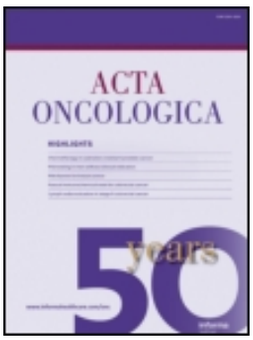

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ORIGINAL ARTICLE

Casting-type calcifications on the mammogram suggest a higher probability of early relapse and death among high-risk breast cancer patients

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Abstract

Introduction. A retrospective analysis of the relation between the presence of casting-type calcifications on the mammogram and the prognosis of breast cancer was performed. *Materials and methods.* The mammographic tumor features and other characteristics (invasive tumor size, histological tumor type, grade, nodal, hormone receptor and HER2 status, presence of lymphovascular invasion) of 55 high-risk breast cancers were studied. *Results.* After a median follow-up time of 29.1 months, the median relapse-free survival and overall survival times among breast cancer patients with tumors associated with casting calcifications were 26.6 and 29.6 months, respectively. The corresponding parameters among patients with tumors not accompanied by casting calcifications were 54.4 and >58.5 months, respectively. Significant associations were found between the presence of casting calcifications and the risks of relapse (HR=3.048, 95% CI: 1.116–8.323, p=0.030) or death (HR=3.504, 95% CI: 1.074–11.427, p=0.038). Positive associations were found between casting calcifications and ER/PR negativity (p=0.015 and p=0.003, respectively) and HER2 overexpression (p=0.019). *Discussion.* Our findings support the theory that breast tumors associated with casting-type calcifications at mammography comprise a disease entity which exhibits significantly more aggressive behavior and a poorer outcome than do cancers with other mammographic tumor features.

Breast cancer is a heterogeneous disease as regards its gene-expression profile [1,2], its pathological and its mammographic appearance, its biological behavior [3–7] and the response to oncological treatment [1,8]. The major progress achieved in the past decade in the adjuvant treatment of early breast cancer has contributed to an improvement in breast cancer-related survival [9]. Improved characterization of the different cancers may promote a better estimation of the outcome of the disease and the potential benefit provided by the various forms of adjuvant therapy [1,8]. The prognostic indicators reflect the stage of the cancer reached during the progression process and the degree of its aggressiveness. The tumor size and nodal status reflecting the stage of the cancer are classical prognostic factors. The histopathological type, the grade, the presence or absence of lymphovascular invasion (LVI), the expression of the hormone receptors and HER2 rather relate to the biological behavior of the cancer [4,10]. Nonetheless, more specific indicators for the better identification of high-risk cases are needed. The mammographic appearance has recently been suggested as an independent prognostic factor for mammography screening-detected breast cancers [4–7,11]. Among cancers measuring <15 mm detected by mammography screening, the presence of casting-type calcifications has been demonstrated to be a prognostic factor which carries a significantly (9-fold) higher risk of death as compared with cancers not associated with this mammographic abnormality [4]. We set out to study whether this mammographic feature might be indicative of a different prognosis in more advanced operable breast cancer cases. Accordingly, we performed a retrospective analysis of the mammographic appearance

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of 55 high-risk breast cancers of patients receiving uniform oncological treatment. Additionally, we studied the relation between the presence of casting-type calcifications and the other characteristics of the tumors.

Material and methods

The tumors and clinical outcomes of 55 consecutive high-risk breast cancer patients enrolled in an adjuvant chemotherapy clinical study after surgery [12] were studied. Eligible patients had operable breast cancer with either ≥ 4 lymph node metastases, *or* a >pT1 grade-III, ER and PR-negative tumor with lymph node metastasis, *or* a grade-III, ER and PR-negative tumor of any size with lymph node metastasis and vessel invasion, *or* a T >3 cm, grade-III, ER and PR-negative tumor. The primary tumor had to have been resected with a clear margin of at least 5 mm, but of at least 10 mm provided an extensive ductal component was present. The presence of distant metastases had to be excluded by means of physical examination, chest x-ray, abdominal ultrasound and bone scan. The study had been approved by the Institutional Review Board of the University of Szeged, and all enrolled patients gave written informed consent before being registered as participating in the study. Forty-seven of the 55 patients enrolled completed 24-week adjuvant dose-dense sequential doxorubicin-paclitaxel-cyclophosphamide chemotherapy, while in eight cases the chemotherapy was terminated earlier. After the chemotherapy, all of the patients underwent post-operative locoregional radiotherapy unless having had a relapse earlier, and those with hormone receptor-positive tumors received tamoxifen [12].

The original mammograms taken before surgery were retrospectively reviewed. All mammograms were classified by a single radiologist (KO) blinded to the pathological and clinical data. The lesions were categorized by their radiomorphological appearance into two groups: the lesions with casting calcifications (BI-RADS: fine linear branching calcifications), including any associated abnormality, and tumors in which casting-type calcifications were absent [3,4].

After a median follow-up time of 29.1 months, the relapse-free survival (RFS) and overall survival (OS) were studied in relation to the mammographic features, the age of the patient and the characteristics of the tumor (the tumor size, the number of involved lymph nodes, the histology, the grade, the hormone receptor status, the HER2 status, and the presence of LVI). RFS was defined as the time from enrolment to any disease recurrence (local, regional, distant relapse or a contralateral breast cancer). OS was defined as the time from enrolment to death.

We wished to learn whether there were significant initial differences between the risks of relapse or death among the patients as a function of the radiomorphological appearance of the tumors. Hence, the 10-year risks of relapse and mortality were calculated on the basis of the conventional prognostic factors (the age, the ER status, grade, size and nodal status of the tumor) using the software Adjuvant! [13]. This system provides predicted outcomes based on the patient and tumor characteristics. Calculations were made both with and without the inclusion of the HER2 status. Estimated risks of relapse and mortality were compared between the cases with and those without casting calcifications.

Statistical analyses

For the categorical parameters, χ^2 or Fisher tests were applied; for the analysis of continuous data, the Mann-Whitney U-test was used. RFS and OS times were calculated by means of the Kaplan-Meier method. Comparisons relating to the presence of casting calcifications were made with the log-rank test. To estimate the effect of casting-type calcifications and the conventional prognostic factors on long-term disease-outcome, the Cox proportional hazards model was used. A stepwise selection method was performed using the likelihood-ratio statistics based on the maximum partial likelihood estimates.

Results

The mean patient age was 51.7 (33–70) years; 49% had ER/PR-negative and 20% HER2-+++/+++ tumors; the median number of positive lymph nodes was 6, and 1/3 of the patients had ≥ 10 involved lymph nodes. Sixty per cent of the tumors were pT2, and 18% were pT1. Most of the breast tumors were grade 3 invasive ductal cancers, and 2/3 exhibited LVI. Among the 55 high-risk breast cancers, ten displayed the characteristics of casting-type calcifications. Patient- and tumor-related data according to the mammographic tumor features are presented in Table I. Significantly more tumors associated with casting calcifications were of grade 3 ($p=0.036$), HER2-positive ($p=0.012$), ER-negative ($p=0.015$) or PR-negative ($p=0.003$) than in the other group. No other characteristics of the tumors were related to the mammographic appearance (Table I).

In order to determine whether there was an *ab ovo* difference in the prognosis of the study patients, depending on the presence or absence of casting-type calcifications, we performed an analysis based

Table I. Patient- and tumor-related characteristics of 55 high-risk breast cancer cases displaying the presence or absence of casting-type calcifications on the mammogram.

Casting-type calcifications	Age (mean, years ± SE)	Tumor size (mean, mm ± SE)	Number of positive nodes (mean ± SE)	Grade 3 (%)	LVI present (%)	ER+ (%)	PR+ (%)	HER2 ++/+++ (%)
Absent (n=45)	51.5 ± 1.2	35.8 ± 3.1	7.7 ± 0.8	23 (52.3%)	32 (71%)	24 (53%)	23 (51%)	8 (18%)
Present (n=10)	51.9 ± 3.8	34.2 ± 7.4	6.9 ± 1.6	9 (90%)	6 (60%)	1 (10%)	0 (0%)	6 (60%)
p	NS	NS	NS	0.036	NS	0.015	0.003	0.012

LVI, lymphovascular invasion.

on the conventional prognostic factors. The risks of relapse and death calculated by means of the software Adjuvant! are shown in Table II. There was a trend toward a higher mortality risk in the group with casting-type calcifications as compared to the group without them, which became statistically significant when the HER2 status was included (Table II).

After a median follow-up time of 29.1 months, seven (70%) of the ten patients with casting calcifications had relapsed, and five (50%) had died. Among these patients, five had distant metastases, one had a local relapse, and one developed a second primary breast cancer. The latter two patients underwent surgery and adjuvant postoperative treatment, and were alive without evidence of disease at the end of the follow-up period. Eleven (24.4%) of those patients who had no casting-type calcifications on the mammogram relapsed, and seven (15.6%) died. Thus, 42% of all death events occurred in the group of patients having had tumors exhibiting casting calcifications. RFS and OS were 26.6 and 29.6 months in the group with casting-type calcifications, and 54.4 and >58.8 months (median), respectively, in the other group (p = 0.022 and 0.028, respectively; log-rank test). In order to estimate long-term prognosis depending on the presence of casting-type calcifications, the tumor grade, the LVI, the expressions of ER/PR and HER2, the tumor size and the nodal status were studied in a Cox proportional hazards model. Figure 1 shows cumulative relapse-free survival and overall survival associated with the presence or absence of casting calcifications on the mammogram. In the presence of casting-type calcifications, the risks of relapse and death were increased, with HR = 3.048 (95% CI: 1.116–8.323, p = 0.030) and HR = 3.504 (95% CI: 1.074–11.427, p = 0.038). No other patient- or tumor-related factor exerted a significant effect on the risk of relapse.

Discussion

This retrospective analysis was performed to assess the value of casting-type calcifications as a mammographic indicator of a poor prognosis in high-risk breast cancer patients. In agreement with earlier studies [3–7,11], we found the presence of casting-type calcifications to be the most powerful independent prognostic factor in a group of high-risk operable breast cancer cases. Our results contribute to and support the earlier finding that breast tumors associated with casting-type calcifications on the mammogram comprise a disease entity which is clearly different from cancers with other mammographic tumor features.

The previous studies on the prognostic role of casting-type calcifications were performed on screen-detected small cancers [3–7,11]. Our study group consisted of more advanced, but operable cases with large and usually node-positive tumors. We found more than 3-times higher risks of relapse and death in the group of tumors associated with casting-type calcifications as compared with the group without them. Tabár et al. reported that the risk of death was 32-times higher in screening-detected invasive breast cancers smaller than

Table II. Risks of relapse and death based on conventional prognostic factors (age, grade, ER status, tumor size, nodal status with or without HER2 status) among the tumor groups with or without casting-type calcifications, as indicated by the software Adjuvant!

	Without inclusion of the HER2 status		With inclusion of the HER2 status	
Casting-type calcifications	Risk of relapse (%)	Risk of death (%)	Risk of relapse (%)	Risk of death (%)
Absent (n=45)	71.6 ± 2.1	56.4 ± 2.4	71.7 ± 2.3	56.2 ± 2.6
Present (n=10)	74.8 ± 4.6	65.9 ± 5.5	78.7 ± 5.1	70.7 ± 6.2
p (Mann-Whitney U-test)	0.395	0.068	0.180	0.033

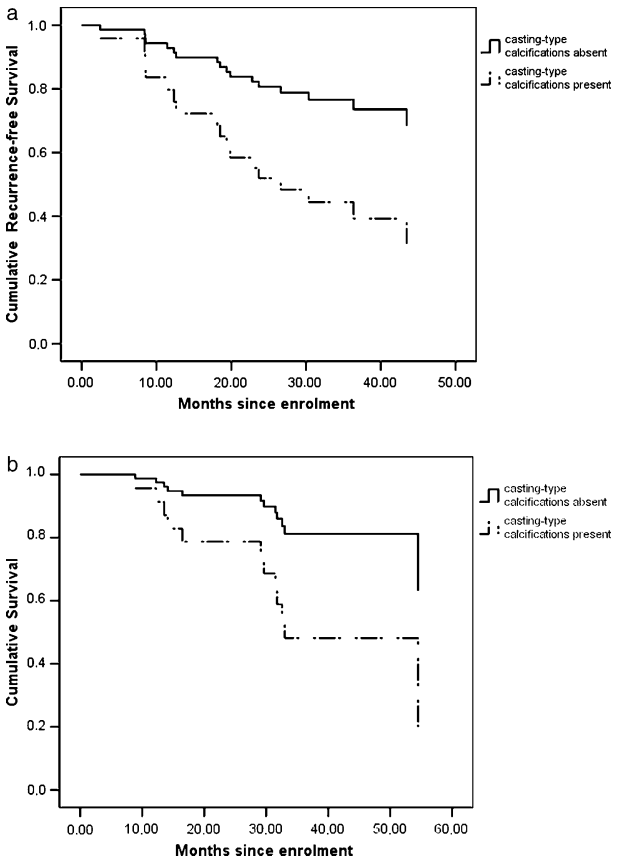

Figure 1. The effect of the mammographic feature of casting-type calcifications on recurrence-free (a) and overall survival (b).

10 mm and associated with casting-type calcifications as compared with those without such calcifications. The difference in the risk of fatality was smaller between the cases with and those without casting-type calcifications when the tumors measured 10–15 mm [5]. We were interested in whether the worse prognosis associated with casting-type calcifications would still exist in a set of high-risk, mostly clinically detected breast cancers, and it emerged that their presence was paralleled by a significantly poorer prognosis.

We analyzed whether the conventional prognostic factors differed between the group of breast tumors associated with casting-type calcifications and the group which did not display this mammographic feature. The tumor size and the nodal status reflecting primarily the stage of the disease did not reveal any difference between the two groups. The grade 3 phenotype was significantly more common among the tumors associated with casting-type calcifications, which is in accordance with the data of other authors [11,14].

Zunzunegui et al. studied a group of 12 breast cancer patients with invasive tumors who exhibited casting-type calcifications [7]. These tumors were smaller than the ones in our study, and all contained an extensive intraductal component. Half of them were ER/PR-negative, while 60% were HER2-positive. Our data are in consistence with those results, since all the tumors associated with casting-type calcifications in our study contained extensive high grade DCIS components. In fact, we found an even higher proportion of hormone receptor-negative cancers among those with casting-type calcifications. Moreover, HER2 positivity was typical in the cancer cases with casting-type calcifications. Our findings also accord with those of Millis et al., who demonstrated that the histological type of the DCIS component in invasive tumors was highly correlated with the grade of the infiltrative part [15], and predicted survival in 215 infiltrating ductal carcinomas after a median follow-up time of 11.2 years [16].

In the study of MacMillan et al., residual microscopic disease after breast conservation surgery was associated with the mammographic appearance of casting calcifications and predicted local recurrence [17]. Casting-type calcifications were the only independent mammographic feature that predicted residual cancer cells in the tumor bed and the consequent risk of local relapse [18]. Among our seven relapsed patients with cancers associated with casting-type calcifications, one had a local relapse on the chest wall.

With a view of analyzing whether the use of conventional prognostic factors could have predicted a significant difference between the groups of tumors with or without casting-type calcifications, we compared the risks of relapse and mortality as predicted by the software Adjuvant! [13]. Although there was a non-significant trend toward a greater mortality risk in the cases exhibiting casting-type calcifications, there was no difference in the risk of relapse. The difference in predicted mortality risk between the two groups became statistically significant when the HER2 status was included. This latter result does not contradict, but rather strengthens the hypothesis that a positive HER2 status and casting-type calcifications are common features of the same tumor type with an extremely poor prognosis.

Tabár et al. proposed that invasive breast cancers associated with casting-type calcifications and grade 3 DCIS comprise a different tumor type in a more advanced stage than indicated by the conventional prognostic factors, compared with their counterparts without this mammographic feature [3–5]. Neoductgenesis in the high-grade DCIS components, as a special process promoting vascular invasion, and consequently excessive lymphatic and hematogenous spread is suggested as a key underlying mechanism for the worse outcome in these tumors [5]. In accordance with the findings of Tabar et al., despite the outstanding difference in outcome, we did not

observe any difference between the tumors with or without casting-type calcifications, as concerns conventional prognostic factors (tumor size, number of positive lymph nodes, LVI) [3,5]. Our study clearly demonstrated that tumors with casting calcifications on the mammogram are typically of ductal type, of grade 3, ER and PR negative and HER2 positive. Based on these results, we believe that tumors associated with casting-type calcifications display different biological behavior with higher rates of proliferation and progression than other breast cancers. It is also probable that tumors with casting-type calcifications are more resistant to chemotherapy than tumors without them. This is indicated by the poor survival of the patients with invasive cancers measuring 1–14 mm associated with casting-type calcifications, irrespective of the therapeutic regimen applied [5]. Our data points to relative therapy resistance. Our study group consisted of high-risk, uniformly treated breast cancer patients. Those patients with casting-type calcifications relapsed and died soon after treatment, despite the administration of adjuvant dose-dense sequential paclitaxel-containing chemotherapy. There is an urgent need for the development of effective treatment methods for this special type of cancer, as none currently exists [5]. Primary systemic treatment could be an appropriate setting in which to test the antitumor potential of new pharmaceuticals, including different cytostatics and molecularly targeted therapies. The two most plausible of the latter group of agents are possibly trastuzumab and bevacizumab. Our results demonstrate that the presence of casting-type calcifications is significantly associated with the overexpression of HER2. Five randomized studies recently provided overwhelming evidence that the addition of trastuzumab to the adjuvant chemotherapy may halve the risk of early relapse [19–22]. The vascular invasion could be prevented and the pathologically leaky vasculature could be normalized by use of the anti-VEGF bevacizumab [23]. Since most of the tumors associated with casting-type calcifications were ER/PR-negative, there is little likelihood of benefit from hormonal therapy in this group of patients.

We believe that the detection of casting-type calcifications at mammography should be a warning sign of aggressive tumor behavior, irrespective of the stage of the tumor. Although the number of patients in our analysis was rather modest, the striking difference in outcome appears to deserve attention. Our observations warrant further analyses, and stress the need for the testing of new treatment options for the high-risk group of breast cancers associated with casting-type calcifications.

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This analysis was inspired by (but is otherwise independent of) the highly stimulating work of László Tabár (Falun Central Hospital, Sweden).

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