ARTICLES

Micrometastatic Breast Cancer Cells in Bone Marrow at Primary Surgery: Prognostic Value in Comparison With Nodal Status

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Background: **Approximately 30% of the patients with primary breast cancer who have no axillary lymph node involvement (i.e., lymph node negative) at the time of surgery will relapse within 10 years; 10%-20% of the patients with distant metastases will be lymph node negative at surgery. Axillary lymph node dissection, as a surgical procedure, is associated with frequent complications. A possible alternative to nodal dissection in terms of prognosis may be the immunocytochemical detection of tumor cells in bone marrow.** ***Purpose:*** **In a prospective study, the value of tumor cell detection (TCD) in bone marrow was compared with axillary lymph node dissection in the prognosis of primary breast cancer after surgery.** ***Methods:*** **Data from 727 patients with primary, operable breast cancer were included in the analysis. All patients had surgery, including axillary lymph node dissection, from May 1985 through July 1994 at the Women's Hospital of the University of Heidelberg (Federal Republic of Germany). Bone marrow aspiration at two sites on each anterior iliac crest was performed immediately after surgery while the patients were under general anesthesia. Most patients received some type of systemic adjuvant therapy. The monoclonal antibody 2E11, directed against the polymorphic epithelial mucin TAG12, was used to detect tumor cells in bone marrow samples. The association of TCD with recognized prognostic indicators was evaluated by means of chi-squared tests. Survival without the development of distant metastases (i.e., distant disease-free survival) and overall survival were estimated by use of the Kaplan–Meier method; the logrank test was used to compare survival curves. A multivariate Cox regression analysis with stratification according to adjuvant treatment type was used to assess the independent prognostic value of TCD in bone marrow in relation to other variables. Reported *P* values are two-sided.** ***Results:*** **Tumor cells were detected in the bone marrow of 203 (55%) of 367 lymph node-positive patients and in 112 (31%) of 360 lymph node-negative patients. TCD was associated with larger tumors (*P*<.001), lymph node involvement (*P* = .001), and higher tumor grade (i.e., more undifferentiated) (*P* = .002). After a median follow-up of 36 months, patients with tumor cells in their bone marrow experienced reduced distant disease-free survival and overall survival (both *P* values <.001). TCD was an independent prognostic indicator for both distant disease-free survival and overall survival that was superior to axillary lymph node status, tumor stage, and tumor grade. Among patients with tumors less than 2 cm in diameter, TCD was the most powerful predictor of outcome.** ***Conclusions and Implications:*** **TCD in the bone marrow of patients with breast cancer is a valuable prognostic tool associated with negligible morbidity. Prospective randomized studies should be performed to determine whether TCD might replace axillary lymph node dissection in a defined subgroup of patients with small tumors. [J Natl Cancer Inst 1996;88:1652-64]**

Breast cancer is a heterogeneous disease characterized by a propensity to early hematogenous spread that is decisive for the patient's fate. Recognized prognostic indicators, such as tumor size, histologic and/or nuclear grade, and steroid hormone receptor status, define tumor proliferation characteristics and the degree of differentiation, thus providing only indirect information about metastatic potential and the likelihood of dissemination. Axillary lymph node status is widely accepted as the best prognostic indicator, and the presence of tumor cells in axillary lymph nodes is believed to mark the beginning of systemic dis-

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See "Note" section following "References."

ease. However, approximately 30% of the patients with node-negative disease at primary surgery will relapse within 10 years, and 10%-20% of those with primary distant metastases will be determined to be axillary lymph node negative (*1,2*). Axillary dissection, as a surgical procedure, is associated with frequent complications, such as infection, bleeding, seroma, skin dysesthesia, and lymph edema (*3*).

Although breast cancer surgery has become increasingly more conservative over the past few decades, this trend has not been extended to axillary lymph node dissection. A possible alternative in terms of prognostic potential may be tumor cell detection (TCD) in bone marrow by means of immunocytochemistry, a method that was first described in 1981 by Dearnaley et al. (*4*). TCD is an indicator of subsequent metastasis not only to the lymph nodes but also to distant sites, and it provides information on hematogenous cell shedding. Significant associations between TCD in bone marrow and tumor size, nodal status, tumor grade, and progesterone receptor status have already been described by us and by others (*5-12*).

The purpose of the present study was to compare the prognostic value of TCD and axillary nodal status and to examine the possibility of omitting axillary dissection in certain subgroups of patients.

Methods

Patient Population

In a prospective study, 805 consecutive patients with primary, operable breast cancer [T1-4, N0-2, and M0; International Union Against Cancer criteria (*13*)] were recruited. The patients had surgery between May 1985 and July 1994 at the Women's Hospital of the University of Heidelberg (Federal Republic of Germany). Exclusion criteria included the presence of visceral and/or bone metastases within 3 months after surgery (n = 12), a breast biopsy and/or a lumpectomy before definitive surgery and bone marrow aspiration (n = 5), anticancer treatment prior to surgery (n = 30), or a history of malignant disease or a simultaneous second primary tumor (n = 9). Patients with incomplete follow-up data (n = 22) were also excluded. Altogether, data from 727 patients were included in the present analysis. Bone marrow samples from 21 patients without malignant disease (15 bone marrow donors and six individuals with benign breast disease) were used as control specimens. The study design was examined and approved by the board of review for ethical practice. Written informed consent was obtained from all participants.

Surgical and Systemic Adjuvant Treatment

Primary surgery consisted of either mastectomy and axillary lymph node dissection (n = 263) or breast-conserving therapy (i.e., lumpectomy with free margins or segmentectomy plus axillary dissection plus irradiation of the remaining breast) (n = 464). The median number of histologically examined lymph nodes was 22 (range, 10-54 lymph nodes). All patients with positive lymph nodes (N+) and those with negative lymph nodes (N0) but with other poor prognostic criteria received adjuvant systemic treatment. Menopausal status, steroid hormone (estrogen/progesterone) receptor status (positive if ≥20 fmol/mg protein; dextran-coated charcoal method), S-phase fraction measured by flow cytometry (cutoff level was 5%), and tumor size were taken into account in terms of therapeutic decisions; TCD was not taken into account in this regard. Patients were treated with 30 mg of tamoxifen daily for 2 years (n = 213); six cycles of standard cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and fluorouracil (5-FU) (600 mg/m^2) (n = 187); six cycles of cyclophosphamide (600 mg/m^2) and epirubicin (60 mg/m^2) with or without 5-FU (600 mg/m^2) (n = 76); or 3.6 mg of goserelin monthly for 2 years (n = 61). One hundred seventy-two patients without axillary lymph node metastases and 18 with one or two positive lymph nodes and good prognostic criteria received no further systemic treatment. Follow-up examinations were performed routinely at the outpatient clinic (chest x ray, liver ultrasound, and bone scan every 12 months and a physical examination and blood tests every 6 months).

Bone Marrow Aspiration and Preparation Technique

Bone marrow puncture and aspiration were performed under general anesthesia immediately after surgery. Ten to 12 milliliters of aspirate were collected from two puncture sites on each anterior iliac crest (total, 40-50 mL) and stored in heparinized Falcon tubes with Dulbecco's modified Eagle medium (DMEM; Gibco, Paisley, U.K.). Components of the aspirate were separated by density centrifugation through Ficoll–Hypaque (Biochrom, Berlin, Federal Republic of Germany; density = 1.077 g/mol). Cells in interphase were washed twice and resuspended with DMEM. Subsequently, 10 µL of the cell suspension (4-5 × 10^6 cells) was smeared on slides. The slides were air-dried and stored at –20 °C.

Immunocytology

Immunocytochemical staining was performed with the aid of the murine monoclonal antibody 2E11. This antibody is an immunoglobulin G3 subtype that binds to the tandem amino acid sequence A-P-D-T-R of the core protein of the tumor-associated glycoprotein TAG12 (*14-16*). The antigen (TAG12) was isolated and purified from cells of the T47D mammary cancer cell line. TAG12 is a polymorphic epithelial mucin that is expressed not only by most breast cancers but also by ovarian and endometrial carcinomas (*17,18*). Before staining, the cells were fixed with 100% methanol. After blocking endogenous phosphatase activity with 20% acetic acid, 2.28% periodic acid, and 2% levamisole, the smears were incubated with biotinylated 2E11 (stock solution, 2 mg/mL; dilution, 1:1000 with phosphate-buffered saline that contained 1% bovine serum albumin; Boehringer Mannheim; Mannheim, Federal Republic of Germany) for 1 hour at room temperature. Immune complexes were made visible by use of avidin–biotin–alkaline phosphatase complexes (ABC-Test; Vectastain; Camon, Wiesbaden, Federal Republic of Germany) and new fuchsin as the substrate. The tested sensitivity of our method was the detection of one tumor cell (T47D) among 10^6 normal bone marrow cells. One negative and one positive smear were used as controls in all staining series. For each patient, four smears were analyzed. The membrane and cytoplasm of the tumor cells stained bright red (Fig. 1). Positive smears were defined as those containing one or more tumor cells; five to 90 cells per slide were detected for most positive smears. All slides included in our study were judged by two independent investigators, with an interobserver agreement of 99%. Discordant findings occurred in only five cases, and the corresponding patients were eventually considered tumor cell negative. The analysis was performed without knowledge of surgical procedure, tumor stage, and other prognostic factors.

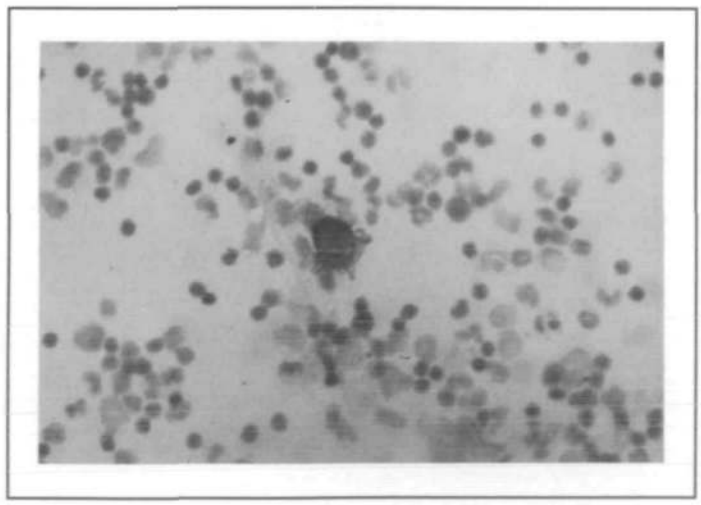

Fig. 1. Breast cancer cell in bone marrow stained with the anti-epithelial mucin (TAG12) monoclonal antibody 2E11. The micrometastatic cancer cell is the large, darkly stained cell in the center of the microscopic field.

Statistical Methods

The association of TCD with established prognostic indicators was analyzed by chi-squared tests. Survival methods were applied to overall survival and distant relapse-free survival. Distant disease-free survival was defined as survival without the development of distant metastases. Locoregional recurrence and death without recurrence were not counted as events; observations of the latter (five cases) were treated as censored observations. All survival curves were calculated by the Kaplan–Meier method, and the comparison of two survival curves was based on the logrank test according to Mantel and Breslow (*19*). A stepwise multivariate Cox regression analysis (*20*) was performed to assess the independent prognostic value of TCD in comparison with other prognostic factors. The impact of each variable in the Cox regression model was tested by the Wald chi-squared test and described by the risk ratio (i.e., the hazard ratio) (*19*). All reported *P* values are two-sided. When risk ratios are interpreted, especially in the comparison of dichotomous versus polychotomous variables, it has to be kept in mind that the indicated value relates to a change of one unit in the prognostic variable. The statistical analysis was done with the aid of SAS (SAS Institute, Inc., Cary, NC) and Systat (Evanston, IL) software.

Results

Patient Characteristics

The median patient age was 53 years (range, 22-83 years), and most tumors were either less than 2 cm (T1) or between 2 and 5 cm (T2) in diameter. Half of the patients were classified as node negative, and most were postmenopausal (59%). Immunocytochemical TCD in bone marrow was positive in 315 (43%) patients. The cell detection frequency did not vary substantially among patients receiving different systemic adjuvant treatments (cyclophosphamide, methotrexate, and 5-FU = 44%; cyclophosphamide and epirubicin with or without 5-FU = 50%; tamoxifen = 48%; and goserelin = 54%). In the untreated low-risk group (n = 190), only 32% of the patients were TCD positive.

TCD in Bone Marrow and Established Prognostic Indicators

Table 1 shows the relationship between conventional prognostic indicators and TCD. The prevalence of positive TCD increased significantly with tumor size ($P<.001$). A similar significant relationship was found between TCD and tumor grade ($P = .002$). In addition, the prevalence of positive findings was significantly higher in patients with axillary lymph node metastases (55%; $P = .001$). However, 31% of the node-negative women also had detectable tumor cells in their bone marrow. Positive cell detection was more frequent in postmenopausal patients ($P = .01$).

TCD in Bone Marrow and Survival Data

The median follow-up time was 36 months (range, 3-108 months). Distant metastases were diagnosed in 143 patients. One hundred nine (76%) of these patients were tumor cell positive. Interestingly, there was no difference in tumor cell positivity between patients whose primary site of metastasis was

Table 1. Clinical and pathologic features of 727 patients with breast cancer in relation to tumor cell detection in bone marrow at primary surgery*

Prognostic indicator	No. of patients	Tumor cell detection: Positive No.	Positive %	Negative No.	Negative %	P†
Tumor size						
T1	258	77	30	181	70	
T2	323	137	42	186	58	<.001
T3	69	43	62	26	38	
T4	77	58	75	19	25	
Nodal status						
N0	360	112	31	248	69	.001
N+	367	203	55	164	45	
Estrogen receptor (n = 617)						
Positive‡	410	186	45	224	55	.74
Negative	207	91	44	116	56	
Progesterone receptor (n = 588)						
Positive‡	341	145	42	196	58	.17
Negative	247	119	48	128	52	
Menopausal status						
Premenopausal	296	112	38	184	62	.01
Postmenopausal	431	203	47	228	53	
Grade (n = 682)						
I + II	403	159	39	244	61	.002
III	279	144	52	135	48	
S-phase fraction, % (n = 646)						
<5	271	113	42	158	58	.21
≥5	375	175	47	200	53	
Tumor cells in bone marrow	727	315	43	412	57	

*Tumor staging according to International Union Against Cancer criteria (*13*); N0 = no axillary lymph node involvement, and N+ = axillary lymph nodes positive for tumor cells.

†Chi-squared test for contingency tables.

‡Positive ≥20 fmol/mg protein.

bone (n = 71; 76%) and those with visceral or multiple metastases (n = 38; 73%). Among the 66 patients with local and/or regional recurrences, 41 (62%) were tumor cell positive. Of the 69 women who died of breast cancer, 57 (83%) had micrometastatic cells in their bone marrow. In patients with distant relapse, this event occurred earlier in the tumor cell-positive group (median, 21.5 months) than in the tumor cell-negative group (median, 33.5 months).

The distant disease-free survival in relation to TCD is shown in Fig. 2. Patients with tumor cells in their bone marrow relapsed earlier and more frequently than those with negative cell detection ($P<.001$). As shown in Fig. 3, a similar significant association was found between TCD and overall survival. Interestingly, cell detection could also predict locoregional relapse ($P = .001$).

To investigate whether TCD in the bone marrow was an independent predictor of clinical outcome, a multivariate Cox regression analysis was performed (Table 2). Concerning distant disease-free survival, TCD was shown to give independent, significant, predictive information (relative risk [RR] = 3.06; 95% confidence interval [CI] = 1.91-4.90; $P<.001$) in addition to that provided by the established prognostic indicators. With respect to overall survival, a similar result was obtained, but it was less pronounced (RR = 2.14; 95% CI = 1.08-4.22; $P = .03$). To control for the possible influence of adjuvant therapy, this factor was treated as a stratification variable in the Cox regression model, with five strata defined by either no adjuvant therapy or one of the four systemic therapies described above. We tested whether interaction terms of cell detection and adjuvant treatment led to a better-fitted model, but this was not the case.

TCD in Bone Marrow and Axillary Lymph Node Status

In Fig. 4, the combination of TCD and nodal status with respect to distant disease-free survival is presented. According to the Kaplan–Meier analysis, the poorest prognosis was found in the group of patients who were both tumor cell positive and lymph node positive, followed by the group who were tumor cell positive and lymph node negative. In the tumor cell-negative group, the presence or absence of axillary lymph node metastases did not appear to differentiate between the two resulting subgroups. Similar data were found in terms of overall survival, as shown in Fig. 5. When the analysis of the prognostic impact of TCD was confined to the subgroup of node-negative patients who received no adjuvant therapy (n = 172), there was still a higher risk of distant metastasis (RR = 1.9; 95% CI = 0.83-4.04; $P = .14$).

A Cox regression analysis was also performed to investigate the prognostic impact of TCD versus nodal status in terms of the probability of metastasis for different tumor stages (Table 3). Here, nodal status was dichotomized as N0 versus N+ to allow a direct comparison of the RRs between TCD and nodal status. TCD was the only significant factor in all subgroups. Nodal status reached statistical significance only in the T2 ($P = .014$) and the T3/4 ($P = .04$) subgroups. Because of the few events in each subgroup, overall survival has not yet been subjected to regression analysis.

Complications of Bone Marrow Aspirations

All intraoperative and postoperative complications were registered and followed-up. In only one of 727 patients did a severe complication occur (serious hemorrhage due to an atypical vessel requiring surgical ligature). Remarkably, no wound infections occurred. In 11 cases, minor hemorrhages were observed immediately after the puncture and required compression. Altogether, 32 transient subcutaneous hematomas were seen, none of which required specific therapy. Some patients (n = 57) had pain at the puncture site, but only two had complaints

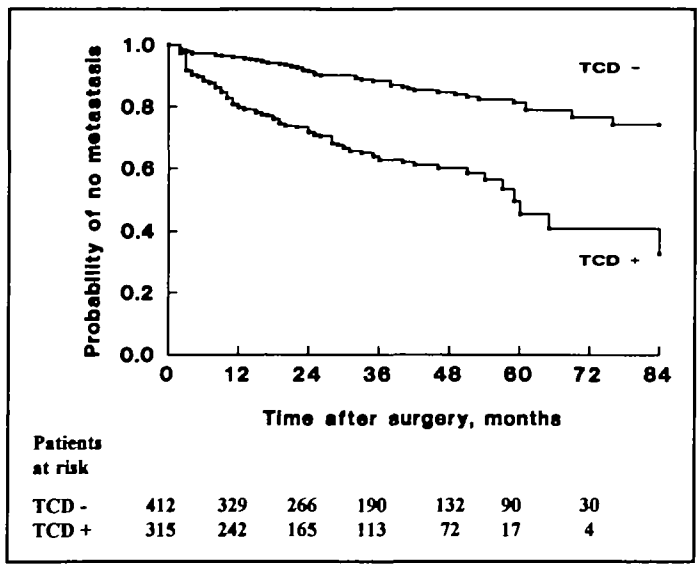

Fig. 2. Distant disease-free survival of patients with primary breast cancer according to the presence or absence of micrometastatic tumor cell detection (TCD) in the bone marrow (TCD+ or TCD–, respectively; $P<.001$; logrank test). Thirty-four of 412 patients in the TCD– group and 109 of 315 patients in the TCD+ group showed distant relapses during the study. The 95% confidence intervals for distant disease-free survival at 3 years are 0.84-0.92 for the TCD– group and 0.56-0.69 for the TCD+ group.

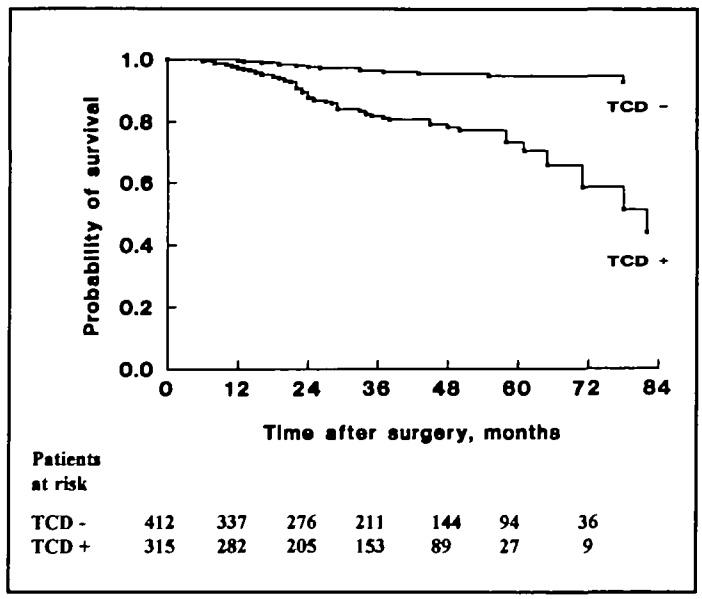

Fig. 3. Overall survival of patients with primary breast cancer according to the presence or absence of micrometastatic tumor cell detection (TCD) in the bone marrow (TCD+ or TCD–, respectively; $P<.001$; logrank test). Twelve of 412 patients in the TCD– group and 57 of 315 patients in the TCD+ group died during the study. The 95% confidence intervals for overall survival at 3 years are 0.93-0.99 for the TCD– group and 0.76-0.86 for the TCD+ group.

Table 2. Results of multivariate analysis comparing tumor cell detection (TCD) in bone marrow with established prognostic indicators in patients with breast cancer*

Variable	*P*	RR	95% CI
		Disease-free survival	
TCD (positive, negative)	<.001	3.06	1.91-4.90
Grade (I + II, III)	.007	1.73	1.16-2.57
Nodal status (N0, N1-3, N4-9, N>9)	<.001	1.68	1.35-2.08
Tumor size (T1, T2, T3, T4)	.14	1.17	0.95-1.44
		Overall survival	
Progesterone receptor (positive†, negative)	<.001	2.75	1.54-4.88
TCD (positive, negative)	.03	2.14	1.08-4.22
Grade (I + II, III)	.06	1.79	0.96-3.32
Nodal status (N0, N1-3, N4-9, N>9)	<.001	1.75	1.29-2.37
Tumor size (T1, T2, T3, T4)	.19	1.23	0.90-1.69

*Cox regression stratified by adjuvant therapy; nodal status and tumor size were each included in the model as one variable with values 1, 2, 3, and 4 given to the groups as indicated. Relative risk (RR), therefore, refers to the comparison of one category with the next. Tumor staging was according to International Union Against Cancer criteria (*13*). CI = confidence interval.

†Positive ≥20 fmol/mg protein.

for longer than 3 days. Systemic analgesics were not required by any patient.

Discussion

Prognostic Value of TCD in Bone Marrow

Since its first description in 1981 (*4*), immunocytochemical TCD in bone marrow has been shown to correlate with the prognosis of various malignant diseases, such as prostate cancer (*21*), neuroblastoma (*22*), melanoma (*23*), lung cancer (*24*), and gastrointestinal tumors (*25*). However, most studies (*4-12,26,27*) have dealt with breast cancer, yielding a detection frequency among patients of 16%-45%. Reliable evaluation of the true prognostic impact of TCD has not yet been possible, since different groups have used different antibodies of varying specificities, low numbers of patients have been investigated, and discordant inclusion/exclusion criteria have been used (*12,28*).

We have presented data on 727 patients with breast cancer, with follow-up observation for a median period of 36 months. Our study population is the largest investigated thus far. After

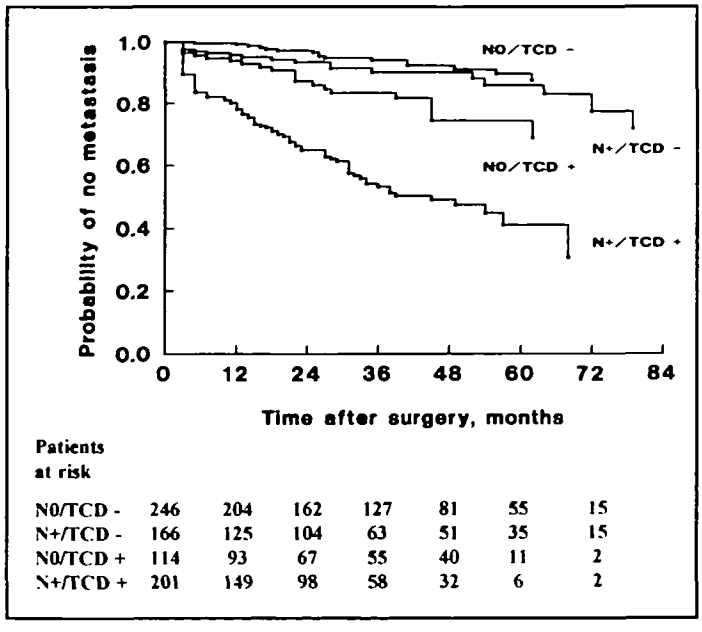

Fig. 4. Distant disease-free survival of patients with axillary lymph node-negative (N0) or node-positive (N+) breast cancer according to the presence or absence of micrometastatic tumor cell detection (TCD) in the bone marrow (TCD+ or TCD–, respectively; $P<.001$; logrank test). Events/numbers of patients at risk plus 95% confidence intervals (in parentheses) for the disease-free survival probability at 3 years for the different groups are as follows: N0/TCD–, 17/246 (0.84-0.96); N+/TCD–, 17/166 (0.90-0.98); N0/TCD+, 18/114 (0.75-0.92); and N+/TCD+, 91/201 (0.45-0.61).

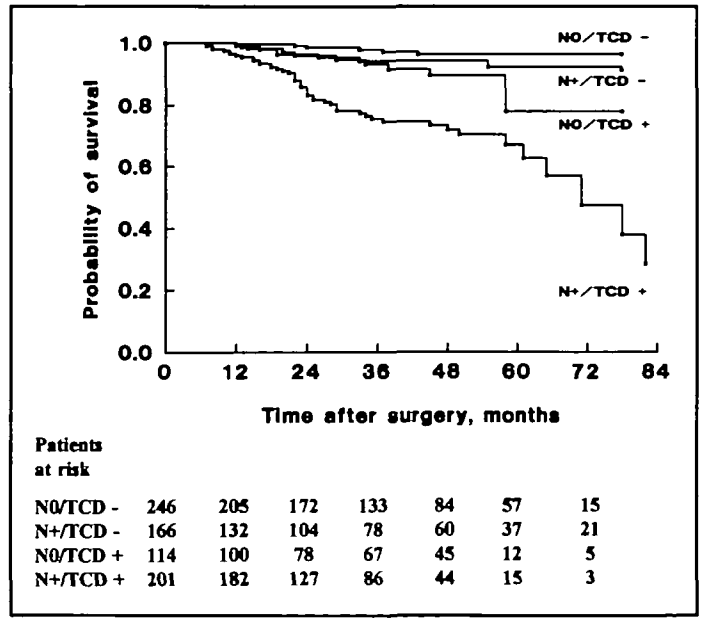

Fig. 5. Overall survival of patients with axillary lymph node-negative (N0) or node-positive (N+) breast cancer according to the presence or absence of micrometastatic tumor cell detection (TCD) in bone marrow (TCD+ or TCD–, respectively; $P<.001$; logrank test). Events/numbers of patients at risk plus 95% confidence intervals (in parentheses) for the overall survival probability at 3 years for the different groups are as follows: N0/TCD–, 4/246 (0.94-1); N+/TCD–, 8/166 (0.91-0.99); N0/TCD+, 9/114 (0.87-0.99); and N+/TCD+, 48/201 (0.67-0.82).

Table 3. Results of multivariate analysis (Cox regression stratified by adjuvant therapy) comparing tumor cell detection (TCD) in bone marrow and dichotomized nodal status in 727 patients with breast cancer of different tumor (T) size*

T size	Prognostic factor	*P*	RR	95% CI
T1 (n = 258)	TCD (positive, negative)	<.001	7.30	2.53-21.2
	Nodal status (N0/N+)	.29	2.00	0.55-7.2
T2 (n = 323)	TCD (positive, negative)	<.001	2.57	1.5-4.4
	Nodal status (N0/N+)	.014	2.43	1.2-4.91
T3-4 (n = 146)	TCD (positive, negative)	.004	4.24	1.6-11.3
	Nodal status (N0/N+)	.04	5.55	1.08-28.6
T1-4 (n = 727)	TCD (positive, negative)	<.001	4.33	2.87-6.52
	Nodal status (N0/N+)	<.001	2.98	1.74-5.1

*Tumor staging according to International Union Against Cancer criteria (*13*). RR = relative risk; CI = confidence interval.

an initial period of testing different antibodies for our cell-detection method, we decided to use the monoclonal antibody 2E11 (also called BM2 = breast mucin 2) (*29*). The detection frequency in our patients has been 43%-45% and has remained unchanged in recent years.

As shown previously, the timing of bone marrow aspiration before or after surgery has no influence on the detection frequency (*11,12*). Tumor cells could not be identified by our immunostaining method in any of 21 cancer-free control subjects. Nevertheless, one of the problems with immunocytologic detection of tumor cells is the distinction of cross-reactive cells. In 22 slides, basophilic myelocytes and monocytes were also stained; all patients except one displayed tumor cells concomitantly on these smears. Therefore, cross-reactivity did not influence our detection results.

An important consideration in assessing the prognostic value of TCD is the selection criteria for the patients. We felt that it was important to exclude all patients who developed metastases shortly after primary therapy. These patients were considered to have been metastasis positive but not recognized by conventional diagnostic means. Thus, 12 women with bone metastases in the first 3 months after surgery were excluded (all of these patients had tumor cells in their bone marrow). Patients who had had a breast lumpectomy performed prior to definitive surgery and bone marrow aspiration (n = 5) were also not included in the study to avoid selection bias caused by a possible reduction in the number of tumor cells in the bone marrow due to the previous removal of the primary tumor (*30*).

TCD and Nodal Status: the Prognostic Impact

Our data clearly show that TCD is an independent prognostic indicator for patients with primary breast cancer, relating significantly to distant disease-free survival and overall survival. One of the most striking findings is the approximately 30% frequency of positive bone marrow smears for patients with small tumors (T1) and for those who were classified as being lymph node negative, suggesting that tumor-cell shedding occurs during breast cancer's early stages. TCD is strongly associated with the subsequent development not only of osseous (76%) but also nonbone metastases (73%) and even with locoregional relapses (62%). These data suggest that tumor cells in bone marrow reflect the ability of the primary tumor to metastasize and, therefore, that the cells represent a marker for systemic disease that is not limited to bone. Multivariate regression analysis revealed that TCD is a significant and independent prognostic indicator for breast cancer. This finding also held true for patients who were not treated further after surgery.

As shown in Figs. 4 and 5, the worst prognosis was associated with the presence of tumor cells in both axillary lymph nodes and bone marrow, followed by positive cell detection in bone marrow and the lymph nodes being classified as negative. If TCD in bone marrow is negative, lymph node status does not provide additional information on prognosis. Thus far, none of the evaluated prognostic indicators has had a similar impact with regard to node-negative disease; however, marrow positivity is associated with the speed of relapse, and the follow-up is modest. At this point, we cannot rule out that TCD might be a marker for tumor burden and, therefore, for early recurrence.

In patients with tumors less than 2 cm in diameter (T1), TCD showed a better ability (RR = 7.3) to predict distant relapse than did nodal status (RR = 2.00). However, regression analysis revealed that the prognostic value of TCD and nodal status for T2 and T3-4 tumors did not differ (Table 3). This direct comparison between tumor cells in bone marrow and nodal status may be biased, since the decision to give adjuvant therapy depended in part on the nodal status of the patients. Although the multivariate statistical analysis was stratified on the basis of adjuvant treatment, it cannot be ruled out that the prognostic value of nodal status is thereby underestimated to some extent.

The results of the present study provide consistent evidence that TCD is a prognostic indicator independent of nodal status. The question might be raised as to whether bone marrow aspiration could replace axillary dissection (i.e., nodal status) in some subgroups of patients with breast cancer whose axillary lymph nodes are expected to be negative (e.g., clinically negative axilla and tumors less than 2 cm in diameter). Axillary lymph node involvement has been the best marker of disease behavior and ultimate outcome until recently (*1,31*). However, since 1985, there has been debate about the extent of axillary dissection that is required and, indeed, whether axillary surgery is necessary at all (*32-36*).

Axillary dissection is done for tumor staging and local disease control (*37,38*). However, there is evidence that axillary lymph nodes are not a barrier to invading breast cancer cells and that hematogenous spread dictates the eventual fate of the patient (*39,40*). TCD provides reliable information on prognosis, especially in patients with small tumors and node-negative disease. If axillary dissection is omitted in patients with clinically uninvolved lymph nodes, TCD will reveal women at risk, not only

for locoregional relapse, but also for distant metastasis. In this situation, adjuvant systemic therapy should be considered to be more important than axillary dissection. In two prospective trials by the National Surgical Adjuvant Breast and Bowel Project (*32*) and the Cancer Research Campaign Working Party (*41*), randomly assigning clinically node-negative patients to either radical mastectomy or simple mastectomy yielded no difference in overall survival rates. Increased numbers of local recurrences could be explained by the inclusion of patients with tumors of more than 2 cm. Furthermore, surgery-related morbidity affects approximately 10% of patients and consists of axillary seromas, dysesthesia, and lymph edema (*3*). In contrast, complications of bone marrow aspiration are negligible, thus making this procedure cost-effective ($150-$200). Nevertheless, our data do not allow any definitive conclusions because all patients received axillary dissection. This aspect can be answered only by a prospective study comparing adjuvant therapies stratified according to TCD and lymph node status in a randomized manner. Important prerequisites for such a study are the confirmation of our results, with good quality control, at other institutions and the definition of cutoff criteria in concert with independent pathologic review.

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Note

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