148 (74)[a]	180 (75)[a]	328 (75)[a]
Node-positive	52 (26)[a]	60 (25)[a]	112 (25)[a]
Definite vascular invasion	28 (14)[a]	52 (20)	80 (17)
Invasive size (mm)			
< 10	54 (26)	59 (23)	113 (24)
< 15	117 (56)	137 (52)	254 (54)
> 15	92 (44)	124 (48)	216 (46)

Note—Data are numbers (percentages) of patients.
[a]Percentages vary because some pathological data were not available for some patients and they were excluded from the calculation.

TABLE 2: Mammographic Features Correlated with Pathology and Age

	Mammographic Feature				
Pathologic Feature	Comedo Calcification	Granular Calcification	Distortion	Ill-Defined Mass	Spiculate Mass
Number	55	72	72	119	200
Grade 1	9 (16)	32 (44)	30 (42)	22 (18)	94 (48)
Grade 2	13 (24)	23 (32)	35 (49)	39 (33)	78 (39)
Grade 3	33 (60)	17 (24)	7 (10)	58 (49)	27 (14)
Node-positive	13 (24)	15 (23)	15 (22)	29 (26)	48 (26)
Node-negative	41 (76)	49 (77)	53 (78)	83 (74)	135 (74)
Invasive size < 10 mm	21 (38)	24 (33)	20 (28)	22 (18)	37 (19)
Age < 60 years	32 (58)	41 (57)	47 (65)	64 (54)	92 (46)
Age 60–69 years	23 (42)	31 (43)	25 (35)	55 (46)	108 (54)
Definite vascular invasion	14 (25)	10 (14)	6 (8)	27 (23)	32 (16)

Note—Data are numbers (percentages) of patients.

The role of fibrosis and its radiologic correlates in breast carcinoma biology, behavior, and outcome is thus poorly understood. Tumor-associated fibroblasts are activated by factors such as platelet-derived growth factor and insulinlike growth factor released by breast cancer cells. These activated fibroblasts enable tumors to invade stroma through the release of metalloproteinases and also to synthesize abnormal collagen [17].

Therefore, we studied the prognostic significance of pathologic and radiologic factors in a univariate and multivariate fashion for a group of screening-detected invasive breast cancers of any size. The assessment of vascular invasion status and mammographic spiculation in relation to prognosis in this patient group is novel.

Materials and Methods

The patient group was a consecutive series of 470 patients with screening-detected invasive breast cancers diagnosed between 1988 and 1998. During this period, patients 50–64 years old underwent two-view mammography at prevalence screening and single-view mammography at incidence screening. The screening interval was 3 years, and all screening before 1992 was prevalence screening (a few women 65–69 years old were self-referred for screening). The films had a single interpretation. Data regarding histologic tumor type, grade, maximum invasive dimension, lymph node status, and the presence or absence of lymphovascular invasion were recorded.

Histologic tumor type was defined according to previously described protocols [19]. Tumor grade was determined using the Nottingham method described by Elston and Ellis [2]. Only women in whom four or more lymph nodes were retrieved at either axillary sampling or axillary dissection were included in the analysis of lymph node stage.

Mammographic features were also recorded. The primary radiologic feature was noted and any associated features were also documented. Microcalcifications were classified as either comedo or granular. Masses were classified as well defined, ill defined, or spiculated. Asymmetric densities and architectural distortions were also noted. At the radiologic review, the radiologists were unaware of the pathologic prognostic features of the tumor or of patient survival.

Women with metastatic breast cancer who died were assumed to have died of breast cancer. In cases of women who died in whom the cause of death was not clear from radiology records, the cause of death was retrieved from the cancer registry. The most recent date these individuals were alive was ascertained from either radiology records or last attendance at either a hospital or a family doctor appointment.

Statistical analysis was performed as follows: Differences in survival were assessed using Kaplan-Meier survival curves and the log-rank test for difference. Patients who died from non–breast cancer causes were excluded. The significance of any correlations was assessed using the chi-square test and the chi-square text for trends. A p value of less than 0.05 was considered significant. Multivariate analysis used a Cox proportional hazards model. This and all other statistical analyses were performed on an Apple Macintosh computer with StatView 5.0.1 software.

Results

During the follow-up period, there were 60 breast cancer deaths and 27 deaths from non–breast cancer causes. The mean length of follow-up in patients who were alive was 8.4 years (median, 8.1 years; range, 0.2–15.8 years). Age at breast cancer diagnosis ranged from 49 to 69 years (mean, 58.6 years; median, 59 years). The prognostic features of the study group are summarized in Table 1.

Associations between radiologic features and other factors are shown in Table 2. The presence of comedo calcification and ill-defined masses was associated with a high histologic grade ($p = 0.016$ and $p = 0.0003$, respectively), whereas distortion and spiculated masses were associated with a low histologic grade ($p = 0.007$ and $p < 0.00001$, respectively). Comedo and granular calcifications were associated with invasive cancers smaller than 10 mm, whereas spiculated masses were associated with invasive sizes equal to or larger than 10 mm. Distortion was associated with younger patient age (< 60 years) at diagnosis ($p = 0.028$).

In univariate analysis, large tumor size ($p = 0.007$), the presence of definite vascu-

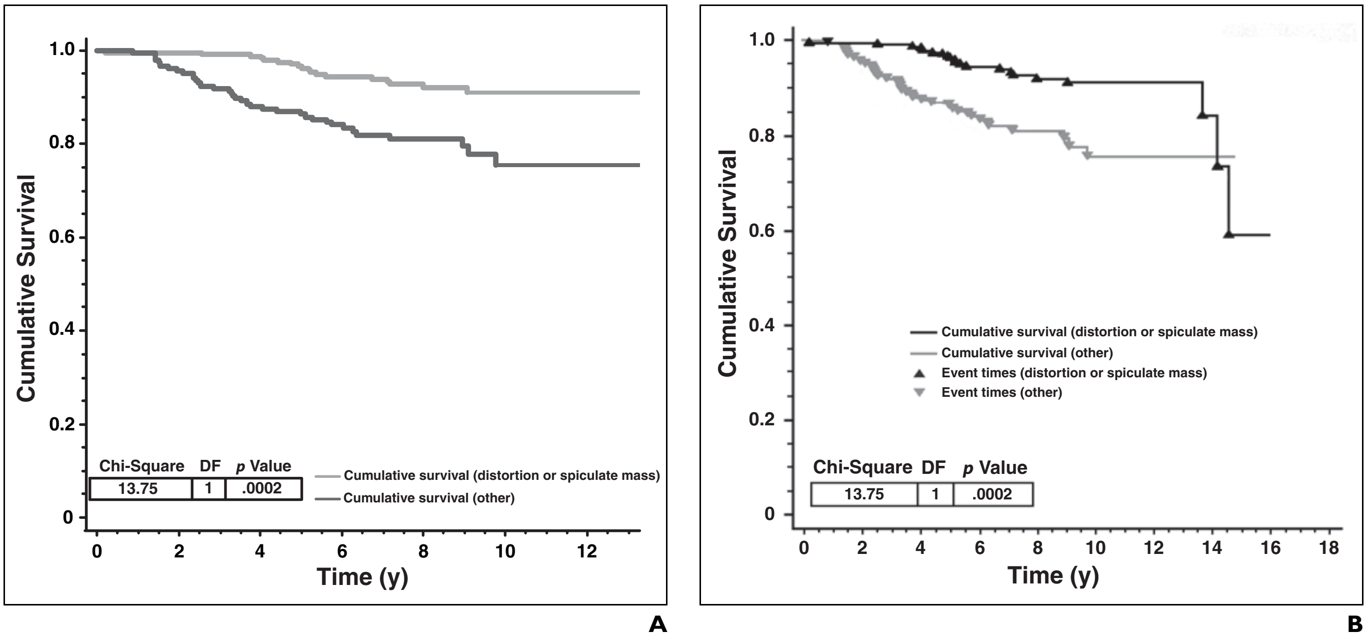

Fig. 1—Graph shows breast-cancer-specific survival according to mammographic appearance. DF = degrees of freedom.
A, Top line indicates cumulative survival for patients with distortion or spiculate mass; bottom line indicates cumulative survival for other patients.
B, Top line and ▲ symbol indicate cumulative survival and event times, respectively, for patients with distortion or a spiculate mass; bottom line and ▼ symbol indicate cumulative survival and event times, respectively, for other patients.

lar invasion ($p < 0.0001$), high histologic grade ($p < 0.0001$), and nodal involvement ($p < 0.0001$) were associated with worsening breast-cancer-specific survival. Mammographic spiculation (the presence of either a spiculated mass or a distortion) was associated with prolonged breast-cancer-specific survival ($p = 0.0002$) (Fig. 1). The prognosis of spiculated lesions detected at prevalence and incidence screening rounds was similar ($p = 0.7$). The presence or absence of mammographic comedo calcification did not influence breast-cancer-specific survival ($p = 0.1$).

At multivariate analysis of factors that were significant in univariate analysis, size, histologic grade, nodal stage, and mammographic spiculation maintained their prognostic significance (Table 3).

TABLE 3: Final Model of Stepwise Multivariate Analysis for Breast-Cancer-Specific Survival

Feature	Correlation Coefficient	SE	Coefficient of SE	Chi-Square Test	*p*	Exp (Coef)
Size	0 0.02	0.01	2.18	4.77	0.029	1.02
Grade	0 0.64	0.23	2.74	7.52	0.006	1.9
Spiculation	−0.72	0.33	−2.16	4.67	0.031	0.49
Nodal stage	1.20	0.19	6.21	38.62	< 0.001	3.33

Note—Data are for all cases (if stage known) and include size, grade, stage, lymphovascular invasion, and spiculation versus other radiologic findings. Exp (Coef) = exponential coefficient.

Discussion

The established prognostic factors for invasive breast cancer are lymph node stage, histologic grade, and histologic invasive size [1–3]. A number of groups have combined a variety of these factors to produce prognostic indexes. One of the most widely used and validated is the Nottingham Prognostic Index (NPI) [20]. However, this and other prognostic indexes have been derived and validated in women with symptomatic breast cancer [6, 7]. These prognostic factors are also valid in screening-detected breast cancer, but the strength of prognostication decreases with prolonged time of follow-up [10].

Our study confirms once again that nodal status is a powerful prognostic factor in screening-detected invasive breast cancer. Histologic grade is also a significant prognostic factor, but with less weight in predicting prognosis than is seen in symptomatic series. This is probably because histologic grade is not as influential in small tumors (< 10 mm), such as small grade 3 invasive cancers, which have been shown to have an excellent prognosis [11, 15]. This good outcome may be explained by the low frequency of systemic spread from such small tumors, as evidenced by the low rates of nodal positivity and vascular invasion in this group of lesions [21]. The Nottingham Prognostic Index places equal weight on nodal status and histologic grade as derived from the weights of these features in multivariate analysis from symptomatic invasive breast carcinomas. For predicting prognosis of screening-detected patients, the NPI may be overweighted with regard to grade in patients with small tumors.

Other pathologic factors known to influence prognosis include lymphovascular invasion status, which is particularly important in patients with node-negative tumors [7–9]. In our study, the presence of definite vascular invasion was a significant prognostic factor in univariate but not in multivariate analysis. This may be because of the close relationship between nodal status and vascular invasion and a weaker association between the presence of vascular invasion and histologic grade. Whether vascular invasion status should influence decisions regarding the use of adjuvant therapy in women with small node-negative tumors is as yet unclear.

Tabar et al. [13] have suggested that the presence of mammographic comedo calcification is a poor prognostic factor in small screening-detected invasive cancers and have postulated a process called "neoductgenesis" as a mechanism [13]. Other groups have varied in their ability to reproduce these findings but have noted a strong association between comedo calcification, high histologic grade, and small size [15, 22]. In the present study, we did not find comedo calcification to be a prognostic factor for screening-detected invasive breast cancer, which was not surprising because this study included screening-detected cancers of all sizes, not just small lesions.

We hypothesized that spiculation would prove to be significantly positively associated with patient survival from breast cancer in univariate analysis because a strong correlation exists between low-histologic-grade lesions and mammographic spiculation [23]. This has been shown by other groups [13]. We expected, however, that the good prognostic effect of spiculation would cease to be significant at multivariate analysis once grade was taken into account.

It was also possible that spiculation might indicate a poor prognosis as a result of histologic fibrotic foci and the role of fibroblasts in tumor progression. This is not the case. The unexpected finding is that mammographic spiculation is a good prognostic feature and remains independent of histologic grade in multivariate analysis. Why spiculation should be a good prognostic feature is not clear. The feature is thought to represent two phenomena: the in-pulling of normal Cooper's ligaments into a tumor and the invasion of tumor cells into the surrounding tissue. It is unclear whether either of these processes dominates in a particular group of spiculated lesions and whether either of these phenomena correlates with tumor-associated fibroblastic activity.

The limitations of this study are that it is from a single center, so the prognostic effect of spiculation should be validated in a data set separate from the one from which it was derived. The mammograms were reviewed by one radiologist, so the question of reproducibility regarding the presence or absence of spiculation has not been addressed. Because the study group dates from the beginning of screening in our center, there is an overrepresentation of prevalent round tumors, which tend to be low grade. Patients in this study were given adjuvant hormone therapy and chemotherapy when appropriate, but estrogen receptor status is unknown for most of the tumors. Others have suggested that spiculation may be associated with estrogen receptor expression [24]. The beneficial effect of spiculation could therefore be a related to improved survival of estrogen receptor–positive tumors because of the benefit derived from adjuvant hormone therapy.

If others confirm the findings we report in this article, identifying the mechanisms of mammographic spiculation may add to our understanding of the natural history of breast cancer.

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