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Micrometastases or Isolated Tumor Cells and the Outcome of Breast Cancer

Maaike de Boer, M.D., Carolien H.M. van Deurzen, M.D., Jos A.A.M. van Dijck, Ph.D., George F. Borm, Ph.D., Paul J. van Diest, M.D., Ph.D., Eddy M.M. Adang, Ph.D., Johan W.R. Nortier, M.D., Ph.D., Emiel J.T. Rutgers, M.D., Ph.D., Caroline Seynaeve, M.D., Ph.D., Marian B.E. Menke-Pluymers, M.D., Ph.D., Peter Bult, M.D., Ph.D., and Vivianne C.G. Tjan-Heijnen, M.D., Ph.D.

ABSTRACT

BACKGROUND

The association of isolated tumor cells and micrometastases in regional lymph nodes with the clinical outcome of breast cancer is unclear.

METHODS

We identified all patients in the Netherlands who underwent a sentinel-node biopsy for breast cancer before 2006 and had breast cancer with favorable primary-tumor characteristics and isolated tumor cells or micrometastases in the regional lymph nodes. Patients with node-negative disease were randomly selected from the years 2000 and 2001. The primary end point was disease-free survival.

RESULTS

We identified 856 patients with node-negative disease who had not received systemic adjuvant therapy (the node-negative, no-adjuvant-therapy cohort), 856 patients with isolated tumor cells or micrometastases who had not received systemic adjuvant therapy (the node-positive, no-adjuvant-therapy cohort), and 995 patients with isolated tumor cells or micrometastases who had received such treatment (the node-positive, adjuvant-therapy cohort). The median follow-up was 5.1 years. The adjusted hazard ratio for disease events among patients with isolated tumor cells who did not receive systemic therapy, as compared with women with node-negative disease, was 1.50 (95% confidence interval [CI], 1.15 to 1.94); among patients with micrometastases, the adjusted hazard ratio was 1.56 (95% CI, 1.15 to 2.13). Among patients with isolated tumor cells or micrometastases, the adjusted hazard ratio was 0.57 (95% CI, 0.45 to 0.73) in the node-positive, adjuvant-therapy cohort, as compared with the node-positive, no-adjuvant-therapy cohort.

CONCLUSIONS

Isolated tumor cells or micrometastases in regional lymph nodes were associated with a reduced 5-year rate of disease-free survival among women with favorable early-stage breast cancer who did not receive adjuvant therapy. In patients with isolated tumor cells or micrometastases who received adjuvant therapy, disease-free survival was improved.

From the Division of Medical Oncology, Maastricht University Medical Center, Maastricht (M.B., V.C.G.T.-H.); Comprehensive Cancer Center East (M.B., J.A.A.M.D.) and the Divisions of Epidemiology, Biostatistics, and HTA (J.A.A.M.D., G.F.B., E.M.M.A.) and Pathology (P.B.), Radboud University Nijmegen Medical Center, Nijmegen; the Division of Pathology, University Medical Center Utrecht, Utrecht (C.H.M.D., P.J.D.); the Division of Medical Oncology, Leiden University Medical Center, Leiden (J.W.R.N.); the Division of Surgery, the Netherlands Cancer Institute, Amsterdam (E.J.T.R.); and the Divisions of Medical Oncology (C.S.) and Surgery (M.B.E.M.-P.), Erasmus Medical Center–Daniel den Hoed Cancer Center, Rotterdam — all in the Netherlands. Address reprint requests to Dr. Tjan-Heijnen at the Division of Medical Oncology, Department of Internal Medicine, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands, or at vcg.tjan.heijnen@mumc.nl.

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The status of the axillary lymph nodes is the most important prognostic factor in breast cancer.[1] These nodes can be sampled by axillary lymph-node dissection or sentinel-node biopsy with or without subsequent axillary lymph-node dissection (these additional lymph nodes are denoted as nonsentinel nodes). Detailed examination of the sentinel node by means of serial sectioning with optional immunohistochemical staining permits the detection of small metastases or isolated tumor cells.[2-4] Isolated tumor cells (staged as pN0[i+], with deposits ≤0.2 mm) and micrometastases (staged as pN1mi, with deposits >0.2 to ≤2.0 mm) have been separate categories in the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* since 2002.[5] The cutoff value of 0.2 mm was chosen arbitrarily.

Most studies of the association of minimal lymph-node involvement with prognosis have included patients who received a diagnosis of breast cancer before the use of sentinel-node biopsy became widespread. Moreover, isolated tumor cells were seldom distinguished from micrometastases, which made their prognostic relevance debatable.[6-10]

The Dutch guidelines regarding the treatment of breast cancer do not recommend systemic adjuvant therapy for low-risk breast cancer with isolated tumor cells in a regional lymph node. Moreover, because of insufficient evidence concerning micrometastases and prognosis, the guidelines provide no advice with respect to systemic adjuvant therapy for low-risk breast cancer with nodal micrometastases.[11] Consequently, some patients with breast cancer and micrometastases in the Netherlands receive systemic adjuvant therapy, and others do not. The aim of the MIRROR (Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish?) study was to evaluate the relationship, if any, between isolated tumor cells or micrometastases in the regional lymph nodes and clinical outcome in patients who had undergone a sentinel-node procedure and who did or did not receive systemic adjuvant therapy.

Methods

Patients

We identified women with invasive breast cancer who had undergone a sentinel-node biopsy before 2006 from the Netherlands Cancer Registry. We included consecutive patients with favorable primary tumor characteristics (i.e., tumors of ≤1 cm in diameter, irrespective of grade, or tumors >1 to ≤3 cm, grade 1 or 2) for whom systemic adjuvant therapy was not indicated according to the Dutch guidelines, version 2002.[12] Among these women, we selected only patients with a final nodal status of isolated tumor cells or micrometastases detected on microscopical examination of the sentinel and nonsentinel lymph nodes (in patients who subsequently underwent axillary lymph-node dissection). If both the sentinel node and the nonsentinel node contained metastases, the largest metastasis determined the final nodal status. According to the guidelines, axillary lymph-node dissection was generally recommended if isolated tumor cells or micrometastases were detected in the sentinel node.[12] Table 1 lists the proportion of patients in each cohort who underwent axillary lymph-node dissection.

In addition to these patients, we randomly selected a control group of 1000 patients who had breast cancer that was classified as low-risk, node-negative disease and who underwent breast surgery and a sentinel-node biopsy with or without an axillary lymph-node dissection in the period from 2000 through 2001. We excluded patients who received neoadjuvant chemotherapy, had bilateral breast cancer, had a history of cancer, or had node-negative disease and received systemic adjuvant therapy. All 113 Dutch hospitals and 60 pathology laboratories participated in the study (see Table 1 of the Supplementary Appendix, available with the full text of this article at NEJM.org). The review board of the Netherlands Cancer Registry approved this study. The ethics committee of Maastricht University Medical Center concluded that no informed consent was required for this retrospective, observational study.

Data Collection

Registration clerks of all eight comprehensive cancer centers in the Netherlands collected data on patient and tumor characteristics, breast surgery, the sentinel-node biopsy, axillary lymph-node dissection, radiotherapy, systemic adjuvant therapy, the recurrence of disease or the occurrence of another malignant condition, and death during follow-up.

Pathological Review

Three pathologists who specialized in breast cancer reviewed all available original slides of the

Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients (N=2707)	Node-Negative, No Adjuvant Therapy (N=856)	Node-Positive, No Adjuvant Therapy (N=856)	P Value†	Node-Positive, Adjuvant Therapy (N=995)	P Value‡
Age at diagnosis — yr				<0.001		0.76
Median	57	59	57		56	
Range	30–93	30–89	32–93		31–88	
Tumor size — no. (%)						
≤1 cm	801 (29.6)	346 (40.4)	236 (27.6)	<0.001	219 (22.0)	<0.001
>1 to ≤2 cm	1523 (56.3)	448 (52.3)	516 (60.3)		559 (56.2)	
>2 to ≤3 cm	383 (14.1)	62 (7.2)	104 (12.1)		217 (21.8)	
Tumor grade — no. (%)						
1	910 (33.6)	317 (37.0)	308 (36.0)	0.25	285 (28.6)	0.003
2	1618 (59.8)	474 (55.4)	499 (58.3)		645 (64.8)	
3	135 (5.0)	49 (5.7)	36 (4.2)		50 (5.0)	
Unknown	44 (1.6)	16 (1.9)	13 (1.5)		15 (1.5)	
Tumor type — no. (%)						
Ductal	2065 (76.3)	652 (76.2)	643 (75.1)	0.03	770 (77.4)	0.52
Lobular	293 (10.8)	76 (8.9)	106 (12.4)		111 (11.2)	
Other	349 (12.9)	128 (15.0)	107 (12.5)		114 (11.5)	
Expression of estrogen receptors, progesterone receptors, or both — no. (%)						
Yes	2468 (91.2)	761 (88.9)	768 (89.7)	0.14	939 (94.4)	0.001
No	160 (5.9)	50 (5.8)	67 (7.8)		43 (4.3)	
Unknown	79 (2.9)	45 (5.3)	21 (2.5)		13 (1.3)	
Nodal status — no. (%)§						
pN0	856 (31.6)	856 (100.0)	—	NA	—	NA
pN0(i+)	819 (30.3)	—	513 (59.9)	NA	306 (30.8)	0.001
pN1mi	1032 (38.1)	—	343 (40.1)		689 (69.2)	
Type of surgery — no. (%)						
Breast-conserving surgery	1922 (71.0)	633 (73.9)	599 (70.0)	0.07	690 (69.3)	0.77
Mastectomy	785 (29.0)	223 (26.1)	257 (30.0)		305 (30.7)	
No. of sentinel lymph nodes removed				<0.001		0.17
Mean	1.9	1.8	2.0		1.9	
Range	1–14	1–9	1–14		1–9	
Axillary lymph-node dissection — no. (%)						
No	1370 (50.6)	736 (86.0)	389 (45.4)	<0.001	245 (24.6)	<0.001
Yes	1337 (49.4)	120 (14.0)	467 (54.6)		750 (75.4)	
Axillary lymph-node dissection, axillary irradiation, or both — no. (%)						
No	1218 (45.0)	732 (85.5)	333 (38.9)	<0.001	153 (15.4)	<0.001
Yes	1489 (55.0)	124 (14.5)	523 (61.1)		842 (84.6)	
Systemic adjuvant therapy — no. (%)						
Hormonal therapy	627 (23.2)	—	—	NA	627 (63.0)	NA
Chemotherapy	60 (2.2)	—	—		60 (6.0)	
Both	308 (11.4)	—	—		308 (31.0)	

* NA denotes not applicable.
† P values are for the comparison of the node-negative, no-adjuvant-therapy cohort with the node-positive, no-adjuvant-therapy cohort.
‡ P values are for the comparison of the node-positive, no-adjuvant-therapy cohort with the node-positive, adjuvant-therapy cohort.
§ Nodal status is the final nodal status after sentinel-node biopsy, with or without axillary lymph-node dissection, and after central review.

sentinel nodes and of positive nodes obtained from patients who underwent an axillary lymph-node dissection. These included slides stained with hematoxylin and eosin, slides stained for immunohistochemical analysis, and frozen sections. Additional sections were not obtained, and new immunohistochemical staining was not performed. The grade of the primary tumor was assessed if it was not available from the original pathology report.

Almost all participating pathology laboratories used a protocol in which the sentinel node was serially sectioned at least every 150 μm and at a minimum of three levels, with the use of keratin immunohistochemical staining if the hematoxylin and eosin staining was negative. In contrast, the nonsentinel nodes were macroscopically sectioned every 2 to 5 mm, and one section per slice was stained with hematoxylin and eosin.[13] Tumor deposits were classified according to the sixth edition of the AJCC *Cancer Staging Manual*.[5]

COHORTS

We identified three cohorts: patients with node-negative disease who did not receive systemic adjuvant therapy (the node-negative, no-adjuvant-therapy cohort), patients with isolated tumor cells or micrometastases in the regional lymph nodes who did not receive systemic adjuvant therapy (the node-positive, no-adjuvant-therapy cohort), and patients with isolated tumor cells or micrometastases in the regional lymph nodes who received systemic adjuvant therapy (the node-positive, adjuvant-therapy cohort). Adjuvant therapy was defined as any type of hormonal therapy, chemotherapy, or both.

To determine whether an association exists between the presence or absence of isolated tumor cells or micrometastases in the regional lymph nodes and outcome, we compared the outcome for patients in the node-negative, no-adjuvant-therapy cohort with the outcome for patients in the node-positive, no-adjuvant-therapy cohort. For this latter cohort, we performed separate assessments of patients with isolated tumor cells and patients with micrometastases. To determine the effect of systemic adjuvant therapy on the outcome in patients with isolated tumor cells or micrometastases, we compared the outcomes in the cohort of patients who did not receive adjuvant therapy with the outcomes in the adjuvant-therapy cohort.

END POINTS

The primary end point was the 5-year rate of disease-free survival. The period of disease-free survival was defined as the interval from the date of diagnosis to locoregional recurrence, distant metastases, contralateral invasive breast cancer or ductal carcinoma in situ, another malignant condition, or death from any cause, whichever occurred first. Recurrence was a composite end point defined as locoregional recurrence, distant metastases, or invasive cancer or ductal carcinoma in situ in the contralateral breast.

STATISTICAL ANALYSIS

The chi-square test for trend was used to assess baseline differences between ordinal variables, and Student's t-test was used for continuous variables. The Kaplan–Meier method was used to estimate the 5-year rate of disease-free survival. For patients who remained alive and disease-free, data were censored at the date of the last contact.

A Cox proportional-hazards model was used to compare the cohorts and to adjust for known prognostic clinical and pathological variables. In the primary analysis, we included age at diagnosis, tumor size, tumor grade, hormone-receptor status, and form of axillary treatment (node dissection, irradiation, or both, or no axillary treatment). We did not include axillary lymph-node dissection as an additional variable in the Cox proportional-hazards model when comparing the node-negative, no-adjuvant-therapy cohort with the node-positive, no-adjuvant-therapy cohort, since axillary lymph-node dissection is not recommended in patients with a negative sentinel node.[14] To exclude axillary lymph-node dissection as a confounder, we performed a secondary analysis in which axillary lymph-node dissection was included, comparing the node-negative, no-adjuvant-therapy cohort and the node-positive, no-adjuvant-therapy cohort. We did not consider hormone-receptor status when comparing the cohort of patients with isolated tumor cells or micrometastases that received adjuvant therapy with the cohort that did not receive such therapy, since hormone-receptor status partially determined whether a patient was included in the node-positive, no-adjuvant-therapy cohort or the node-positive, adjuvant-therapy cohort.

All reported P values are two-sided, and con-

fidence intervals are at the 95% level. All analyses were performed with the use of SAS software, version 8.2.[15]

RESULTS

PATIENTS

We identified 3181 women with breast cancer from the Netherlands Cancer Registry. We excluded 146 patients (4.6%) because of incomplete or unavailable material for pathological review and 26 patients (0.8%) because of missing baseline characteristics. After pathological review, 302 patients (9.5%) were ineligible because of macrometastases (in 185 patients), unfavorable primary tumor characteristics (in 68 patients), noninvasive breast cancer (in 7 patients), unmeasurable size of metastasis (in 2 patients), or receipt of systemic adjuvant therapy despite favorable node-negative disease (in 40 patients).

The final study involved 2707 women: 856 women with node-negative disease who did not receive systemic adjuvant therapy (31.6%), 856 women with isolated tumor cells or micrometastases who did not receive adjuvant therapy (31.6%), and 995 women with isolated tumor cells or micrometastases who received adjuvant therapy (36.8%).

Table 1 shows the baseline characteristics of the three cohorts. In the node-positive, no-adjuvant-therapy cohort as compared with the node-negative cohort, the tumors were larger (P<0.001), more patients had lobular carcinoma (P=0.03), and more patients had undergone axillary lymph-node dissection (P<0.001). In the node-positive, adjuvant-therapy cohort as compared with the node-positive, no-adjuvant-therapy cohort, the tumors were larger (P<0.001), the differentiation grade was poorer (P=0.003), more patients had micrometastases in the regional nodes (P<0.001), and more patients had undergone axillary lymph-node dissection (P<0.001). Other differences (e.g., age at diagnosis, number of sentinel nodes removed, and hormone-receptor status) were small in absolute terms, though they were statistically significant (Table 1).

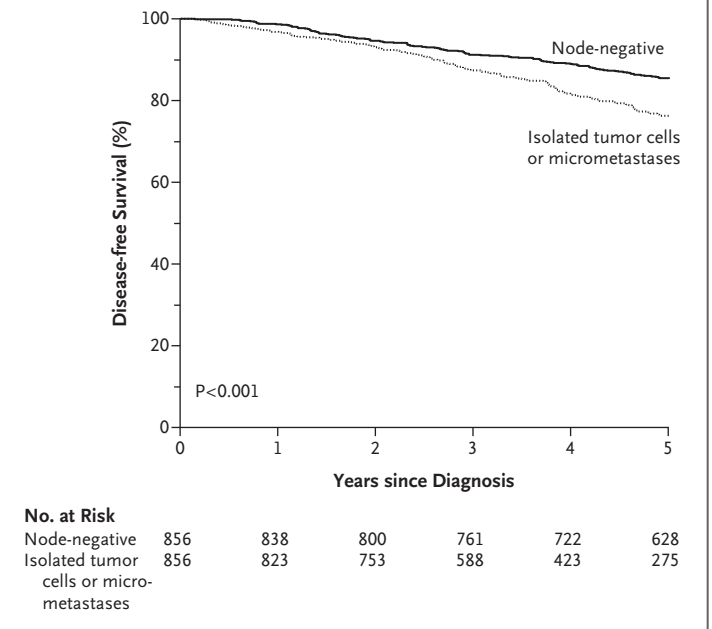
The median duration of follow-up was 5.1 years (range, 0.04 to 9.3). Ninety-five patients (3.5%) were lost to follow-up within 0.04 to 5.6 years after diagnosis. At the last follow-up, 2261 patients (83.5%) were free of disease.

The components of the composite end point of recurrence (contralateral breast cancer, locoregional recurrence, and distant metastases) all showed the same trend as that reported for the overall end point of disease recurrence (see Table 2 in the Supplementary Appendix). More detailed analyses of each of the components were not possible, however, because of the small number of events.

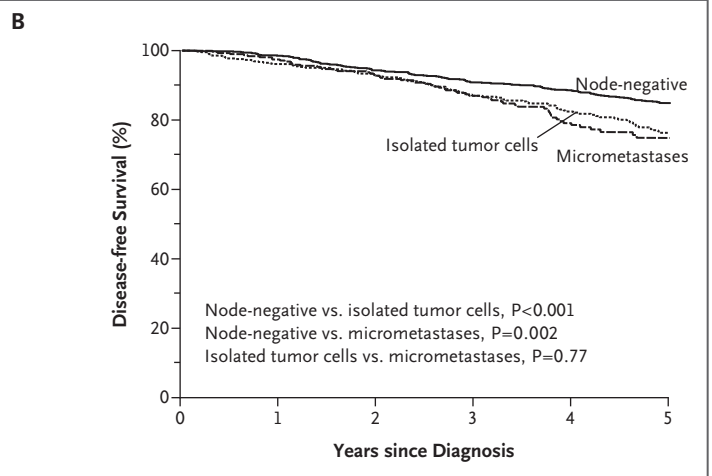
NODE-NEGATIVE, NO-ADJUVANT-THERAPY COHORT VS. NODE-POSITIVE, NO-ADJUVANT-THERAPY COHORT

The unadjusted 5-year rate of disease-free survival in the node-positive, no-adjuvant-therapy cohort was significantly reduced as compared with that in the node-negative, no-adjuvant-therapy cohort (76.5% vs. 85.7%, P<0.001) (Fig. 1A). Patients with isolated tumor cells who did not receive adjuvant therapy had a significantly reduced 5-year rate of disease-free survival as compared with patients in the node-negative, no-adjuvant-therapy cohort (77.2% vs. 85.7%, P<0.001) (Fig. 1B), and patients with micrometastases who did not receive adjuvant therapy had a significantly reduced 5-year rate of disease-free survival as compared with patients in the node-negative, no-adjuvant-therapy cohort (75.9% vs. 85.7%, P=0.002) (Fig. 1B). In the cohort of node-positive patients who did not receive adjuvant therapy, the 5-year rate of disease-free survival was similar among patients with isolated tumor cells and those with micrometastases (77.2% and 75.9%, respectively; P=0.77).

After adjustment for age at diagnosis, tumor size, tumor grade, and hormone-receptor status, there was an increased risk of events in the node-positive, no-adjuvant-therapy cohort as compared with the node-negative, no-adjuvant-therapy cohort (hazard ratio, 1.51; 95% confidence interval [CI], 1.20 to 1.90) (Table 2). The hazard ratio among women with isolated tumor cells who did not receive adjuvant therapy, as compared with the node-negative, no-adjuvant-therapy cohort, was 1.50 (95% CI, 1.15 to 1.94), and the hazard ratio among women with micrometastases, as compared with the node-negative women, was 1.56 (95% CI, 1.15 to 2.13) (Table 2). Age at diagnosis, tumor size, tumor grade, and hormone-receptor status were also associated with the risk of events (Table 2). When axillary lymph-node dissection was included in the model, the results were essentially the same (Table 3 in the Supplementary Appendix).



No. at Risk						
Node-negative	856	838	800	761	722	628
Isolated tumor cells or micrometastases	856	823	753	588	423	275



No. at Risk						
Node-negative	856	838	800	761	722	628
Isolated tumor cells	513	493	453	367	282	199
Micrometastases	343	330	301	222	142	76

Figure 1. Disease-free Survival among Patients with Early Breast Cancer with or without Isolated Tumor Cells or Micrometastases Who Did Not Receive Systemic Adjuvant Therapy.

Panel A shows disease-free survival among patients with node-negative disease and among patients with isolated tumor cells or micrometastases. Panel B shows disease-free survival among patients with node-negative disease, patients with isolated tumor cells, and patients with micrometastases.

NO ADJUVANT THERAPY VS. ADJUVANT THERAPY AMONG NODE-POSITIVE PATIENTS

The unadjusted 5-year rate of disease-free survival among women with isolated tumor cells or micrometastases who did not receive adjuvant therapy was significantly reduced as compared with the rate in the node-positive, adjuvant-therapy cohort (76.5% vs. 86.2%, P<0.001) (Fig. 2A). Patients with isolated tumor cells who did not receive adjuvant therapy had a significantly reduced 5-year rate of disease-free survival as compared with women who did receive adjuvant therapy (77.2% vs. 83.0%, P=0.04) (Fig. 2B). Among women with micrometastases, the 5-year rate of disease-free survival was significantly reduced in the no-adjuvant-therapy cohort as compared with the adjuvant-therapy cohort (75.9% vs. 87.9%, P<0.001) (Fig. 2C). Within the node-positive, adjuvant-therapy cohort, the 5-year rate of disease-free survival did not differ significantly between patients with isolated tumor cells and those with micrometastases (83.0% and 87.9%, respectively; P=0.09).

After adjustment for age at diagnosis, tumor size, tumor grade, and axillary treatment or no axillary treatment, there remained a reduced risk of events in the node-positive, adjuvant-therapy cohort as compared with the node-positive, no-adjuvant-therapy cohort (hazard ratio, 0.57; 95% CI, 0.45 to 0.73) (Table 3). The hazard ratios were similar for patients with isolated tumor cells (0.66; 95% CI, 0.46 to 0.95) and those with micrometastases (0.50; 95% CI, 0.35 to 0.72) (Table 3). Also, age at diagnosis, tumor size, tumor grade, and axillary treatment or no axillary treatment were associated with the risk of events (Table 3).

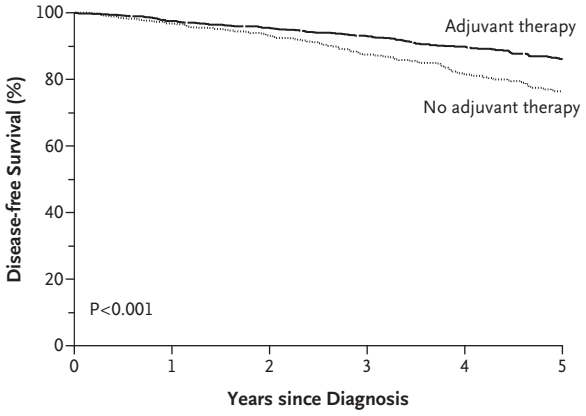
In the node-positive, adjuvant-therapy cohort, the subgroup of patients who received chemotherapy only was small (60 patients), which limited statistical analysis according to treatment, though patients who received combined chemotherapy and endocrine treatment seemed to have the largest benefit, as compared with patients in the node-positive, no-adjuvant-therapy cohort (adjusted hazard ratio, 0.34; 95% CI, 0.21 to 0.55). The outcomes according to the type of adjuvant systemic therapy are shown in Tables 4 and 5 in the Supplementary Appendix.

Table 2. Cox Proportional-Hazards Model of the Effect of Variables on Events According to the Presence or Absence of Isolated Tumor Cells or Micrometastases.

Variable	Node-Negative vs. Isolated Tumor Cells or Micrometastases, All with No Adjuvant Therapy		Node-Negative vs. Isolated Tumor Cells, Both with No Adjuvant Therapy		Node-Negative vs. Micrometastases, Both with No Adjuvant Therapy	
	Hazard Ratio for Events (95% CI)	P Value	Hazard Ratio for Events (95% CI)	P Value	Hazard Ratio for Events (95% CI)	P Value
Node-negative	1.00		1.00		1.00	
Isolated tumor cells or micrometastases	1.51 (1.20–1.90)	<0.001	—	—	—	—
Isolated tumor cells	—	—	1.50 (1.15–1.94)	0.003	—	—
Micrometastases	—	—	—	—	1.56 (1.15–2.13)	0.005
Age at diagnosis — yr*	1.01 (1.00–1.02)	0.02	1.02 (1.01–1.03)	0.002	1.01 (1.00–1.02)	0.17
Tumor size†	1.22 (1.02–1.46)	0.03	1.25 (1.03–1.52)	0.02	1.20 (0.97–1.49)	0.10
Tumor grade						
1	1.00		1.00		1.00	
2	1.54 (1.19–1.99)	0.001	1.76 (1.31–2.36)	<0.001	1.51 (1.10–2.08)	0.01
3	2.14 (1.27–3.60)	0.004	2.40 (1.35–4.27)	0.003	2.31 (1.27–4.22)	0.006
Expression of estrogen receptors, progesterone receptors, or both						
Yes	1.00		1.00		1.00	
No	1.50 (1.03–2.20)	0.04	1.62 (1.06–2.46)	0.02	1.32 (0.80–2.16)	0.28

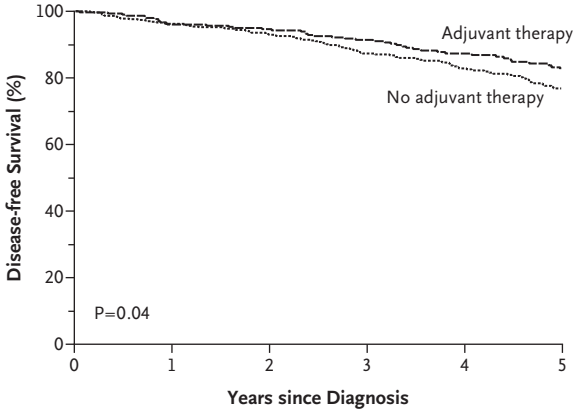
* Age was modeled as a continuous variable.
† The hazard ratio is for a doubling of the tumor diameter.

A Patients with Isolated Tumor Cells or Micrometastases



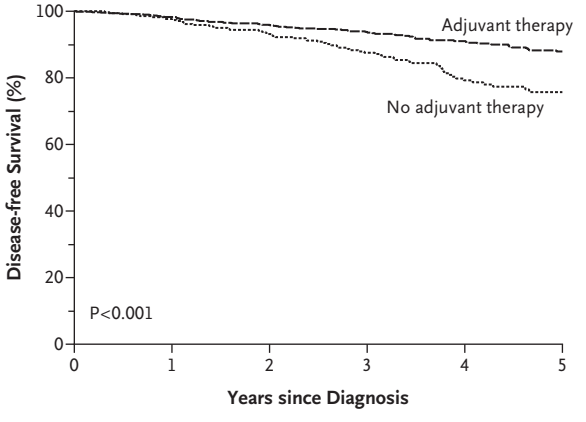
No. at Risk						
No adjuvant therapy	856	823	753	588	423	275
Adjuvant therapy	995	968	929	751	565	402

B Patients with Isolated Tumor Cells



No. at Risk						
No adjuvant therapy	513	493	453	367	282	199
Adjuvant therapy	306	293	285	249	199	148

C Patients with Micrometastases



No. at Risk						
No adjuvant therapy	343	330	301	222	142	76
Adjuvant therapy	689	675	644	502	366	254

Figure 2 (facing page). Disease-free Survival among Patients with Early Breast Cancer and Isolated Tumor Cells or Micrometastases Who Received Systemic Adjuvant Therapy and Those Who Did Not.

Panel A shows disease-free survival among all patients with isolated tumor cells or micrometastases, Panel B shows disease-free survival among patients with isolated tumor cells, and Panel C shows disease-free survival among patients with micrometastases.

DISCUSSION

In this study, we determined whether a relationship exists between disease-free survival and the presence of isolated tumor cells or micrometastases as the final nodal status in women with favorable primary-tumor characteristics who underwent a sentinel-node biopsy. All sentinel nodes and positive nonsentinel nodes were centrally reviewed, and separate analyses of the outcomes of patients who did or did not receive systemic adjuvant therapy were performed. We found that micrometastases or isolated tumor cells in the regional lymph nodes were associated with an absolute reduction in the 5-year rate of disease-free survival of nearly 10 percentage points. Among patients who received systemic adjuvant therapy, the 5-year rate of disease-free survival was significantly improved, with an absolute benefit of nearly 10 percentage points.

The presence of tumor-cell deposits in regional lymph nodes may reflect the potential of the primary tumor to metastasize. The size of the tumor deposit may not be an influence on the outcome, since patients with isolated tumor cells or micrometastases had a comparably poor 5-year rate of disease-free survival. We did not differentiate between single tumor cells (which may not have metastatic potential)[16,17] and clusters of cells with an unknown potential for metastasis; this difference requires clarification. In current staging systems for breast cancer, lymph nodes containing micrometastases are classified as node-positive (pN1mi), whereas nodes containing isolated tumor cells are classified as node-negative (pN0[i+]).[5,18] In view of our results, a reevaluation of the current AJCC classification is warranted.

Since the introduction of the sentinel-node biopsy, there has been renewed interest in the prognostic implications of the presence of isolated tumor cells and micrometastases. Most previous studies have shown reduced survival among women with occult metastases in lymph nodes, as compared with women with no nodal metastases, although the difference was not always confirmed in multivariate analyses.[6-8,19,20] Large studies that included women who received a diagnosis before the sentinel-node era showed that micrometastases, defined as 2 mm or smaller in diameter and including isolated tumor cells, were associated with reduced overall survival.[9,10,21-24] In these studies, however, the axillary nodes were examined by means of hematoxylin and eosin staining at just one level. Thus, we cannot compare these studies with ours, which involved a detailed examination of the sentinel node. The few previous studies of sentinel nodes were limited by small samples, lack of multivariate analyses, or short follow-up.[25-27]

A drawback of our study is that most of our patients received a diagnosis when the Dutch guidelines for management of breast cancer were conservative, advising systemic adjuvant therapy in patients with node-negative disease only if the estimated 10-year probability of overall survival was less than 80%.[12] Now, because of changes in the guidelines, more patients receive systemic therapy.[11] Therefore, isolated tumor cells or micrometastases should have a smaller influence on disease-free survival among patients with early-stage breast cancer. However, since chemotherapy now usually consists of potent third-generation regimens, instead of the first- or second-generation regimens that were given in 69% and 29%, respectively, of our patients who received chemotherapy, the impact of systemic therapy should be increased.

In this cohort study, the decision to administer systemic adjuvant therapy was at the discretion of the physician. We corrected for factors that might have influenced this decision, such as age at diagnosis, tumor size, and tumor grade. To rule out axillary lymph-node dissection as a confounder, we performed an additional analysis of the node-negative, no-adjuvant-therapy cohort versus the node-positive, no-adjuvant-therapy cohort with this variable included in the model, with essentially the same outcome (Table 3 in the Supplementary Appendix). No conclusion was possible regarding the effect of axillary lymph-node dissection on disease-free survival and the recur-

Table 3. Cox Proportional-Hazards Model of the Effect of Variables on Events According to Whether Adjuvant Therapy Was Received.

Variable	Node-Positive, No Adjuvant Therapy vs. Node-Positive, Adjuvant Therapy		Isolated Tumor Cells without Therapy vs. Isolated Tumor Cells with Therapy		Micrometastases without Therapy vs. Micrometastases with Therapy	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Node-positive, no-adjuvant-therapy cohort	1.00		—	—	—	—
Isolated tumor cells	—	—	1.00		—	—
Micrometastases	—	—	—	—	1.00	
Node-positive, adjuvant-therapy cohort	0.57 (0.45–0.73)	<0.001	—	—	—	—
Isolated tumor cells	—	—	0.66 (0.46–0.95)	0.02	—	—
Micrometastases	—	—	—	—	0.50 (0.35–0.72)	<0.001
Age at diagnosis — yr*	1.02 (1.01–1.03)	<0.001	1.03 (1.02–1.05)	<0.001	1.01 (1.00–1.03)	0.08
Tumor size†	1.28 (1.05–1.57)	0.01	1.34 (1.03–1.75)	0.03	1.19 (0.87–1.61)	0.27
Tumor grade						
1	1.00		1.00		1.00	
2	1.34 (1.03–1.75)	0.03	1.38 (0.95–1.99)	0.09	1.28 (0.86–1.89)	0.22
3	1.83 (0.98–3.44)	0.06	1.71 (0.64–4.59)	0.28	1.76 (0.77–4.04)	0.18
Axillary lymph-node dissection, axillary irradiation, or both						
Yes	1.00		1.00		1.00	
No	1.36 (1.06–1.76)	0.02	1.24 (0.89–1.74)	0.20	1.63 (1.07–2.48)	0.02

* Age was modeled as a continuous variable.
† The hazard ratio is for a doubling of the tumor diameter.

rence rate in the axilla. To address that question, analyses have to be based on the sentinel-node status instead of the final nodal status.

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