Treatment and Survival of Female Patients with Nonpalpable Breast Carcinoma

JOHN G.M. TINNEMANS, M.D., PH.D, THEO WOBBES, M.D., PH.D., ROLAND HOLLAND, M.D., PH.D.,*
JAN H.C.L. HENDRIKS, M.D., PH.D.,† RIGTJE F. VAN DER SLUIS, M.D., and HERMAN H.M. DE BOER, M.D., PH.D.

Since 1971, 151 nonpalpable breast cancers (100 invasive carcinomas, 39 *in situ* ductal carcinomas, and twelve lobular carcinomas *in situ*) have been diagnosed and treated at the St. Radboud University Hospital. Of the 100 clinically occult invasive carcinomas, 53 had pathologic diameters of more than 10 mm, 29 were of sizes between 6 and 10 mm, and 18 were tumors of 5 mm or less. Residual tumor outside the "excisional" biopsy cavity was encountered in 76 of the 118 mastectomy specimens (64.4%) fully capable of evaluation. Invasive residual tumor would have been left behind in 34 of 86 mastectomy specimens (39.5%). Of 27 axillas studied, no patient with *in situ* carcinoma had evidence of axillary lymph node metastases. Invasive carcinoma, however, showed axillary lymph node involvement in 7.7% of mastectomy specimens when the size of the primary tumor was not more than 5 mm, in 12.5% when the size was between 6 and 10 mm, and in 29.5% when the primary tumor was more than 10 mm in diameter.The 10-year recurrence-free survival (RFS) of patients with clinically occult invasive carcinomas greater than 10 mm in size was 71.9% and differed significantly from the 90.9% for patients with the invasive tumors ≤ 5 mm, as well as from the 100% RFS of patients with invasive tumors of between 6 and 10 mm and noninvasive tumors. Although the 10-year RFS was 92.6% for the patients with negative axillary nodes and 80.0% for the patients with positive axillary nodes, this difference did not reach statistical significance. However, the disease-specific overall survival after 10 years was significantly different between node-negative patients (96.4%) and node-positive patients (78.8%). Multivariate analysis disclosed that the relationship between size of the primary tumor and RFS was independent of the presence of axillary lymph node metastases. In conclusion, the validity of the concept of minimal breast cancer has been re-enforced. However, the results of this study suggest that the upper limit of the original definition of minimal breast cancer is too narrow and should be extended, so that, apart from the noninvasive tumors—regardless of their size—all invasive tumors having a maximum diameter less than or equal to 10 mm should be regarded as minimal breast cancers.

Reprint requests and correspondence: Dr. J.G.M. Tinnemans, Department of Surgery, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ AMSTERDAM Z.O., The Netherlands.

Submitted for publication: May 31, 1988.

From the Departments of General Surgery, Pathology, and Radiology† of the St. Radboud University Hospital, Nijmegen, The Netherlands.*

THE TERM *occult* or *subclinical* breast cancer is reserved for nonpalpable cancers that are usually demonstrable by mammographic means only. In the absence of any roentgenologic abnormality in the breast, occult breast cancer may also be a serendipitous finding when performing excision of breast tissues on other grounds. Through the use of mammography in population and individual screening, an ever increasing number of nonpalpable breast cancers is emerging, representing a special subgroup of clinically occult cancers among the T_1 tumors. The prognosis of clinically occult breast cancers has recently been reported to be excellent, with long-term survival rates of 95%[1] and 96.8%[2] in small series of patients.

In this report, we present our experience with a relatively large series of clinically occult breast cancers in relation to residual tumor after excisional biopsy, and analyze survival as it relates to tumor size and nodal status.

Patients and Methods

In 1970, modern mammographic equipment with a molybdenum anode was installed at the St. Radboud University Hospital at Nijmegen, The Netherlands, and since then, clinically occult breast carcinomas that are visible radiographically only have been diagnosed and treated with increasing frequency.

Effective since January 1, 1975, a population screening program aimed at all women over 35 years of age has been conducted in the city of Nijmegen. Patients with suspicious findings were referred to the surgical department of one of the two hospitals serving the city. Thus

TABLE 1. *Residual Tumor Outside the Biopsy Cavity After "Excisional" Biopsy Because of Clinically Occult Breast Cancer*

Primary Diagnosis	Total Number	Number of Mastectomy Specimens Capable of Evaluation	Number with Residual Tumor: Invasive	Number with Residual Tumor: Noninvasive	Percentage with Residual Tumor
Invasive carcinoma	100	86	34	21	64.0
Noninvasive carcinoma	51	32	0	21	65.6

our patient material includes a part of the population "screenees."

When a biopsy was indicated, the nonpalpable, mammographic abnormality was excised and diagnosed pathologically, as we have described previously.[3,4] Since 1978, all mastectomy specimens were examined using Egan's technique of correlating radiographic and histopathologic findings.[5-7] The data gathered before 1978 were based on routine pathology reports. In the case of invasive breast carcinoma, the pathologic diameter was primarily used. In twelve cases where this was not available, we had to resort to the radiographic measurements. We defined residual tumor as any ductal or lobular carcinomatous tissue, either invasive or noninvasive, left behind outside the biopsy cavity within the mastectomy specimen.

The treatment modality has changed with time. Before 1977, radical mastectomy was the usual treatment for lateral carcinomas, whereas centrally and medially seated tumors were treated by simple total mastectomy combined with postoperative irradiation of the regional lymph nodes. Since 1977, modified radical mastectomy has been the treatment of choice for both lateral and central/medial tumors. This applied to invasive carcinomas, whether ductal or lobular, and noninvasive ductal carcinoma *in situ* (DCIS). Patients with lobular carcinoma *in situ* (LCIS) were kept under close observation for the remainder of their lives.

At the close of this study on March 1, 1986, a 100% follow-up of the 151 patients had been attained. However, for the survival analysis, all patients with prior, synchronous or metachronous, contralateral breast malignancies that were palpable have been excluded, leaving 111 patients with solely nonpalpable breast cancer, 102 unilateral and nine bilateral. Of these 111 patients, ten have died (five died of the disease, and the remaining five died of causes unrelated to breast cancer) and 101 are alive (two of whom have recurrent disease). The mean observation time was 68.5 months (range of 1–174 months).

The estimated survival was calculated according to the life-table method.[8] Statistical p values were calculated using the logrank test (Mantel-Cox). The Cox proportional hazards regression model was used to examine the relative contribution of axillary lymph node involvement when analyzing survival by size of the primary tumor.

Results

From January 1971 to February 1986, 151 nonpalpable breast carcinomas were treated at the Department of General Surgery of the St. Radboud University Hospital. This represents 17% of the total of 889 cancers treated with surgery during this 15-year period.

Sixty-seven cancers were found as a result of population screening, whereas the remaining 84 cancers were detected at the surgical out-patients' department through individual screening.

Clusters of microcalcifications were the most frequent mammographic lesion (73 patients, or 48.3%), followed by stellate-shaped masses (44 patients, or 29.1%), masses with microcalcifications (17 patients, or 11.3%), circumscribed or nodular masses (twelve patients, or 8%), disturbed architecture (two patients, or 1.3%), and least frequent, no abnormalities (three patients, or 2%).

The mean age of the patients was 56.5 years (range of 37–78 years). Only three patients were younger than 40 years of age; one patient, 37 years of age, had LCIS, another patient, 38 years of age, had DCIS, and the third patient, also 38 years of age, had a tubular carcinoma with a diameter of 7 mm.

Table 1 notes the incidence of residual tumor outside the biopsy cavity in the 118 mastectomy specimens fully capable of evaluation histologically after prior "excisional" biopsy. The overall incidence of residual tumor, including LCIS, was 76 of 118 mastectomy specimens, or 64.4%. The rate of residual carcinoma was the same in the nonpalpable invasive group, as well in the nonpalpable noninvasive group: 64% *versus* 65.6%, respectively. When looking at the clinically occult invasive breast cancers alone, then invasive cancerous tissue would have been left behind in 34 of 86 mastectomy specimens (39.5%) capable of evaluation.

The axillary lymph node involvement of the different subgroups of nonpalpable breast cancers is presented in Table 2. One patient primarily had evidence of distant metastases (pathologic fracture of the sternum and bone marrow involvement as proven by a needle aspiration biopsy of the iliac crest).

The other 16 patients had positive lymph nodes in the axilla. The noninvasive breast cancers did not show any

TABLE 2. *Axillary Status of Patients with Clinically Occult Breast Cancer*

Primary Diagnosis	Total Number	Number of Axillas Capable of Evaluation	Number with Positive Nodes	Percentage with Positive Nodes
Invasive carcinoma > 10 mm	53	44	13*	29.5
Invasive carcinoma 6–10 mm	29	24	3	12.5
Invasive carcinoma ≤ 5 mm	18	13	1	7.7
DCIS	39	25	0	0
LCIS	12	2	0	0
Total	151	108	17	15.7

* Includes one patient with distant metastases.

secondary spread into the axillary lymph nodes, but the invasive breast cancers showed that, with increasing diameter of the carcinoma, there was more regional lymph node involvement: 7.7% in the invasive cancers equal to or smaller than 5 mm, 12.5% in the invasive cancers between 6 and 10 mm, and 29.5% in the invasive cancers more than 10 mm.

The recurrence-free interval of the four different subgroups (noninvasive, and invasive ≤ 5 mm, 6–10 mm, and > 10 mm) is depicted in Figure 1. The 10-year recurrence-free survival (RFS) rate of the invasive tumors > 10 mm was 71.9%, and of the invasive tumors ≤ 5 mm was 90.9%. The global p-value for the four groups was 0.017. It is clear from the curves that this difference is caused by the group with an invasive tumor > 10 mm.

Figure 2 shows the recurrence-free interval of the tumors when divided according to nodal status. The estimated RFS after 10 years was 92.6% for the patients with negative lymph nodes and 80% for the patients with positive lymph nodes. This difference did not reach statistical significance ($p = 0.1083$). However, the disease-specific overall survival after 10 years differed significantly ($p = 0.0131$) between node-negative patients (96.4%) and the node-positive patients (78.8%).

The relationship between size of the tumor and RFS was independent of the presence of regional lymph node metastases ($p = 0.0076$, Cox multivariate regression analysis).

No statistically significant differences have been found in RFS ($p > 0.05$) between pre- and postmenopausal women. Furthermore, patients with nonpalpable breast cancer originating from the population screening program had no better RFS ($p > 0.05$) than patients who were detected as a result of individual screening.

After a mean observation period of 65.4 months (range of 4–174 months), noninvasive DCIS and LCIS were not associated with positive axillary nodes and the RFS was 100%.

Discussion

When the concept of minimal breast cancer (MBC) was first proposed in 1971,[9] it was intended, entirely on hypothetical grounds, to delineate a certain subgroup of breast carcinoma patients with a highly favorable prognosis. According to its original definition, MBC included LCIS, DCIS, and minimally invasive carcinoma (MIC), either lobular or ductal, not exceeding 5 mm in diameter. Based on this definition, it was assumed that axillary lymph node involvement would occur in less than 10% of patients, and it was predicted that the long-term survival rate would be approximately 95%.[10]

To date, only a few authors have published their results with regard to axillary status and long-term follow-up.[11-14] Their results, summarized recently,[15] do support the validity of the original concept, showing a 5.5% rate of positive axillary nodes and a RFS of well over 96%. The vast majority of the lesions in the above-mentioned reports was self-discovered as a palpable mass.

The favorable outcome of MBC, however, has been challenged by the large interinstitutional survey of the American College of Surgeons.[16] Also, controversy exists with regard to the upper limit of MIC of either lobular or ductal type whose maximum diameter has been extended and which may be equal to but does not exceed 1 cm, as

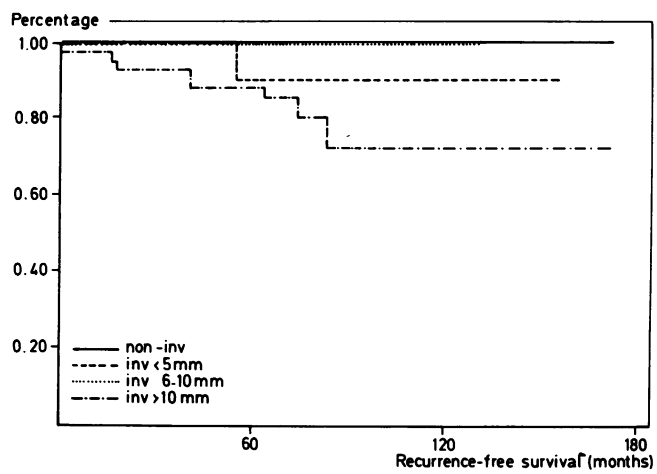

FIG. 1. RFS in nonpalpable breast cancer according to tumor size: noninvasive carcinoma (n = 44), invasive carcinoma < 5 mm (n = 13), invasive carcinoma 6-10 mm (n = 21), and invasive carcinoma > 10 mm (n = 42).

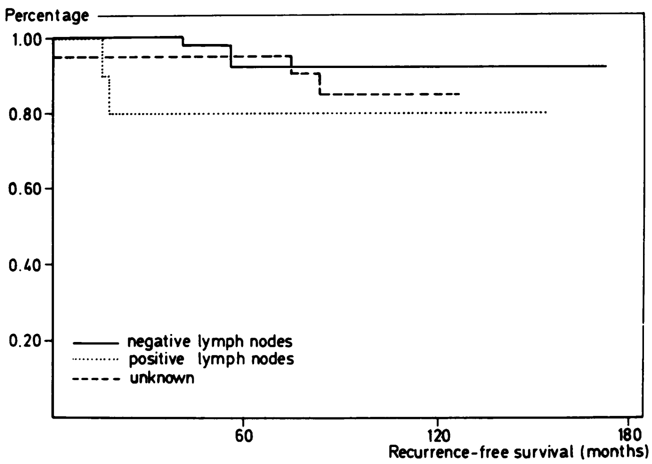

FIG. 2. RFS in nonpalpable breast cancer according to axillary nodal status: lymph nodes negative (n = 78), lymph nodes positive (n = 14),* and lymph nodes unknown (n = 28).
*Includes one patient with distant metastases

defined by the American College of Surgeons,[16] and which may be less than 1 cm, as recommended by the American Cancer Society and as in use by the Breast Cancer Detection Demonstration Projects of the National Cancer Institute.[17] Other authors either limited themselves to DCIS and MIC of the ductal type ≤ 5 mm[14] or extended the definition of MBC to all invasive cancers 1 cm or less in diameter presenting in the outer half of the breast only and having no clinical evidence of axillary lymph node metastases, as well as to some low-grade infiltrating cancers like adenoid cystic carcinoma, colloid carcinoma, intracystic papillary carcinoma, tubular carcinoma and malignant cystosarcoma phyllodes.[11]

"Occult" or "subclinical" breast carcinoma refers to any carcinoma, whether invasive or noninvasive, that is not palpable at physical examination and is usually detected mammographically. Therefore, occult breast cancer more than 0.5–1 cm may not be minimal when buried deeply within a large or nodular breast; however, the majority of the occult cancers will be minimal. Depending on which definition of MBC is used, 69 of 151 patients (45.7%) of our series had *in situ* carcinoma or MIC ≤ 5 mm, and 98 of 151 patients (64.9%) had *in situ* carcinoma or MIC ≤ 10 mm.

"Early" cancer refers to any carcinoma not associated with axillary lymph node metastasis, irrespective of size—that is, mainly stage I ($T_1N_0M_0$) disease but also a few of stage II ($T_2N_0M_0$) and IIIA ($T_3N_0M_0$)—according to the American Joint Committee on Cancer Classification.[18] Most occult cancers will also be early, but positive axillary lymph nodes do occur. Again, depending on the definition, the occurrence of positive axillary lymph nodes is one of 40 (2.5%) if we consider the *in situ* carcinomas and MIC ≤ 5 mm, and four of 64 (6.3%) if *in situ* carcinomas and MIC ≤ 10 mm are counted. Conversely, many early cancers are too large to fit in either the clinically occult or subclinical diagnoses.

The occult tumors differ from those T_1 tumors that surfaced clinically as a palpable mass through their lead time, which is estimated to be approximately 3 years.[19,20] Length bias also plays a role because fast-growing interval cancers, which become palpable between two roentgenologic screening examinations, are not detected mammographically.[21,22] Schwartz et al.[23] have proposed that, for staging of nonpalpable breast cancer, in addition to considering the mammographic size of the mass, a special notation (m) should be made if the mass was discovered by mammography—for instance, T_1 (m), T_2 (m). The nonpalpable breast cancers detected by clustered microcalcifications and areas of distorted architecture without a roentgenologic mass should then be staged T_O (m). Similarly, T_{is} could be modified as T_{is} (m) if it refers to an occult DCIS or LCIS detected mammographically.

On the basis of our results, we conclude that the prognosis of clinically occult breast cancer is extremely good, if node-negative and if the tumors are noninvasive or invasive but 10 mm or less in diameter. So, nodal status (negative *vs.* positive) and size of the invasive primary tumor (≤ 10 mm *vs.* > 10 mm) are both strong determinants of prognosis in clinically occult breast cancer. As a result of this, we concur with the American College of Surgeons' definition[16] of the upper limit of MIC which states that this upper limit is at 10 mm and that MBC includes, apart from noninvasive DCIS and LCIS, all invasive lesions 10 mm or less.

Contrary to others[2] who found better survival in women over 50 years of age with clinically occult breast cancer, we did not find any difference in relation to menopausal status. Also, the prognosis was not influenced by whether or not the patient was detected by population or individual screening, and this means that the mammogram itself has a certain predictive value *per se*.

The high rate (64%) of residual tumor after "excisional" biopsy in nonpalpable breast cancer implies that the whole breast must be subject to treatment, whether surgical or radiotherapeutical. This has already been discussed by us in detail elsewhere.[7] The only exceptions are patients with noninvasive LCIS who must have periodical follow-up examinations for the rest of their lives.[24]

There remains the question of whether or not an axillary dissection should be performed. Although positive axillary nodes have been described in association with DCIS,[25,26] we did not encounter any axillary lymph node involvement in 27 specimens of axillas fully capable of evaluation in patients with noninvasive carcinoma. That is why we believe that axillary dissection in noninvasive carcinoma is unwarranted, provided that the whole breast is thoroughly examined histopathologically in order to rule out hidden foci of invasive cancer.

In invasive cancer, however, the rate of positive axillary lymph nodes in our patients with invasive carcinoma ≤ 10 mm in diameter is low (four of 37 patients, or 10.8%), albeit not insignificant. Of these four patients, one patient had one positive lymph node at level 1, two patients had three positive nodes at level II, and one patient had one positive node at level III. All four patients are alive and disease-free after 157, 44, 7, and 2 months, respectively. We therefore believe that the removal of only the basal, level I nodes in invasive cancer ≤ 10 mm is insufficient locoregional treatment and that a complete axillary dissection should be performed. Similarly, invasive breast cancer > 10 mm, with axillary metastases at a rate of 29.5%, must be treated by full axillary dissection.

Although possible lead time and length bias[21] should be taken into account, the above reported long-term recurrence-free and overall survival results of nonpalpable breast cancer from one single institution show an excellent prognosis and support the view derived from various population screening program[27-29] that secondary prevention of breast cancer can save more lives.

Acknowledgments

Thanks to the staff of the Department of Radiation Therapy (Professor W.A.J. van Daal, M.D., Ph.D.) for their help in accumulating data and to Ir. A.A.M. Hart for his statistical advice.

References

1. Rodes ND, Lopez MJ, Pearson DK, et al. The impact of breast cancer screening on survival. A 5- to 10-year follow-up study. Cancer 1986; 57:581–585.
2. Letton AH and Mason EM. Routine breast screening: survival after 10.5 years follow-up. Ann Surg 1986; 203:470–473.
3. Tinnemans JGM, Wobbes Th, Hendriks JHCL, et al. Localization and excision of nonpalpable breast lesions: a surgical evaluation of three methods. Arch Surg 1987; 122:802–806.
4. Tinnemans JGM, Wobbes Th, Holland R, et al. Mammographic and histopathologic correlation of nonpalpable lesions of the breast and the reliability of frozen section diagnosis. Surg Gynecol Obstet 1987; 165:523–529.
5. Egan RL. Multicentric breast carcinomas: clinical-radiographic-pathologic whole organ studies and 10-year survival. Cancer 1982; 49:1123–1130.
6. Holland R, Veling SHJ, Mravunac M, Hendriks JHCL. Histologic multifocality of T_{is}, $T_{1\text{-}2}$ breast carcinomas: implications for clinical trials of breast-conserving surgery. Cancer 1985; 56:979–990.
7. Tinnemans JGM, Wobbes Th, van der Sluis RF, et al. Multicentricity in nonpalpable breast carcinoma and its implications for treatment. Am J Surg 1986; 151:334–338.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481.
9. Gallager HS, Martin JE. An orientation to the concept of minimal breast cancer. Cancer 1971; 28:1505–1507.
10. Gallager HS. Minimal breast cancer: origin of concept and definition. *In* SA Feig, R McLelland, eds. Breast Carcinoma: Current Diagnosis and Treatment. New York: Masson Publishing USA, Inc., 1983; 251–255.
11. Wanebo HJ, Huvos AG, Urban JA. Treatment of minimal breast cancer. Cancer 1974; 33:349–357.
12. Frazier TG, Copeland EM, Gallager HS, et al. Prognosis and treatment in minimal breast cancer. Am J Surg 1977; 133:697–701.
13. Peters TG, Donegan WL, Burg EA. Minimal breast cancer: a clinical appraisal. Ann Surg 1977; 186:704–710.
14. Nevin JE, Pinzon G, Moran TJ, Baggerly JT. Minimal breast carcinoma. Am J Surg 1980; 139:357–359.
15. Gallager HS. Minimal breast cancer: results of treatment and long-term follow-up. *In* SA Feig, R McLelland, eds. Breast Carcinoma: Current Diagnosis and Treatment. New York: Masson Publishing USA, Inc., 1983; 291–294.
16. Bedwani R, Vana J, Rosner D, et al. Management and survival of female patients with "minimal" breast cancer: as observed in the long-term and short-term surveys of the American College of Surgeons. Cancer 1981; 47:2769–2778.
17. Beahrs OH, Smart CR. Diagnosis of minimal breast cancers in the BCDDP: the 66 questionable cases. Cancer 1979; 43:848–850.
18. Beahrs OH, Myers MH, eds. Manual for Staging of Cancer, 2nd ed. Philadelphia: JB Lippincott Co., 1983; 127–133.
19. Lundgren B. Observations on growth rate of breast carcinomas and its possible implications for lead time. Cancer 1977; 40:1722–1725.
20. Hendriks JHCL. Population screening for breast cancer by means of mammography in Nijmegen, 1975–1980, thesis. Nijmegen, 1982; 74–78.
21. Shwartz M. Estimates of lead time and length bias in a breast cancer screening program. Cancer 1980; 46:844–851.
22. Holland R, Mravunac M, Hendriks JHCL, Bekker BV. So-called interval cancers of the breast, pathologic and radiologic analysis of sixty-four cases. Cancer 1982; 49:2527–2533.
23. Schwartz GF, Feig SA, Rosenberg AL, et al. Staging and treatment of clinically occult breast cancer. Cancer 1984; 53:1379–1384.
24. Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer 1978; 42:737–769.
25. Ashikari R, Hajdu S, Robbins GF. Intraductal carcinoma of the breast (1960–1969). Cancer 1971; 28:1182–1187.
26. Rosen PP. Axillary lymph node metastases in patients with occult noninvasive breast carcinoma. Cancer 1980; 46:1298–1306.
27. Verbeek ALM, Hendriks JHCL, Holland R, et al. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project, 1975–1981. Lancet 1984; 1:1222–1224.
28. Collette HJA, Day NE, Rombach JJ, de Waard F. Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case-control study. Lancet 1984; 1:1224–1226.
29. Tabár L, Fagerberg CJG, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography: randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1985; 1:829–832.