ARTICLE

Breast Cancer Prognosis and Occult Lymph Node Metastases, Isolated Tumor Cells, and Micrometastases

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Background	The prognostic relevance of isolated tumor cells and micrometastases in lymph nodes from patients with breast cancer has become a major issue since the introduction of the sentinel lymph node procedure. We conducted a systematic review of this issue.
Methods	Studies published from January 1, 1977, until August 11, 2008, were identified by use of MEDLINE, EMBASE, and the Cochrane Library. A total of 58 studies (total number of patients = 297 533) were included and divided into three categories according to the method for pathological assessment of the lymph nodes: cohort studies with single-section pathological examination of axillary lymph nodes (n = 285 638 patients), occult metastases studies with retrospective examination of negative lymph nodes by step sectioning and/or immunohistochemistry (n = 7740 patients), and sentinel lymph node biopsy studies with intensified work-up of the sentinel but not of the nonsentinel lymph nodes (n = 4155 patients). We used random-effects meta-analyses to calculate pooled estimates of the relative risks (RRs) of 5- and 10-year disease recurrence and death and the multivariably corrected pooled hazard ratio (HR) of overall survival of the cohort studies.
Results	In the cohort studies, the presence (vs the absence) of metastases of 2 mm or less in diameter in axillary lymph nodes was associated with poorer overall survival (pooled HR of death = 1.44, 95% confidence interval [CI] = 1.29 to 1.62). In the occult metastases studies, the presence (vs the absence) of occult metastases was associated with poorer 5-year disease-free survival (pooled RR = 1.55, 95% CI = 1.32 to 1.82) and overall survival (pooled RR = 1.45, 95% CI = 1.11 to 1.88), although these endpoints were not consistently assessed in multivariable analyses. Sentinel lymph node biopsy studies were limited by small patient groups and short follow-up.
Conclusion	The presence (vs the absence) of metastases of 2 mm or less in diameter in axillary lymph nodes detected on single-section examination was associated with poorer disease-free and overall survival.
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Axillary lymph node status is the most important prognostic factor in breast cancer. Prognosis decreases as the number of tumor-positive lymph nodes increases (1). In 1948, Saphir and Amromin (2) reported that a limited number of sections, instead of many sections, taken from axillary lymph nodes were not sufficient to determine whether metastases were present or absent. They serially sectioned lymph nodes that showed no tumor in random sections and called the metastases that were so discovered "obscure" axillary lymph node metastases. Since then, the presence of tumor deposits in axillary lymph node dissection specimens that were initially assessed as negative on routine histological examination has been reported (3–11). In these studies, the frequency of such occult metastases has varied widely, but their prognostic value has remained unclear. In daily clinical practice, moreover, examining all axillary lymph nodes by serial sectioning is not feasible.

This view changed soon after introduction of the sentinel lymph node procedure in the late 1990s (12). To prevent false-negative results and undertreatment, the limited numbers of lymph nodes removed by the sentinel lymph node procedure are now routinely examined by use of a step-sectioning procedure, with or without immunohistochemical staining. However, as could be expected, intensive examination of sentinel lymph nodes resulted in an increased detection of small metastatic tumor deposits, including isolated tumor cells and micrometastases (13), and reopened the discussion on the prognostic value of these small tumor deposits.

Before the sentinel lymph node era, all tumor deposits of 2 mm or less in diameter were classified as lymph node–positive micrometastatic disease. However, the *Cancer Staging Manual of the American Joint Committee on Cancer* (6th edition) in 2002 (14) distinguished between isolated tumor cells and micrometastases because of doubt about the prognostic relevance of isolated tumor cells (6,15–18). Isolated tumor cells are defined as tumor cell clusters that are not more than 0.2 mm in largest diameter and are

denoted as lymph node negative (pN0[i+]). Micrometastases are defined as metastases that are larger than 0.2 mm in diameter but 2 mm or smaller, denoted as lymph node positive (pN1mi).

Systematic reviews (19,20) have been published on the chance of additional nonsentinel lymph node involvement. The chance of an additional nonsentinel lymph node metastasis was approximately 20% among patients with micrometastases in the sentinel lymph nodes (19) and 12% among patients with isolated tumor cells in the sentinel lymph nodes (20). Although several reviews (21–31) have been published on the association between isolated tumor cells and micrometastases in lymph nodes and survival, none have given a complete overview of existing evidence in a systematic way. In this systematic review, we evaluated the association between occult metastases, isolated tumor cells, and micrometastases in axillary lymph nodes of patients with invasive breast cancer and disease-free and overall survival.

Patients and Methods

Literature Search Strategy
We used a protocol according to guidelines for systematic reviews in health care (32) to carry out this systematic review. The literature search was conducted in MEDLINE (from January 1, 1977, through August 1, 2008), EMBASE (from January 1, 1980, through August 11, 2008), and the Cochrane Library (from issue 1, January 1, 1996, through issue 3, July 1, 2008). The search strategy included the following key words that could be variably combined: breast cancer, (sentinel) lymph node(s), isolated tumor cell(s), micrometastases, occult metastases, prognosis, survival rate, mortality, survival analysis, cause of death, disease-free survival, recurrence, and follow-up prediction. All papers in English, German, French, and Dutch were considered. Additionally, the reference lists of selected papers were searched for additional papers.

Study Inclusion Criteria
The following criteria were applied to the papers that were identified by the literature search. Studies were included if patients with occult metastases, isolated tumor cells, or micrometastases in axillary lymph nodes were compared with lymph node–negative patients, after a sentinel lymph node procedure and/or axillary lymph node dissection. Endpoints had to be described in terms of disease-free survival, breast cancer–specific survival, or overall survival. Studies that did not evaluate survival outcomes by life-table analyses or Kaplan–Meier methods were excluded. An exception was made for studies in patients who had undergone a sentinel lymph node procedure (ie, sentinel lymph node biopsy studies), in which survival analyses were rarely carried out because the follow-up time was short. Studies that reported on detection methods by use of molecular biology approaches (such as reverse transcriptase–polymerase chain reaction) and studies in which neoadjuvant chemotherapy was administered were excluded. If duplicate or updated studies were identified, only the more recent study was included. Only full papers that were based on original data were included.

Data Collection
Two independent investigators (M. de Boer and J. A. A. M. van Dijck) extracted data to rule out potential bias or errors.

CONTEXT AND CAVEATS

Prior knowledge
Introduction of the sentinel lymph node biopsy procedure has increased interest in the prognostic value of isolated tumor cells and micrometastases in lymph nodes from patients with breast cancer.

Study design
Systematic review of the literature on the association of isolated tumor cells and micrometastases in lymph nodes with survival that were reported from three study types: cohort studies with single-section pathological examination of axillary lymph nodes, retrospective examination of negative lymph nodes by step sectioning and/or immunohistochemistry, and sentinel lymph node biopsy studies with intensified work-up of the sentinel but not of the nonsentinel lymph nodes.

Contribution
The presence (vs the absence) of metastases that were 2 mm or less in diameter in axillary lymph nodes was associated with poorer overall survival among cohort studies and with poorer overall survival and 5-year disease-free survival among occult metastases studies, although these last two endpoints were not consistently assessed in multivariable analyses. Conclusions could not be drawn from sentinel lymph node biopsy studies because studies were limited by small patient groups and short follow-up.

Implications
Additional studies are required to determine the association between metastases of 2 mm or less in diameter in sentinel lymph nodes and survival.

Limitations
Most studies in this review did not carry out multivariable analyses because of their small size. Individual treatment data were not available from many studies.

From the Editors

Discrepancies were resolved by consensus and if necessary by discussion with a third investigator (V. C. G. Tjan-Heijnen). The following data were extracted from the included papers: pathological assessment of removed lymph nodes; definition of isolated tumor cells, micrometastases, and occult metastases; number of patients without metastases; number of patients with lymph nodes containing isolated tumor cells, micrometastases, or occult metastases; included stages of disease; duration of follow-up; administration of adjuvant systemic therapy; performance of axillary lymph node dissection; definition of endpoints; disease-free, breast cancer–specific, and/or overall survival rates; and results of and factors taken into account in multivariable analyses. When data with respect to survival were not provided in text or a table of an article, they were extracted from the survival curves. Some studies did not report on exact data with respect to outcome of statistical analyses and only reported that there was no statistically significant difference in survival between the lymph node–negative and lymph node–positive group. Therefore, a complete dataset could not always be obtained for every study group evaluated in each study.

Study Categories

We categorized the included studies according to the method for pathological assessment of the lymph nodes, including single or multiple sectioning with or without immunohistochemical staining. In this way, we aimed to show more clearly the differences and similarities between previous and current practice, which includes the sentinel lymph node procedure. We additionally categorized studies according to study type. The first category contained cohort studies of patients with micrometastases and/or isolated tumor cells that were detected through a single-section histological examination without routine use of immunohistochemical staining. The second category contained occult metastases studies of patients who were lymph node negative by histological examination of axillary lymph nodes but had occult metastases (including isolated tumor cells, micrometastases, and macrometastases) by retrospective pathological examination that included step sectioning and/or immunohistochemical staining. The third category contained sentinel node biopsy studies of patients who underwent a sentinel lymph node biopsy optionally followed by an axillary lymph node dissection. In most of the sentinel lymph node biopsy studies, the sentinel lymph node(s) were evaluated by step sectioning with or without immunohistochemical staining, whereas the nonsentinel lymph nodes were evaluated in a single section that was stained with hematoxylin–eosin.

Statistical Analysis

For each cohort study or occult metastases study, we calculated the 5- and 10-year relative risk (RR) of disease recurrence and/or death from any cause for the group with metastases that had a diameter of 2 mm or less or the group with occult metastases; the comparison group for both analyses was the lymph node–negative group. We used random-effects meta-analyses to calculate pooled estimates of the relative risks of 5- and 10-year disease recurrence and death. For some studies, the relative risks were an estimation because they had to be deduced from the Kaplan–Meier curves, and therefore, the standard error of the estimate could not be determined accurately. In that case, we estimated the lower and the upper boundary for the standard error and used the average of the two to carry out the meta-analysis. In a sensitivity analysis, we repeated the meta-analyses that were based on the standard errors that varied between the boundaries. To prevent overlap of data from studies that described subpopulations besides a total population (7,10,33,34), only the total population was taken into account for calculation of the pooled estimates of the relative risks. For cohort studies that were based on overlapping selections from the Surveillance, Epidemiology, and End Results database (35–37), only the largest study was used for calculation of the pooled hazard ratio (HR) (35). For the cohort studies that reported the results of a multivariable proportional hazard analysis, we pooled the hazard ratios of overall survival that were associated with the presence of metastases with a diameter of 2 mm or less by use of a random-effects approach. The heterogeneity index (I^2) was used to evaluate inconsistency between the study results (38). We reported 95% confidence intervals (CIs). All analyses were performed in SAS (version 8.2) (SAS Institute, Cary, NC) (39). All statistical tests were two-sided.

Results

Literature Search

The systematic literature search yielded 953 articles. After screening of abstract and title, full texts of 129 articles were obtained and 45 articles were selected on the basis of the described selection criteria. Four articles (40–43) were excluded because they were based on the same study populations as other, more recent, articles. Five additional articles (16,17,44–46) were included that were identified by the manual review of references of selected articles. Consequently, 46 articles were included. Of these 46 articles, nine (7,10,11,15,16,33,34,47,48) reported data on 21 populations and 37 (3–6,8,9,18,35–37,44,49–52,53–74) reported data on 37 populations. All populations were regarded as separate studies, resulting in the inclusion of 58 studies (with 297 533 patients) for further evaluation in this systematic review. Twelve studies in 10 articles (34–37,44,47,49–52) were categorized as cohort studies (with 285 638 patients); 37 studies in 27 articles (3–11,15,16,18,33,48,53–65) were categorized as occult metastases studies (with 7740 patients); and nine studies in nine articles (66–74) were categorized as sentinel lymph node biopsy studies (with 4155 patients).

Cohort Studies

Characteristics of the 12 cohort studies included in this review are shown in Table 1. Except for Colleoni et al. (50), these studies defined micrometastases as metastases of 2 mm or less in diameter. No distinction was made between micrometastases and isolated tumor cells, as opposed to the current definition of micrometastases (which is tumor deposit[s] >0.2 mm and ≤2 mm in size) and isolated tumor cells (which is tumor deposit[s] ≤0.2 mm) in the sixth edition of the *Cancer Staging Manual* (14). Colleoni et al. (50) distinguished micrometastases (from >0.2 to ≤2 mm in diameter) from isolated tumor cells (≤0.2 mm in diameter) but analyzed isolated tumor cells and micrometastases as one group. In all studies, axillary lymph node dissections were carried out without previous sentinel lymph node biopsy procedures, except in the studies of Colleoni et al. (50) and Chen et al. (35). In these studies, 43% and 28%, respectively, of the patients had undergone a sentinel lymph node biopsy procedure that could be followed by an axillary lymph node dissection. Because most patients had undergone an axillary lymph node dissection only, we included these two studies in the cohort studies instead of in the sentinel lymph node biopsy studies. The axillary (nonsentinel) lymph nodes were examined by use of hematoxylin–eosin staining in one level without step sectioning; however, in one study (52), immunohistochemical staining was used in case of doubt.

The included study populations were heterogeneous with respect to breast cancer stage, ranging from stage I (37,47) to stage III (51). The median follow-up in these studies was 10 years (range = 4.1–16.7 years). Whether or not adjuvant systemic therapy had been administered was not reported in eight (35–37,44,47,49,51) of 12 studies.

Disease-free survival from univariate analyses was reported in four studies (44,47,50). Nine studies reported the 5-year overall survival from univariate analyses (34,35,37,44,49–52), and all but two (44,50) showed a worse 5-year overall survival in the group with metastases that were 2 mm or less in diameter than in the

Table 1. Overview of breast cancer cohort studies reporting on the prognostic value of metastases of 2 mm or less in diameter in lymph nodes*

Author (reference)	PA	No. of patients		Stage	% AST in mi arm/pN0 arm	FU, y	Survival, % (mi vs pN0)†				Remarks	MVA
		pN0 arm	mi arm				5-y DFS	5-y OS	10-y DFS	10-y OS		
Fisher et al. (44)	1 H&E section	287	21	I–II	NR/NR	4.1‡	58 vs 84 (P = .2)	91 vs 90	—	—	4-y survival data	No
Fracchia et al. (51)	1 H&E section	58	15	III	NR/NR	10	—	41 vs 82	—	41 vs 75	mi group: 9-y survival data	No
Rosen et al. (47)	1 H&E section	471	29	I	NR/NR	10§	89 vs 76	—	81 vs 69	—		No
Rosen et al. (47)	1 H&E section	282	41	IIa	NR/NR	10§	85 vs 88	—	70 vs 84 (P = .01)	—		No
Clayton and Hopkins (49)	1 H&E section	378	62	NR	NR/NR	16.7||	—	80 vs 87	—	76 vs 78	pN0 vs mi (1–2 mm)	No
Colleoni et al. (50)	1 H&E section	1400	232	I–IIIa	100/6	4.2||	84 vs 91	98 vs 97	—	—	44% SLN procedure performed¶	Yes
Kuijt et al. (34) (no AST)	1 H&E section	4263	87	I–IIIa	0/0	#	—	79 vs 85	—	57 vs 70	Subgroup of patients without AST	Yes
Kuijt et al. (34)	1 H&E section	4377	179	I–IIIa	51/3	#	—	80 vs 84	—	62 vs 69		Yes
Maibenco et al. (37)	1 H&E section	41 197	1293	I	NR/NR	14**	—	95 vs 97	—	88 vs 93 (P < .001)	5- and 12-y survival data (BCSS); data from SEER database; mi in maximum one lymph node	Yes
Chen et al. (35)	1 H&E section	154 569	11 405	I–III	NR/NR	NR	—	86 vs 90	—	71 vs 76	Data from SEER database; 28% SLN procedure performed¶	Yes
Grabau et al. (52)	1 H&E section (optional IHC)	4767	427	I–III	100/11	10.2||	—	84 vs 88	—	72 vs 76 (P = .04)	Mi in maximum three lymph nodes	Yes
Truong et al. (36)	1 H&E section	57 980	1818	I–IIa	NR/NR	7.3||	—	—	—	68 vs 76 (P < .001)	Data from SEER database	Yes

* AST = adjuvant systemic therapy; BCSS = breast cancer–specific survival; DFS = disease-free survival; FU = follow-up; H&E = hematoxylin–eosin staining; IHC = immunohistochemical staining; mi = metastases less than or equal to 2 mm or less in diameter; MVA = multivariable analysis; NR = not reported; OS = overall survival; PA = pathological assessment of lymph nodes; pN0 = negative lymph node; SEER = Surveillance, Epidemiology and End Results; SLN = sentinel lymph node. Survival differences (if statistically tested) were assessed by log-rank tests. Some studies did not report whether one- or two-sided statistical tests were used.

† Data with respect to statistical significance reported between brackets if supplied.

‡ Data are the mean.

§ Data are the minimum.

|| Data are the median.

¶ No data with respect to PA of sentinel lymph nodes.

Diagnosis was in 1975–1997, and FU was until April 2002.

** Data are the maximum.

lymph node–negative group (Figure 1, A) (pooled estimate for RR of death = 1.39, 95% CI = 1.19 to 1.62; I^2 = .38). Eight cohort studies reported the 10-year overall survival (34–37,49,51,52), and all found a worse survival in the group with metastases that were 2 mm or less in diameter than in the lymph node–negative group (Figure 1, B) (pooled estimate for RR of death = 1.21, 95% CI = 1.13 to 1.30; I^2 = .17). The results of the sensitivity analyses were similar.

In all seven studies (34–37,50,52) that carried out multivariable analyses, primary tumor size was taken into account in a model that also contained the presence of metastases that were 2 mm or less in diameter. Age or menopausal status was taken into account in six studies (34–37,52). In three studies (35,37,50), tumor grade and/or hormone receptor status were taken into account. One study (37) carried out multivariable analysis on the prognostic
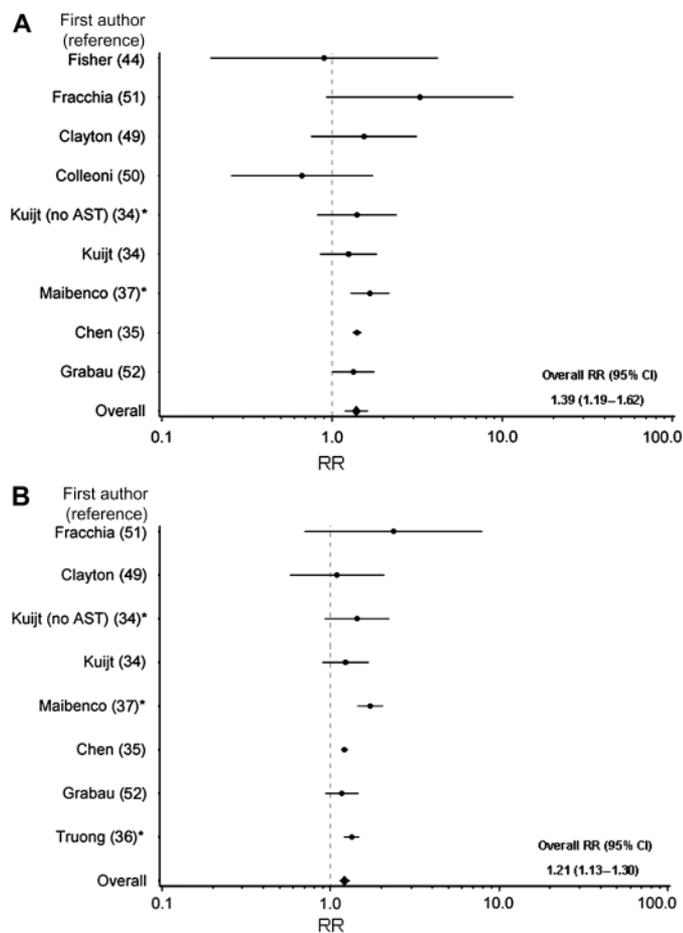
impact on breast cancer–specific survival of metastases that were 2 mm or less in diameter. Six studies (34–36,50,52) carried out multivariable analyses of the prognostic value of metastases of 2 mm or less in diameter on overall survival (Figure 2), five (34–36,52) of which showed a negative prognostic impact on overall survival of metastases that were 2 mm or less in diameter (from a pooled analysis, HR of death for the presence of metastases that were 2 mm or less in diameter = 1.44, 95% CI = 1.29 to 1.62; I^2 = .34).

Only one study (34) included a population that had been treated either with or without adjuvant systemic therapy, with separate analyses per subgroup. The presence of metastases that were 2 mm or less in diameter was associated with lower overall survival in the total population (HR of death = 1.32, 95% CI = 1.03 to 1.69). However, in the subpopulation that had not been treated with adjuvant systemic therapy and contained 49% of the total population, the presence of metastases that were 2 mm or less in diameter was associated with even lower overall survival (HR of death = 1.51, 95% CI = 1.11 to 2.06).
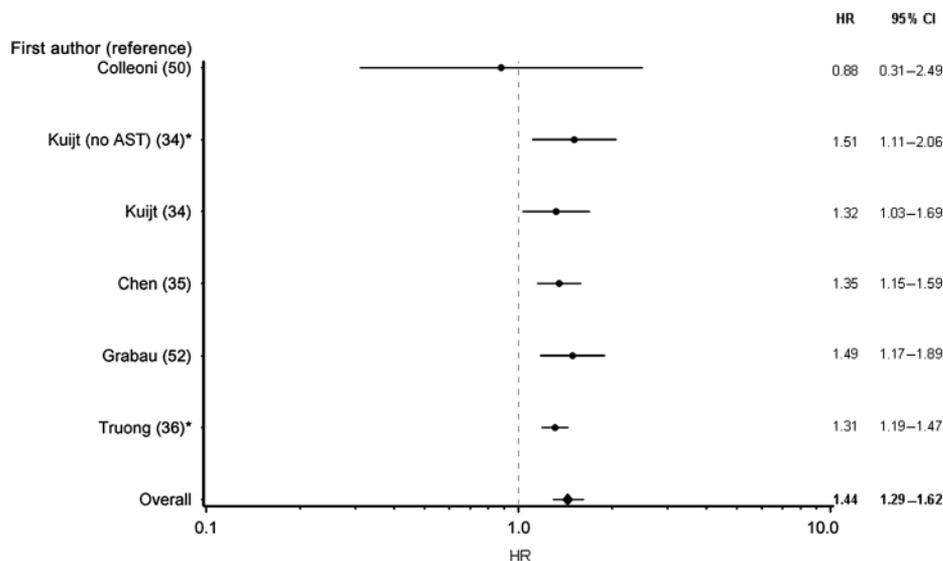
Occult Metastases Studies

Characteristics of the 37 occult metastases studies (3–11,15,16,18,33,48,53–65) included in this review are shown in Table 2. The pathological assessment of the axillary lymph nodes in the occult metastases studies was very heterogeneous. In six studies (3,15,18,57,64), step sectioning was carried out; in 18 studies (5,7,9–11,33,53,55,59–61), step sectioning was combined with immunohistochemical staining; and in 13 studies (4,6,8,16,48,54,56,58, 62,63,65), only immunohistochemical staining was carried out. The sizes of the occult metastases were heterogeneous, ranging from single tumor cells (10,33) to macrometastases that were 10 mm in diameter (7). Breast cancer stage of the included patients was not described in 20 studies (3,7–9,11,16,18,33,55,56,60–62,65). In 16 studies (5,6,10,15,48,53,54,57–59,63,64), patients with stage I and/ or II disease were included. Median follow-up of the occult metastases studies was 8 years (range = 3.6–24 years). Data regarding the administration of adjuvant systemic therapy were not reported in seven studies (5,6,9,16,61,62,65). Adjuvant systemic therapy was administered to all or some of the included patients in six studies (8,10,15,58), and no systemic therapy was administered in 24 studies (3,4,7,11,15,16,18,33,48,53–57,59,60,63,64).

After a 5-year follow-up among the group with occult metastases, compared with the lymph node–negative group, the pooled estimates for risk of disease recurrence (RR = 1.55, 95% CI = 1.32 to 1.82; I^2 = .15) (Figure 3, A) and for risk of death (RR = 1.45, 95% CI = 1.11 to 1.88; I^2 = .17) (Figure 3, B) were similar. In an analysis after a 10-year follow-up that compared the same groups, the pooled estimates for risk of disease recurrence was similar to that at the 5-year follow-up (RR = 1.58, 95% CI = 1.22 to 2.05; I^2 = .67) (Figure 4, A), but the risk of death was lower (RR = 1.31, 95% CI = 1.05 to 1.63; I^2 = .56) (Figure 4, B). The results of the sensitivity analyses were similar to the results above.

Separate analyses for patients with isolated tumor cells and patients with micrometastases were carried out in five studies (7,10,11,33,48). All five studies found that reduced disease-free or overall survival rates were associated with micrometastases, and all but one study (33) found that a reduced disease-free or overall

Figure 1. Cohort studies: association between risk of death after follow-up and the presence of metastases of 2 mm or less in diameter in axillary lymph nodes. **A**) A 5-year follow-up. (I^2 for heterogeneity = .38.) **B**) A 10-year follow-up. (I^2 = .17.) Each **circle** indicates the magnitude of the relative risk (RR), and the **horizontal line through the circle** indicates the 95% confidence interval (CI). The relative risks and their 95% confidence intervals were combined to obtain a pooled relative risk, as shown by the **diamond** and its 95% confidence interval. In both pooled analyses, the studies marked with an **asterisk** were not taken into account. The study of Kuijt et al. (34) in patients without adjuvant systemic therapy (AST) was not taken into account because it was based in part on the same population as in the total population of that study. The studies of Maibenco et al. (37) and Truong et al. (36) were not taken into account because they were in part based on the same population as in the study of Chen et al. (35).

Figure 2. Cohort studies: multivariably corrected associations between overall survival (OS) and lymph nodes containing metastases of 2 mm or less in diameter vs lymph nodes with no metastases. (I^2 for heterogeneity = .34.) Hazard ratios (HR, **circles**) and 95% confidence intervals (95% CIs, **horizontal line through circles**) were abstracted from each study and combined to obtain a pooled estimate of the association between the presence of micrometastases in lymph nodes and OS (**diamond**). Studies marked with an **asterisk** were not taken into account in the pooled analysis. The study of Truong et al. (36) was not taken into account because it was based in part on the same population as that used in the study of Chen et al. (35); the study of Kuijt et al. (34) in patients without adjuvant systemic therapy (AST) was not taken into account because it was based in part on the same population that was analyzed in the total study group of that study.

First author (reference)	HR	95% CI
Colleoni (50)	0.88	0.31–2.49
Kuijt (no AST) (34)*	1.51	1.11–2.06
Kuijt (34)	1.32	1.03–1.69
Chen (35)	1.35	1.15–1.59
Grabau (52)	1.49	1.17–1.89
Truong (36)*	1.31	1.19–1.47
Overall	**1.44**	**1.29–1.62**

survival rate was associated with isolated tumor cells; the comparison group for both studies was the lymph node–negative group.

The impact of occult metastases on disease-free survival was determined by multivariable analyses in only 12 (3,5,6,8,9, 11,33,48,53,61,63) of the 37 occult metastases studies, eight (3,5,9,11,33,53,61,63) of which found no negative impact. In multivariable analyses, in three (4,11,61) of six (4,8,11,48,61) studies on the impact of occult metastases on overall survival, occult metastases had no negative impact. Most of the studies (3–5,33,61,63) that carried out multivariable analyses on disease-free and/or overall survival and found no negative impact described the impact as "not [statistically] significant" without providing specific results. Therefore, we could not pool the results of multivariable analyses from these studies.

Sentinel Lymph Node Biopsy Studies

Characteristics of the nine sentinel lymph node biopsy studies (66–74) are shown in Table 3. Eight studies (67–74) processed the sentinel lymph nodes by using step sectioning and immunohistochemical staining; in one study (66), only step sectioning was used. In six studies (66–68,70,71,73), no details on the breast cancer stage of included patients were reported. Median follow-up of the patients in all sentinel lymph node biopsy studies was 3 years (range = 1.2–6.1 years). Data regarding the administration of adjuvant systemic therapy were not reported in four studies (66,68,69,72). In five studies (67,70,71,73,74), adjuvant systemic therapy was administered to a part of the patient population. Only one study (74) carried out multivariable analyses, in which the impact of systemic therapy was taken into account. With exception of the studies of Cox et al. (73) (that included 273 patients) and Gobardhan et al. (74) (that included 99 patients), almost all studies were small, including up to 45 patients who had lymph nodes containing isolated tumor cells or micrometastases. Four studies carried out survival analyses: one (74) was based on final lymph node status and three (67,70,73) were based on sentinel lymph node status. In all nine studies, the proportion of axillary lymph node dissection ranged from 0% to 100% in patients with isolated tumor cells or micrometastases and from 0% to 44% in patients with lymph node–negative disease.

Five studies (66–68,70,71) considered patients with micrometastases and isolated tumor cells as one group and found no reduced recurrence-free survival rates for these patients as compared with lymph node–negative patients, although the rates were not statistically tested in one study (68). Two studies (72,73) carried out separate analyses for patients with isolated tumor cells. One study (72) (with 145 patients in total and six with isolated tumor cells) found a higher recurrence rate in patients with isolated tumor cells, but a survival analysis was not carried out because of small numbers of patients and events. The other larger study (73) (with 2381 patients in total and 151 with isolated tumor cells) did not find a lower relapse-free survival rate for patients with isolated tumor cells.

Four studies (69,72–74) assessed the prognostic impact of micrometastases (that were >0.2 mm but ≤2 mm in diameter). Statistical analyses were not carried out in two studies (69,72). Two studies (72,73) reported a higher recurrence rate for patients with micrometastases; however, results were based on sentinel lymph node status, and additional macrometastatic disease was found in some patients after axillary lymph node dissection. The other two studies (69,74) reported no reduced survival rates for these patients. Only the data in Gobardhan et al. (74) were based on final lymph node status. Although they did not find that the presence of micrometastases had a negative prognostic impact on disease-free and overall survival, they did find an increased risk of distant metastases among patients with micrometastases as final lymph node status (HR of distant metastases = 4.85, 95% CI = 1.79 to 13.18) compared with patients who were lymph node negative or who had isolated tumor cells. Random-effects meta-analyses to calculate pooled estimates of the relative risks could not be carried out because of the few studies that carried out survival analyses and because the follow-up in such studies was short.

Discussion

In this systematic review, we analyzed the association between presence of micrometastases and isolated tumor cells and outcome

Table 2. Overview of breast cancer occult metastasis studies that report the prognostic value of occult metastases, micrometastases, and isolated tumor cells in lymph nodes*

Author (reference)	PA‡	No. of patients		FU, y	Stage	% AST in OM arm/ pN0 arm	Survival, % (occult vs pN0)†				Remarks	MVA
		pN0 arm	OM arm				5-y DFS	5-y OS	10-y DFS	10-y OS		
Fisher et al. (57)	SS (20 μm), H&E	59	19	5.1§	I	0/0	71 vs 68	—	—	—	—	No
Rosen et al. (64)	SS (48 μm), H&E	19	9	NR	I	0/0	89 vs 69	—	62 vs 61	—	Only patients with intramammary lymph vessel invasion	No
Wilkinson et al. (18)	SS (24–48 μm), H&E	436	89	5‖	NR	0/0	—	82 vs 80	—	64 vs 70	—	No
IBCSG (no peri-op CT) (15)	SS (48 μm), H&E (6 levels)	555	53	5¶	I–II	0/0	61 vs 76 (log-rank test P = .006)	—	—	—	Only OMs located in a lymph node	No
IBCSG (peri-op CT) (15)	SS (48 μm), H&E (6 levels)	283	30	5¶	I–II	100/100	54 vs 68 (log-rank test NS)	—	—	—	Only OMs located in lymph nodes	No
Galea et al. (59)	H&E + IHC (2 levels)	89	9	NR	I–IIA	0/0	—	100 vs 74	—	65 vs 62	—	No
Noel et al. (63)	IHC (on original H&E slide)	137	31	NR	IIA	0/0	84 vs 81	—	66 vs 71	—	In MVA, OMs were NS (ie, recurrence)	Yes
Byrne et al. (54)	IHC (2 levels)	34	5	3.6§	I	0/0	—	—	—	—	OMs = three of the five patients had recurrences, pN0 = three of 34 patients had recurrences. P < .001 (log-rank test)	No
de Mascarel et al. (3)	SS (1500 μm), H&E (1 level)	785	120	6.9¶	NR	0/0	80 vs 88	89 vs 95	43 vs 78 (log-rank test P = .005)	61 vs 86 (log-rank test P = .037)	OMs < 0.5 mm. In MVA, mi NS (recurrence and BCSS)	Yes
Elson et al. (56)	IHC (2 levels)	77	20	5.7§	NR	0/0	69 vs 71	83 vs 91	—	—	—	No
Hainsworth et al. (4)	IHC (1 level)	302	41	6.6¶	I–II–III	0/0	68 vs 84 (log-rank test P < .05)	87 vs 85	—	—	OMs found on IHC and H&E slides. In MVA, OMs = NS (OS)	Yes
Nasser et al. (<0.2 mm) (33)	SS (150 μm), H&E (5 levels) + IHC (1 level)	109	31	11§	NR	0/0	93 vs 81	—	78 vs 68	—	OMs < 0.2 mm; subgroup of Nasser et al. (33)	No
Nasser et al. (>0.2 mm) (33)	SS (at150 μm) H&E (5 levels) + IHC (1 level)	109	19	11§	NR	0/0	62 vs 81	—	51 vs 68	—	OMs > 0.2 mm; subgroup of Nasser et al. (33)	No
Nasser et al. (total group) (33)	SS (150 μm) H&E (5 levels) + IHC (1 level)	109	50	11§	NR	0/0	81 vs 81	—	68 vs 68	—	OM analysis: in MVA, OMs = NS (DFS)	Yes
Tsuchiya et al. (65)	IHC (3 consecutive levels)	182	3	NR	NR	NR/NR	100 vs 91	—	—	—	—	No
Clare et al. (55)	SS (150 μm) H&E + IHC (5 levels)	75	11	6.7¶	NR	0/0	71 vs 84	90 vs 95	—	—	—	No

(Table continues)

Table 2 (continued).

Author (reference)	PA‡	No. of patients		FU, y	Stage	% AST in OM arm/ pN0 arm	Survival, % (occult vs pN0)†				Remarks	MVA
		pN0 arm	OM arm				5-y DFS	5-y OS	10-y DFS	10-y OS		
Gerber et al. (5)	H&E + IHC (2–6 levels)	141	18	4.3§	I–IIA	NR/NR	70 vs 86 (log-rank test P = .003)	—	—	—	In MVA, OMs = NS (DFS)	Yes
Cote et al. (6)	IHC (1 level)	588	148	12¶	I–II	NR/NR	69 vs 74	—	55 vs 63 (log-rank test P = .09)	73 vs 78 (log-rank test P = .10)	In MVA, HR = 1.73 (95% CI = 1.17 to 2.74), P = .007 in postmenopausal patients (recurrence)	Yes
Braun et al. (53)	H&E + IHC (3 levels)	137	13	4¶	I–II	0/0	91 vs 83 (log-rank test P = .31)	91 vs 95 (log-rank test P = .63)	—	—	In MVA of mi, P = .87 (DFS) and P = .36 (BCSS)	Yes
Cummings et al. (9)	SS (100 µm) H&E + IHC (4 levels)	150	53	10.3¶	NR	NR/NR	67 vs 86	83 vs 93	67 vs 82 (log-rank test P = .029)	75 vs 87	OMs > 0.5 mm. In MVA, RR = 2.17 (95% CI = 1.16 to 4.05), P = .015 (DFS) and P = NS (OS)	Yes
de Mascarel et al. (IDC group) (16)	SS (1500 µm) IHC (1 level)	116	13	24¶	NR	0/0	84 vs 94	—	67 vs 89	—	Patients with IDC only	No
de Mascarel et al. (ILC group) (16)	SS (1500 µm) IHC (1 level)	52	37	18¶	NR	NR/NR	91 vs 94	—	85 vs 87	—	Patients with ILC only	No
Fisher et al. (58)	IHC (of original H&E)	213	63	9§	I–II	100/100	—	88 vs 93	—	89 vs 87	Postoperative treatment group only. 9-y survival data	No
Millis et al. (ITC) (7)	H&E and IHC (1 level)	417	23	13.2¶,# 18.9¶,**	NR	0/0	—	83 vs 87	—	69 vs 77	Only ITC = subgroup of Millis et al. (7)	No
Millis et al. (mi) (7)	H&E and IHC (1 level)	417	57	13.2¶,# 18.9¶,**	NR	0/0	—	84 vs 87	—	78 vs 77	Only mi = subgroup of Millis et al. (7)	No
Millis et al. (total group) (7)	H&E and IHC (1 level)	417	60	13.2¶,# 18.9¶,**	NR	0/0	—	85 vs 87	—	80 vs 77	Overall group. In MVA, OMs = ns (BCSS)	No
Umekita et al. (8)	IHC	127	21	8.2¶	NR	100	75 vs 95 (log-rank test P < .001)	86 vs 99 (log-rank test P < .001)	—	—	7-y survival data. In MVA, mi RR = 4.81 (P = .005) (DFS) and RR = 5.75 (P = .004) OS	Yes
Gebauer et al. (60)	Routine examination, SS (H&E 6 levels), followed by H&E + IHC (2 levels)	198	14	NR	NR	0/0	86 vs 88	85 vs 91	66 vs 84	72 vs 76	Only IHC-detected OMs	No
Reed et al. (ITC) (48)	IHC (1 level)	340	21	25.6¶	I–IIA	0/0	—	81 vs 91	75 vs 78	74 vs 84	Only ITC	No

(Table continues)

Table 2 (continued).

Author (reference)	PA‡	No. of patients pN0 arm	No. of patients OM arm	FU, y	Stage	% AST in OM arm/pN0 arm	Survival, % (occult vs pN0)† 5-y DFS	5-y OS	10-y DFS	10-y OS	Remarks	MVA
Reed et al. (mi) (48)	IHC (1 level)	340	16	25.6¶	I–IIA	0/0	—	80 vs 91	75 vs 78	75 vs 84	Only mi. In MVA, OMs (ITC and mi) HR = 1.79 (95% CI = 1.00 to 3.20) (recurrence), HR = 1.82 (95% CI = 1.03 to 3.20) (OS)	Yes
Kahn et al. (61)	H&E + IHC (1 level)	175	29	8¶	NR	NR/NR	70 vs 77	89 vs 87	67 vs 69	79 vs 72	In MVA, OMs = NS (DFS and OS)	Yes
Marinho et al. (62)	IHC	162	26	6.8¶	NR	NR/NR	82 vs 90	78 vs 89	78 vs 78	69 vs 79	ITC detected by IHC; mi detected by IHC and H&E	No
Querzoli et al. (itc) (10)	SS (100 µm) H&E (4 levels) + IHC (3 levels)	328	24	8¶	I–II	33.3/27	83 vs 95	—	—	—	Only itc = subgroup of Querzoli et al. (10); endpoint = metastatic relapse	No
Querzoli et al. (mi) (10)	SS (100 µm) H&E (4 levels) + IHC (3 levels)	328	25	8¶	I–II	33.3/27	93 vs 95	—	—	—	Only mi = subgroup of Querzoli et al. (10); endpoint = metastatic relapse	No
Querzoli et al. (total group) (10)	SS (100 µm) H&E (4 levels) + IHC (3 levels)	328	49	8¶	I–II	33.3/27	88 vs 95	—	—	—	In MVA, for ITC and mi HR = 2.10 (95% CI = 0.96 to 4.58), P = .063 (distant metastases)	Yes
Tan et al. (ITC) (11)	SS (50 µm) H&E + IHC (2 levels)	285	61	17.6¶	NR	0/0	77 vs 88	87 vs 92	68 vs 83	70 vs 80	Only ITC. In MVA, RR = 1.7 (95% CI = 1.0 to 2.9) (DFS), RR = 1.4 (95% CI = 0.9 to 2.2) (OS)	Yes
Tan et al. (mi) (11)	SS (50 µm) H&E + IHC (2 levels)	285	17	17.6¶	NR	0/0	59 vs 88	94 vs 92	41 vs 83	59 vs 80	Only mi. In MVA, RR = 4.2 (95% CI = 2.1 to 8.5) (DFS), RR = 2.5 (95% CI = 1.3 to 4.6) (OS)	Yes

* AST = adjuvant systemic therapy; BCSS = breast cancer–specific survival; CI = confidence interval; CT = chemotherapy; DFS = disease-free survival; FU = follow-up; H&E = hematoxylin–eosin staining; HR = hazard ratio; IBCSG = International Breast Cancer Study Group; IDC = invasive ductal carcinoma; IHC = immunohistochemical staining; ILC = invasive lobular carcinoma; ITC = isolated tumor cells of 0.2 mm or less in diameter (ie, pN0i+); mi = micrometastases of greater than 0.2 to 2 mm or less (ie, pN1mi); MVA = multivariable analysis; NR = not reported; NS = not statistically significant; OM = occult breast cancer metastasis; OS = overall survival; PA = pathological assessment; peri-op = perioperative; RR = relative risk; SS = step sectioning. Survival differences (if statistically tested) were assessed by log-rank tests. Some studies did not report whether one- or two-sided statistical tests were used.

† Data with respect to statistical significance are in parentheses, if supplied.

‡ PA of lymph nodes after original PA.

§ Data are the mean.

‖ Data are the minimum.

¶ Data are the median.

Patients with occult metastases.
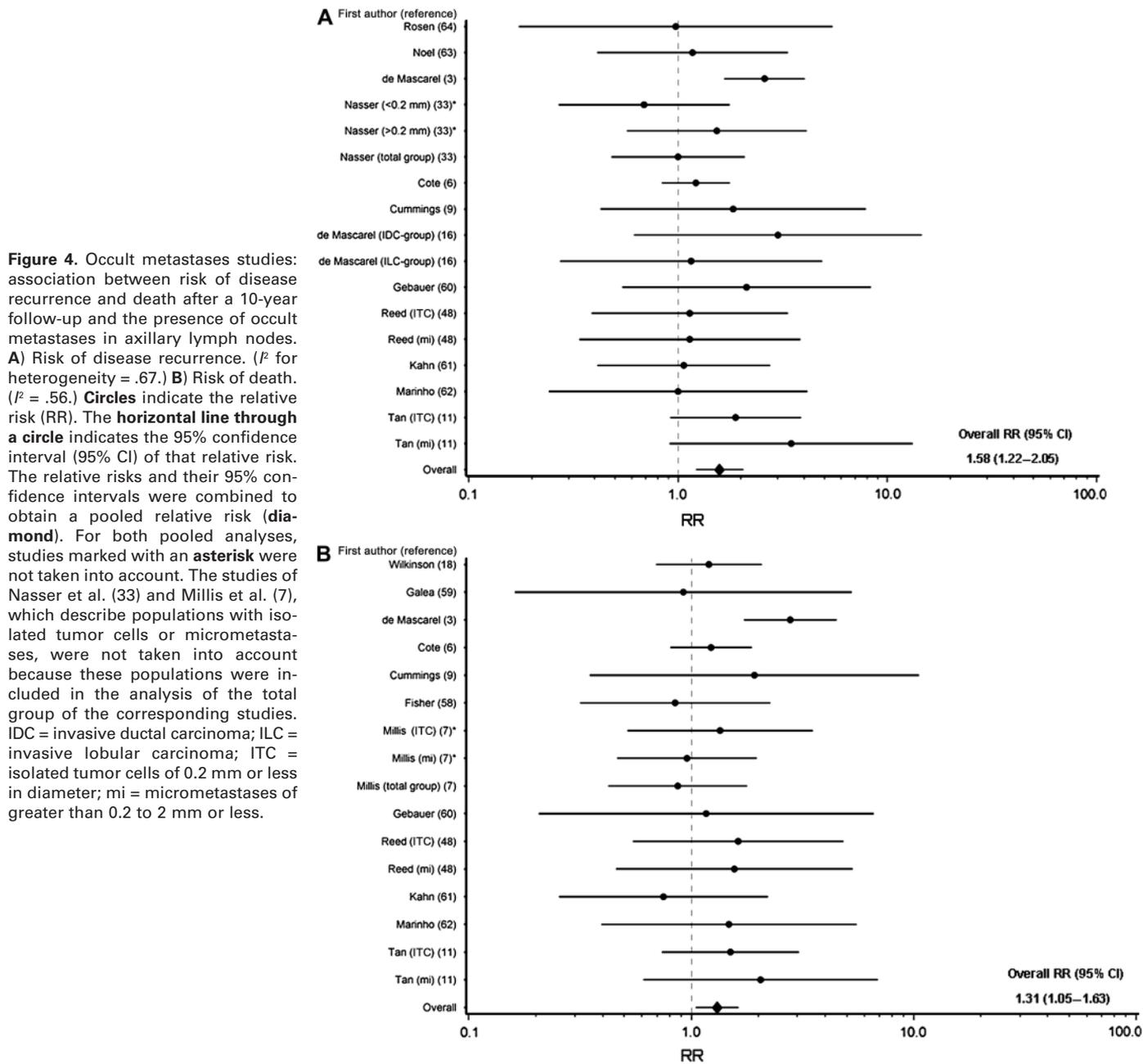
** Lymph node–negative patients.

Figure 3. Occult metastases studies: associations between risk of disease recurrence or death after a 5-year follow-up and the presence of occult metastases in axillary lymph nodes. **A**) Risk of disease recurrence. (I^2 for heterogeneity = .15.) **B**) Risk of death. (I^2 = .17.) **Circles** indicate the relative risk (RR). The **horizontal line through the circle** indicates the 95% confidence interval (CI) of that relative risk. The relative risks and their 95% confidence intervals were combined to obtain a pooled relative risk (**diamond**). For both pooled analyses, the studies marked with an **asterisk** were not taken into account. The studies of Nasser et al. (33), Querzoli et al. (10), and Millis et al. (7), which describe populations with isolated tumor cells or micrometastases, were not taken into account because these populations were included in the analysis of the total group in the corresponding study. IBCSG = International Breast Cancer Study Group; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ITC = isolated tumor cells of 0.2 mm or less in diameter; mi = micrometastases of greater than 0.2 to 2 mm or less; peri-op CT = perioperative chemotherapy.
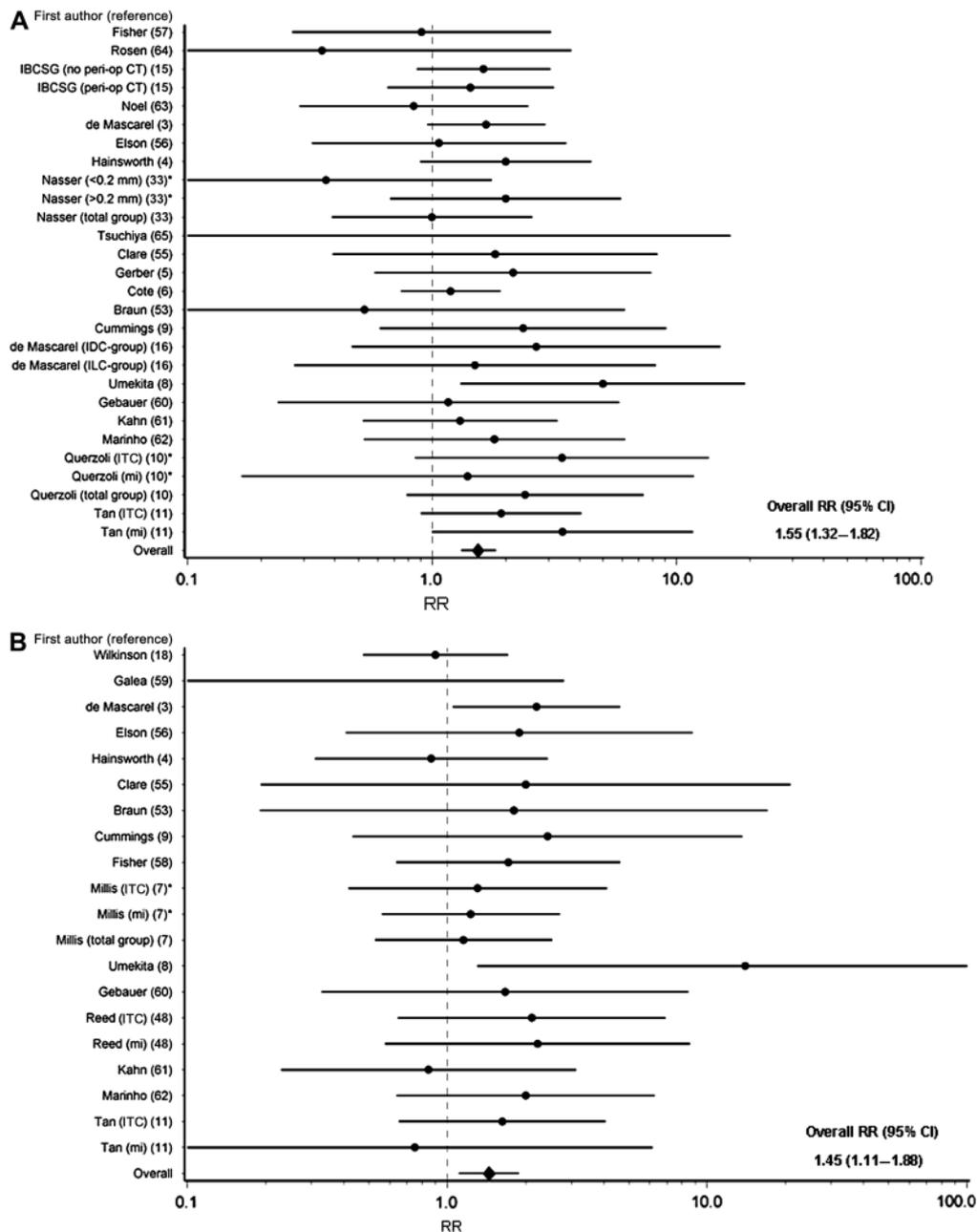
in 58 studies reported before August 11, 2008. These studies were categorized by the method of pathological assessment of the lymph nodes. In pooled analyses of long-term overall survival, we found that the presence of metastases of 2 mm or less in diameter, as detected by staining with hematoxylin–eosin in one section of each axillary lymph node, was associated with decreased overall survival, even after correction for other prognostic factors. The prognostic value of occult metastases (including isolated tumor cells, micrometastases, and macrometastases) after intensified pathological assessment of all axillary lymph nodes or of sentinel lymph nodes alone remained undetermined because of heterogeneity in methodology, small sample size, or short follow-up.

After approximately 40 years, more than 50 studies have been carried out to clarify the prognostic impact of isolated tumor cells

and micrometastases in axillary lymph nodes in patients with breast cancer, but the issue has still not been elucidated completely. Its relevance, however, has become a major issue since the introduction of the sentinel lymph node biopsy procedure. Because the sentinel lymph node is routinely examined by use of step sectioning and immunohistochemical staining, isolated tumor cells and micrometastases are now frequently detected. Because of inconsistent findings in old studies, different policies on adjuvant systemic therapy are recommended by the American Society of Clinical Oncology, the St Gallen Breast Cancer Treatment Consensus, and the Dutch Treatment of Breast Cancer Guideline Group in patients who have otherwise favorable primary tumor characteristics (12,75,76). To our knowledge, we are the first to use a systematic review to analyze the evidence that these small

Figure 4. Occult metastases studies: association between risk of disease recurrence and death after a 10-year follow-up and the presence of occult metastases in axillary lymph nodes. **A**) Risk of disease recurrence. (I^2 for heterogeneity = .67.) **B**) Risk of death. (I^2 = .56.) **Circles** indicate the relative risk (RR). The **horizontal line through a circle** indicates the 95% confidence interval (95% CI) of that relative risk. The relative risks and their 95% confidence intervals were combined to obtain a pooled relative risk (**diamond**). For both pooled analyses, studies marked with an **asterisk** were not taken into account. The studies of Nasser et al. (33) and Millis et al. (7), which describe populations with isolated tumor cells or micrometastases, were not taken into account because these populations were included in the analysis of the total group of the corresponding studies. IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ITC = isolated tumor cells of 0.2 mm or less in diameter; mi = micrometastases of greater than 0.2 to 2 mm or less.

lymph node metastases are associated with disease-free survival and overall survival among patients with invasive breast cancer. The ultimate aim of this systematic review was to provide guidance for present practice that is based on previous studies.

The cohort studies (34–37,44,47,49–52) that we analyzed in this study included almost all patients who had been diagnosed with breast cancer before the introduction of the *Cancer Staging Manual* in 2002 (14). Therefore, micrometastases were considered to be deposits of tumor cells that were 2 mm or less in diameter, and no distinction was made between micrometastases and isolated tumor cells (≤0.2 mm in diameter) and micrometastases (from >0.2 mm in diameter to ≤2 mm). In pooled analyses, the presence of metastases with a diameter of 2 mm or less was associated with decreased overall survival (HR of death = 1.44, 95% CI = 1.29 to

1.62), after correction for other prognostic factors. These known prognostic factors were, in general, more important prognostic factors than the presence of micrometastases.

In the occult metastases studies (3–11,15,16,18,33,48,53–65) that we analyzed in this study, most sample sizes of patients with occult metastases were small. In general, after 5 years of follow-up, an occult metastasis status was associated with worse survival than a lymph node–negative status (pooled RR of disease recurrence = 1.55, 95% CI = 1.32 to 1.82; and pooled RR of death = 1.45, 95% CI = 1.11 to 1.88). The occult metastases studies were heterogeneous with respect to pathological assessment, patient population, duration of follow-up, and methodology. Despite this heterogeneity, results of the studies were fairly homogenous, and the pooled estimate was inside the confidence intervals of all studies.

Table 3. Overview of breast cancer sentinel lymph node biopsy studies that report the prognostic value of isolated tumor cells and micrometastases in sentinel lymph nodes*

Author (reference)	PA	No. of patients pN0 arm	ITC arm	mi arm	FU, y	Stage	% ALND in ITC/mi/pN0 arm	% AST in ITC/mi/pN0 arm	SA	MVA	Remarks
Liang et al. (66)	SS (40 μm) H&E (4 levels)	144	—	15†	1.2‡	NR	—/73/0	100/NR	No	No	No recurrences in both groups; based on SLN status
Chagpar et al. (67)	H&E (8 levels) + IHC (2 levels)	69	2	12	3.3§	NR	0/0/0	33/79	Yes	No	5-y DFS (OM vs pN0) 100% vs 96% (P = .54); 5-y OS (OM vs pN0) 100% vs 96% (P = .54) from SLN status
Fan et al. (68)	SS (40–100 μm) H&E (3 levels), optionally IHC (3 levels)	276	—	45†	2.6§	NR	—/40/14	NR/NR	No	No	IHC only positive staining not assumed as metastasis; recurrence after 31 mo, mi 1/45 (2.2%) vs pN0 9/276 (3.3%), from SLN status
Soni and Spillane (69)	H&E + IHC	101	—	18	1.8‡	0–IIa	—/40/0	NR/NR	No	No	mi = 0/18 recurrences; pN0 = 2/101 recurrences after 22-mo FU (mean) from SLN status
Imoto et al. (70)	H&E + IHC (2 levels)	147	17	1	6.1§	NR	28 (itc+mi)/44	56/41	Yes	No	6-y RFS (mi/itc vs pN0) = 94% vs 88% (P = .39) from SLN status
Nagashima et al. (71)	H&E, optionally IHC	241	—	19†	2.3 (pN0) 4.0 (mi)§	NR	—/53/0	74/76	No	No	Recurrences: 1.2% in pN0 group and 5.3% in pN1mi group from SLN status
Rydén et al. (72)	FS + SS (60–100 μm) H&E + IHC (3 levels)	123	6	16	3.0§	I–IIa	100 (itc+mi)/0	NR/NR	No	No	RFS in pN0 vs mi vs macro groups = 97% vs 94% vs 86; in ITC group, 1/6 patients local recurrence from SLN status
Cox et al. (73)	SS (50 μm) H&E + IHC (2 levels)	2108	151	122	1.5 (mi) 2.0 (itc) 2.1(pN0)§	NR	71/80/0	48–45/39	Yes	No	For DFS in mi vs pN0 groups, P = .006; for DFS in ITC vs pN0 groups, P = .48; for OS mi vs pN0 groups, P <.001. For OS in ITC vs pN0 groups, P = .99 from SLN status
Gobardhan et al. (74)	SS (250 μm) H&E + IHC (4 levels)	423	18	81	3.3§	I–II	?/100/0	65/19	Yes	Yes	For ITC included in pN0 group, HR for DFS in the mi group = 1.43 (95% CI = 0.67 to 3.02), P = .36 (vs pN0); HR for OS in the mi group = 0.59 (95% CI = 0.14 to 2.58), P = .49 from final lymph node status

* ALND = axillary lymph node dissection; AST = adjuvant systemic therapy; CI = confidence interval; DFS = disease-free survival; FU = follow-up; H&E = hematoxylin–eosin staining; HR = hazard ratio; IHC = immunohistochemical staining; ITC = isolated tumor cells of 0.2 mm or less in diameter (ie, pN0i+); macro = macrometastases of greater than 2 mm; mi = micrometastases of greater than 0.2 to 2 mm or less (ie, pN1mi); MVA = multivariable analysis; NR = not reported; OM = occult metastatis; OS = overall survival; PA = pathological assessment of sentinel lymph node biopsy; RFS = recurrence-free survival; SA = survival analysis; SLN = sentinel lymph node; SS = step sectioning.

† Micrometastases of 2 mm or less without distinction in isolated tumor cells.

‡ Data are the mean.

§ Data are the median.

Multivariable analyses were carried out infrequently and did not consistently confirm the univariate results. We were not able to calculate pooled hazard ratios for the occult metastases studies because of the lack of data with respect to multivariable analyses.

The sentinel lymph node biopsy studies (66–74) that we analyzed in this study could have provided evidence for or against an association between outcome and the presence of isolated tumor cells and micrometastases that are detected by use of current protocols. However, the studies in this analysis were hampered by small numbers of patients, short follow-up times, analyses that were based on sentinel lymph node status, and lack of multivariable analyses. The only study (74) in this group of studies that carried out a multivariable analysis did not report a negative association of micrometastases (from >0.2 to ≤2 mm) with disease-free and overall survival, although an almost five times higher risk for the presence of distant metastases (HR of distant metastases = 4.85, 95% CI = 1.79 to 13.18) being associated with the presence of micrometastases was reported. If the cohort studies (35,50) in which sentinel lymph node biopsies were performed in a part of the patient population were taken into account in the category of sentinel lymph node biopsy studies, the presence of metastases of 2 mm or less in diameter in (sentinel) axillary lymph nodes was associated with lower disease-free survival (50) and overall survival (35).

In the cohort studies, it should be noted that the axillary lymph nodes were generally processed only by use of a single section that was stained with hematoxylin–eosin. In the past, the practice in many pathology departments was to slice any lymph node in half when it was too large to fit into a cassette, and so only one half of the lymph node was examined. When a lymph node was found to be negative after hematoxylin–eosin staining at one level, additional step sectioning with hematoxylin–eosin staining and/or immunohistochemical staining was used. By this method, occult metastases were detected in 9% to 42% of patients (3–11,15,16,18,33,48,53–65), depending on the level of detail of the work-up. The frequency of detection of small metastases increases with a more detailed work-up (77,78). In sentinel lymph nodes, approximately 40% of positive lymph nodes were found to have been missed when lymph nodes are grossly bisected and then one routine histological section was examined from each lymph node half (79). Therefore, in the cohort studies, the lymph node–negative groups might have contained patients with undetected (macro) metastases.

From the occult metastases studies (3–11,15,16,18,33,48,53–65) and from the sentinel lymph node biopsy studies (66–74), the distinct impact of systemic adjuvant therapy on survival could not be determined. In fact, the use of adjuvant systemic therapy may have obscured a true difference in survival rates in some studies because we were not able to consider this confounding parameter in the analyses. Among the cohort studies, Kuijt et al. (34) found that patients with metastases of 2 mm or less in diameter who were not treated with adjuvant systemic therapy had a higher risk of mortality than all patients, 51% of whom had received systemic adjuvant therapy. The results of this small study underline the importance of studying the relationship of micrometastases and isolated tumor cells to prognosis among patients who have not received adjuvant systemic therapy.

This study had several limitations. Most studies did not carry out multivariable analyses because they were too small to obtain a meaningful result. Future studies on prognostic factors should be powered to obtain meaningful conclusions. It should be recognized that, in systematic reviews and pooled analyses that are based on published data, there is always the drawback of lack of individual patient data with missing information (eg, treatment information). This lack of treatment information would tend to underestimate of the risk because patients with micrometastases would be more likely to receive chemotherapy. In addition, biases in reported nonrandomized studies carry over to this current analysis because we have used the results of these studies in our pooled analyses. Finally, publication bias would also tend to overestimate the risk because negative studies would be less likely to be submitted for publication.

Because of nonstandardized pathological examinations of lymph nodes across studies, comparison of the results from cohort and occult metastases studies with studies that use the sentinel lymph node procedure and an extensive pathological examination, which is currently common practice, is difficult. Nevertheless, although the studies included in this systematic review were limited by several methodological problems, we have shown that small metastases appear to be associated with worse outcome. Ongoing or recently closed sentinel lymph node trials will hopefully provide definitive data regarding the relationship of micrometastases and isolated tumor cells to breast cancer prognosis.

Results from the International Breast Cancer Study Group 23-01 study (80) should provide data to determine whether metastatic involvement of 2 mm or less in diameter in sentinel lymph nodes of patients with clinically lymph node–negative breast cancer is associated with prognosis. The American College of Surgeons Oncology Group Z0011 trial among patients with stage I or IIA breast cancer is evaluating the prevalence and prognostic significance of micrometastases and isolated tumor cells, as detected by immunocytochemistry, in the sentinel lymph node and in the bone marrow (81). Unfortunately, this trial has been stopped because of poor accrual. The National Surgical Adjuvant Breast and Bowel Project Protocol B-32 (82) is evaluating among patients who are sentinel lymph node–negative by routine pathological assessment whether a more detailed pathology investigation of sentinel lymph nodes can identify a group of patients with a potentially increased risk of systemic recurrence. The last study on this topic is the Micrometastasis and Isolated Tumor Cells: Relevant and Robust or Rubbish Trial from the Dutch Breast Cancer Trialists' Group (83). A preliminary report from this study found that the presence of both isolated tumor cells and micrometastases as final lymph node status was negatively associated with disease-free survival among patients who had undergone a sentinel lymph node procedure and did not receive systemic adjuvant therapy; however, if patients with isolated tumor cells and micrometastases received systemic adjuvant therapy, disease-free survival improved.

In conclusion, since the introduction of the sentinel lymph node procedure in the late 1990s, interest has been renewed in the association of isolated tumor cells and micrometastases with prognosis. To our knowledge, we are the first to evaluate systematically the impact of these small lymph node metastases on disease-free survival and overall survival among patients with invasive breast

cancer. We found in pooled analyses of long-term overall survival that the presence of metastases of 2 mm or less in diameter, as detected by staining with hematoxylin–eosin in one section of each axillary lymph node and without differentiation between isolated tumor cells and micrometastases, was negatively associated with prognosis. The independent prognostic value of occult metastases (including isolated tumor cells, micrometastases, and macrometastases) after intensive pathological assessment of all axillary lymph nodes remained undetermined. Because of nonstandardized pathological examination, the translation of the evidence from these older studies to the current practice of intensified examination of the sentinel lymph node but conventional examination of the nonsentinel lymph nodes is limited. In addition, studies in the sentinel lymph node era that have been published in peer-reviewed journals are hampered by small sample size and short follow-up. Therefore, results of the ongoing sentinel lymph node studies are eagerly awaited to provide data on the association of isolated tumor cells and micrometastases with prognosis and on the need for systemic adjuvant therapy.

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Notes

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