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## **Prognostic and predictive impact of central necrosis and fibrosis in early breast cancer: Results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy**

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**Title:** Prognostic and predictive impact of central necrosis and fibrosis in early breast cancer.

Results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy

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**Short title:** Central necrosis affects efficacy of chemoendocrine adjuvant therapies

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## ABSTRACT

**Purpose:** A minority of early invasive breast cancers show a pattern of central necrosis and fibrosis (CNF). Previous studies have documented an adverse prognostic impact and association with other adverse pathological features, but its predictive importance for therapy selection is unknown.

**Methods:** We examined the prognostic and predictive value of CNF in two randomized clinical trials comparing chemoendocrine therapy with endocrine therapy alone in patients with node-negative breast cancer. A total of 1850 patients randomly assigned to treatment groups comparing endocrine with chemoendocrine therapy, and with centrally-assessed CNF, ER, PgR and HER2 were included in the analytic cohort. The median follow up was 10 years.

**Results:** CNF was present in 84 of 1850 trial patients (4.5%). It was associated with tumor characteristics suggesting poor outcome, but was an independent adverse factor for disease-free survival. In the presence of CNF outcome was worse regardless of tumor grade, whereas in the absence of CNF, patients with grade 3 tumors had poorer outcome than those with grade 1-2 tumors. Among patients with estrogen receptor-absent tumors chemoendocrine therapy was superior to endocrine therapy alone only in the absence of CNF [HR (chemoendocrine:endocrine)=0.46 in CNF-absent, 0.90 in CNF-present], while among those with receptor-positive disease chemoendocrine therapy was beneficial only in the presence of CNF [HR=0.34 CNF-present, 0.96 CNF-absent].

**Conclusion:** The results suggest that the presence of CNF reflects a biological difference in early breast cancer that is important in modulating the efficacy of standard therapies. Accordingly we believe that its presence should be routinely reported.

**Key words:** central necrosis, fibrosis, chemotherapy, endocrine therapy, breast cancer

## INTRODUCTION

Extensive central (or geographic) necrosis has long been recognized as a pathological feature in some cases of primary breast cancer. Analysis of patients participating in an early trial of the National Surgical Adjuvant Breast Project (NSABP-04) found that necrosis was likely to be marked in tumors classified as medullary, in larger tumors, in those exhibiting squamous metaplasia or vessel invasion and in those occurring in younger patients (1). Necrosis was seen also in a smaller percentage of cases of infiltrating ductal carcinoma without specific features, especially those of higher histological grade, and in some other histologic types. Recently, several studies have reported on the clinico-pathological characteristics of a distinct subset of breast cancer, showing central acellular zones occupied by necrotic or fibrotic tissues (CNF) (2-10). These studies emphasized that patients harboring invasive ductal breast carcinomas (IDC) with large acellular areas were at higher risk for developing lung and brain metastases and showed poorer survival, in comparison with conventional IDC of comparable tumor grade. Different criteria were employed by the cited authors to assess CNF, such as extension for 30% or more of the tumor area (5), for 70% or more of the tumor cross-section (6) or detection at low power view (7). Additional features detected in IDC with CNF were: the absence of coagulative necrosis, of squamous metaplasia or keratinization, of osseous or cartilaginous metaplasia, and of matrix-producing features (5); abrupt transition from necrosis/fibrosis to viable tumor cells; high proliferation (4, 9, 11), especially in the tumor fibroblasts; (8) and pushing tumor-host interface (6).

More recently, CNF has been reported as a common morphological feature of the tumors belonging to the molecular class of basal-like breast cancers (10,12,13) and is associated with activation of Ras oncogene signaling, an activated wound healing signature and a poor prognosis 76-gene signature (10).

The present study was designed to investigate the impact of CNF on patient outcome, in particular the interrelation of tumor grade and CNF on outcome, and investigate the impact of CNF on the relative effects of chemoendocrine and endocrine therapies in two randomized controlled trials conducted by the International Breast Cancer Study Group for women with lymph node-negative breast cancer.

## **PATIENTS AND METHODS**

Patients were enrolled in one of two randomized clinical trials conducted by the International Breast Cancer Study Group (IBCSG) which have been reported elsewhere (14,15). Briefly, Trial VIII enrolled pre/peri-menopausal women with lymph node-negative breast cancer. The trial evaluated whether sequential treatment with six 28-day courses of “classical” cyclophosphamide, methotrexate, fluorouracil (CMF) chemotherapy followed by 18 monthly subcutaneous implants of goserelin significantly improved disease-free survival (DFS) as compared with either six 28-day courses of classical CMF alone, or 24 monthly implants of goserelin alone. From 1990 through 1999, a total of 1063 assessable patients were randomized. Trial IX enrolled postmenopausal women with lymph node-negative breast cancer and evaluated whether sequential treatment with three 28-day courses of classical CMF chemotherapy followed by tamoxifen for 57 months significantly improved DFS as compared

with tamoxifen alone for 5 years. From 1988 through 1999, a total of 1669 eligible and assessable patients were randomized. Institutional review boards reviewed and approved the protocols, and informed consent was required according to the criteria established within the individual countries. Toward the end of enrollment, on the basis of evidence from other trials (16,17) and after some 94% of patients had been entered, the protocols were amended to restrict enrollment to patients whose tumors were estrogen receptor (ER)-positive.

### **Central Pathology Review**

Retrospective tissue collection was carried out in accordance with institutional guidelines and national laws. More than 80% of patients randomized in Trials VIII and IX had archival tumor material available for review in the IBCSG Central Pathology Laboratory. Central pathology review was conducted without knowledge of patient treatment assignment or outcome. CNF was assessed during central pathology review according to the following criteria:

- extension of necrosis/fibrosis for 1mm or more of the cross section of tumors
- absence of coagulative necrosis
- abrupt transition from necrosis/fibrosis to viable tumor cells
- pushing tumor borders
- lack of squamous metaplasia or keratinization
- no evidence of osseous or cartilaginous metaplasia and of matrix-producing features



Expression of ER, progesterone receptors (PgR), HER2 and Ki-67 labeling index (LI) in the primary tumors were determined by immunohistochemistry (IHC) (18,19).

### **Analytic Cohort**

Tumor blocks and/or slides were available and assessable for CNF for 776 of 1063 patients (73%) in Trial VIII and 1427 of 1669 patients (86%) in Trial IX. Because of the low prevalence of CNF, the two trial cohorts were analyzed together. The present study compared endocrine therapy alone (goserelin alone in Trial VIII or tamoxifen alone in Trial IX) with chemoendocrine therapy (sequential treatment with CMF followed by goserelin in Trial VIII, or CMF followed by tamoxifen in Trial IX). Patients in Trial VIII assigned to chemotherapy alone were not included in the analytic cohort. A further 81 patients whose tumors could not be assessed for any of ER, PgR and HER2 were also excluded. Thus a total of 1850 patients randomly assigned to treatment groups comparing endocrine with chemoendocrine therapy were included in the analytic cohort. The median follow up of the analytic cohort was 10 years.

### **Statistical Methods**

Patient age at randomization, treatment assignment, tumor size and tumor grade were obtained from trial case report forms. Centrally-determined ER and PgR status were classified as present ( $\geq 1\%$  immunoreactive cells) or absent (0%), HER2 was considered as over-expressed if the intensity was scored 3+ vs. (0, 1+, 2+), and Ki-67 was classified as high for  $\geq 19\%$  immunoreactive cells by dichotomizing expression at the median value, as in previous analyses (18,19). A triple-negative tumor was defined as one that was absent of ER and PgR expression and did not overexpress HER2.

Logistic regression modeling was used to examine the association of patient and tumor features with presence of CNF. The association of the presence of CNF with DFS, accounting for other patient and tumor features, was evaluated using Cox proportional hazards modeling. DFS was defined as in the trials as the length of time from the date of randomization to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. In all modeling, dummy categories were used to accommodate unavailable values; pairwise comparisons of interest were made using model contrasts which produced likelihood-ratio tests (logistic) or Wald tests (proportional hazards), and all p-values were obtained from two-sided tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the treatment comparisons were estimated from the proportional hazards models. The analysis used SAS version 9.1 (SAS Institute Inc., Cary, NC).

## **RESULTS**

CNF was identified in tumors from 84 of 1850 trial patients (4.5%). Patient and tumor characteristics of the analytic cohort are summarized in Table 1 according to presence or absence of CNF.

### **Associations of CNF with patient and tumor features**

The CNF-positive tumors were equally distributed across the two treatment groups. CNF was observed among 3.6% and 4.9% of the Trial VIII (premenopausal) and Trial IX (postmenopausal) patients' tumors respectively. There was no association between CNF and trial cohort (i.e., menopausal status) or patient age at randomization. Presence of CNF was associated with the following other poor prognostic features (each  $P < 0.001$ ): larger and higher grade tumors;

absence of ER and PgR; high Ki-67 LI. Although CNF was not significantly associated with HER2 overexpression *per se* ( $P=0.88$ ), it was markedly associated with triple-negative tumors lacking ER, PgR and HER2 expression (17.9% of triple negative vs. 2.8% of other tumors had CNF;  $P<0.001$ ). Much of this association between CNF and triple-negative status was contributed by the absence of ER. In multivariable logistic regression modeling that included trial cohort and selected among tumor features, the tumor triple-negative status, Ki-67 LI status and size were most strongly associated with presence of CNF (each  $P<0.01$ ; Table 2). In this model, there was a marginal association of trial cohort and CNF ( $P=0.09$ ; Table 2). Tumor grade was not independently associated with CNF (OR=1.40, 95% CI 0.80 to 2.44; grade 3 vs. grade 1-2) in the multivariable model.

### **Disease-free survival**

CNF was associated with poorer DFS (HR=1.6, 95% CI 1.1 to 2.3;  $P<0.01$ ; Figure 1) in univariate analysis. Estimated 5-year DFS was  $70\% \pm 5.0$  and  $84\% \pm 0.9$  among patients having tumors with and without CNF respectively (Table 3). There was evidence of an interaction of tumor grade and CNF ( $P=0.03$ ) with DFS, such that the presence of CNF was associated with poorer outcome among patients with grade 1 or 2 tumors (HR=2.5, 95% CI 1.4 to 4.3), but this was not seen among patients with grade 3 tumors (HR=1.1, 95% CI 0.7 to 1.8) (Figure 2A). Conversely, the interaction suggests that in the presence of CNF there was poor outcome regardless of tumor grade whereas in the absence of CNF, patients with grade 3 tumors had poorer outcome than those with grade 1-2 tumors. DFS according to the combination of CNF and tumor grade – as

grade 1, grade 2, grade 3 (each without CNF) and any grade with CNF – is summarized in Figure 2B. These results persisted in multivariable analysis.

The relative benefit of chemoendocrine vs. endocrine therapy alone on DFS in the presence and absence of CNF was examined separately for patients whose tumors did or did not express ER, because of both biological and statistical considerations ( $P=0.03$  for 3-way interaction of ER-status, treatment and CNF). The observed patterns appeared strikingly different (Figure 3). In patients with ER-absent tumors, for whom the benefit of chemoendocrine therapy over endocrine therapy alone might be most expected, this benefit was seen in the majority whose tumors did not show CNF (HR=0.46, 95% CI 0.31 to 0.70), but was less apparent in the minority with CNF present (HR=0.90, 95% CI 0.33 to 2.41). The outcomes for the three patient groups (CNF-present with either treatment, and CNF-absent treated with endocrine therapy alone) were similar and markedly inferior to that for patients with CNF-absent tumors allocated chemoendocrine therapy (Figure 3A). By contrast, among patients with ER-expressing tumors, there was benefit of chemoendocrine therapy over endocrine therapy alone in the minority of patients whose tumors did show CNF (HR=0.34, 95% CI 0.11 to 1.04) but not in the majority whose tumors did not show CNF (HR=0.96, 95% CI 0.78 to 1.18). Outcome was similar and relatively good, except for patients whose tumors showed CNF and who were allocated endocrine therapy alone (Figure 3B).

## **DISCUSSION**

The strength of examining the prognostic and predictive value of tumor markers in the context of prospective clinical trials has been noted by previous authors (1): the treatments and follow-

up are more likely to be standardized than would be true of a convenience sample. CNF is a relatively uncommon finding in early invasive breast cancer, and our observation of a prevalence of 4.5% among patients with node-negative breast cancer is consistent with previous reports (1,6). We found associations between CNF and larger tumors, those lacking hormone receptors and those with a high proliferative fraction, findings again consistent with earlier reports (3, 6, 8, 9, 11).

It appears from the present study that the presence of CNF provides information in addition to the prognostic and predictive factors normally recorded in such trials. CNF was associated with a poorer outcome irrespective of histologic grade, and indeed all grades had similarly poor outcomes in the presence of CNF.

Because the treatment effect of chemoendocrine versus endocrine therapy depends on hormone receptor status as observed in the overall trial results (14,15,19), and because each of the trials was prospectively stratified by estrogen receptor status, we chose to primarily examine the relationship between CNF and treatment effect separately in receptor-absent and receptor-present cohorts. In the receptor-absent cohort, where the benefit of chemoendocrine therapy over endocrine therapy alone had been observed in the trials overall, we indeed found this benefit among the majority of patients without CNF, but the benefit appeared to be completely abrogated by the presence of CNF (Figure 3A). The reason is not clear. It may reflect poorer penetration of chemotherapeutic agents into micro-metastatic tumor deposits in tumors prone to show CNF, perhaps due to associated hypoxia (9, 11, 20-24) or some undefined cellular characteristic which reduces the efficacy of the chemotherapeutic agents

used. The effect of CNF in receptor-positive disease was equally dramatic: whereas endocrine therapy alone appeared adequate for the majority of patients, the outcome was inferior among patients whose tumors showed CNF and who were allocated endocrine therapy alone (Figure 3B). Here the more efficacious therapy may be thought to be the tamoxifen, so it is again possible that the mechanism reflects poorer drug access to the tumor, though an intrinsic characteristic of tumor cells which compromises endocrine efficacy cannot be excluded.

Whatever the mechanism, these results suggest that the presence of CNF identifies a biologically distinct subgroup within early breast cancer and that the difference is important in determining the efficacy of standard chemotherapy and endocrine therapy. We recommend that the presence or absence of CNF, as defined in previous reports (3, 6-9, 11, 20) and in the current paper become a standard part of the pathological reporting of early breast cancer.

**Table 1. Association of patient and tumor features with presence of CNF<sup>1</sup>.**

	CNF absent N (%)	CNF present N (%)	Odds Ratio (95% CI)	P-value
<i>Number of patients</i>	1766 (95.5)	84 (4.5)		
Treatment				0.91
Endocrine-only	882 (95.6)	41 (4.4)		
CMF → endocrine	884 (95.4)	43 (4.6)		
Trial				0.31
VIII (pre/perimenopausal)	480 (96.4)	18 (3.6)		
IX (postmenopausal)	1286 (95.1)	66 (4.9)		
Age (y), median (IQR)	57 (50-63)	59 (50-63)		0.69
Tumor size (cm)				<0.001
≤ 2.0	1069 (97.3)	30 (2.7)	1 (ref)	
> 2.0	662 (92.6)	53 (7.4)	2.9 (1.8, 4.5)	
Unknown	35	1		
Tumor grade				<0.001
1,2	1075 (97.7)	25 (2.3)	1 (ref)	
3	628 (91.8)	56 (8.2)	3.8 (2.4, 6.2)	
Unknown	63	3		
ER				<0.001
Absent	292 (85.9)	48 (14.1)	6.4 (4.0, 10.0)	
Present (≥1%)	1354 (97.5)	35 (2.5)	1 (ref)	

Unknown	120	1		
PgR				<0.001
Absent	496 (90.0)	55 (10.0)	4.6 (2.9, 7.5)	
Present (≥1%)	1131 (97.7)	27 (2.3)	1 (ref)	
Unknown	139	2		
HER2				0.88
Over-expressed (3+)	265 (95.3)	13 (4.7)	1.0 (0.6, 1.9)	
Not over-expressed (0,1+,2+)	1477 (95.4)	71 (4.6)	1 (ref)	
Unknown	24	0		
Triple-negative				<0.001
Yes	183 (82.1)	40 (17.9)	7.5 (4.8, 11.9)	
No	1485 (97.2)	43 (2.8)	1 (ref)	
Unknown	98	1		
Ki-67 LI				<0.001
High (≥19%)	732 (91.4)	69 (8.6)	7.7 (3.8, 15.6)	
Low (<19%)	737 (98.8)	9 (1.2)	1 (ref)	
Unknown	297	6		

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<sup>1</sup>Percentages sum across the rows. P-values from univariate logistic regression models.



**Table 2. Multivariable logistic regression model for presence of central necrosis/fibrosis**

	<b>Estimate ± SE</b>	<b>Odds Ratio (95% CI)</b>	<b>P-value</b>
Trial IX postmenopausal (vs. Trial VIII premenopausal)	0.48 ± 0.28	1.61 (0.93, 2.81)	0.09
Triple-negative (vs. not)	1.54 ± 0.25	4.65 (2.88, 7.52)	<0.0001
High Ki-67 LI (vs. low Ki-67 LI)	1.53 ± 0.37	4.62 (2.23, 9.57)	<0.0001
Tumor size >2cm (vs. ≤ 2cm)	0.65 ± 0.24	1.92 (1.19, 3.10)	<0.01

**Table 3. Associations of patient and tumor features with disease-free survival (DFS)<sup>1</sup>**

	Number of patients	Number of events	10yr DFS % $\pm$ SE	Hazard Ratio (95% CI)	P-value
<i>All patients</i>	1850	516	71 $\pm$ 1.2	--	--
Treatment					P=0.02
Endocrine-only	923	277	68 $\pm$ 1.7	1 (ref)	
CMF $\rightarrow$ endocrine	927	239	73 $\pm$ 1.7	0.81 (0.68, 0.96)	
Trial					P=0.41
VIII (pre/perimenopausal)	498	124	73 $\pm$ 2.2	1 (ref)	
IX (postmenopausal)	1352	392	70 $\pm$ 1.4	1.09 (0.89, 1.33)	
Tumor size					P<0.001
$\leq$ 2 cm	1099	260	74 $\pm$ 1.5	1 (ref)	
>2 cm	715	248	65 $\pm$ 1.9	1.53 (1.29, 1.82)	
Tumor grade					P<0.001
1	300	53	82 $\pm$ 2.6	1 (ref)	
2	800	216	71 $\pm$ 1.8	1.57 (1.17, 2.13)	
3	684	230	66 $\pm$ 2.0	2.08 (1.54, 2.81)	
ER status					P=0.04
Absent	340	113	66 $\pm$ 2.7	1.25 (1.02, 1.55)	
Present	1389	372	72 $\pm$ 1.4	1 (ref)	
PgR status					P=0.01
Absent	551	178	67 $\pm$ 2.2	1.26 (1.05, 1.52)	
Present	1158	302	72 $\pm$ 1.5	1 (ref)	
HER2					P=0.38

Over-expressed	1548	425	71 ± 1.3	1 (ref)	
Not over-expressed	278	85	69 ± 3.1	1.11 (0.88, 1.40)	
Triple-negative					P=0.04
Yes	223	77	64 ± 3.4	1.30 (1.02, 1.66)	
No	1528	413	72 ± 1.3	1 (ref)	
Ki-67					P<0.001
High (≥19%)	801	259	65 ± 1.9	1.41 (1.17, 1.70)	
Low (<19%)	746	184	74 ± 1.8	1 (ref)	
CNF					P<0.01
Absent	1766	482	71 ± 1.2	1 (ref)	
Present	84	34	57 ± 5.7	1.60 (1.13, 2.27)	
Tumor grade - CNF					P<0.001
Grade 1 – CNF absent	298	52	83 ± 2.6	1 (ref)	
Grade 2 – CNF absent	777	204	72 ± 1.8	1.55 (1.14, 2.10)	
Grade 3 – CNF absent	628	210	66 ± 2.1	2.10 (1.54, 2.83)	
Any grade – CNF present	84	34	57 ± 5.7	2.61 (1.69, 4.02)	

<sup>1</sup>Hazard ratios, 95% confidence intervals, P-values from univariate Cox proportional hazards regression models.

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## FIGURE CAPTIONS

**Figure 1.** Disease-free survival by presence or absence of central necrosis fibrosis (CNF) among the 1850 patients with node-negative breast cancer from two International Breast Cancer Study Group randomized trials.

**Figure 2.** Disease-free survival according to tumor grade and central necrosis fibrosis (CNF), comparing grade 1-2 with and without CNF versus grade 3 with and without CNF (A) and comparing grades 1, 2 and 3 without CNF vs. any grade with CNF (B).

**Figure 3.** Disease-free survival according to treatment and presence or absence of central necrosis fibrosis (CNF) for patients with ER-absent tumors (A) and ER-present tumors (B).