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Breast Conservation for Mammographically Occult Carcinoma

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Objective
Preoperative mammography is an essential part of the evaluation of patient eligibility for breast conserving therapy.

Summary Background Data
It is uncertain whether factors that contribute to the nonvisualization of carcinoma on mammograms are indications for mastectomy. The purpose of this study was to determine if the failure to identify clinically evident carcinoma on a mammogram is a contraindication to breast conserving therapy.

Methods
An analysis of 268 women with 269 clinically evident carcinomas who were treated from June 1988 to September 1993 was performed. Contraindications to breast preservation included multicentric tumors, diffuse indeterminate microcalcifications, pregnancy, prior irradiation to the breast region, the inability to achieve negative margins after two surgical procedures, and a large tumor to breast ratio.

Results
Mammographically occult tumors (MO) were present in 52 patients (19%). The mean age of patients with MO tumors was 52 *versus* 57 for mammographically evident (ME) tumors ($p = 0.009$), but the incidence by decade did not vary. Special histologic tumor types were more frequent among MO than ME tumors (13.5% *vs.* 1.8%, $p < 0.001$). Tumor size, the incidence of axillary node metastases, and stage did not vary. An equal proportion of patients with MO and ME tumors were candidates for breast preservation (67% *vs.* 70%), and a large tumor to breast ratio was the most common contraindication in both groups.

Conclusions
Even with modern mammographic technology, MO tumors remain a significant problem. This study did not demonstrate an association between MO tumors and factors such as size, unfavorable histology, or multicentricity which would preclude the use of breast conserving therapy. These results support the treatment of MO tumors with breast conserving surgery after a detailed clinical evaluation.

Breast conservation therapy (BCT) is a standard treatment option for the patient with early-stage breast carcinoma. Careful mammographic assessment of the extent of the primary tumor is an important part of the evaluation of patient eligibility for BCT,[1–3] and aids in the determination of the extent of breast resection needed to obtain negative margins.[4] However, 9% to 22% of patients with palpable breast cancer have tumors that are not visible by mammography,[5–11] and little information is available on the ability of these patients to undergo BCT. Hollingsworth et al.[5] reported that "diffuse histology" was a principal cause of false negative mammograms, which suggests that such patients might be poor candidates for BCT. This study was undertaken to determine whether mammographically occult (MO) tumors represent a contraindication to BCT and to compare patients with MO tumors to a concurrently treated group with mammographically evident (ME) tumors.

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METHODS

The patient population for this study was part of a group of 456 women with ductal carcinoma *in situ* or clinical Stage 1 and 2 breast cancer who were prospectively evaluated for local therapy by a multidisciplinary team from June 1988 to September 1993. Within this group, there were 19 women (4.1%) who did not have a mammogram before the surgical biopsy and 169 women (38.7%) who had mammographically identified carcinomas that were clinically occult. The 268 women (61.3%) who had 269 clinically evi-

Table 1. INCIDENCE OF MAMMOGRAPHICALLY OCCULT TUMORS BY AGE

Age	# Patients	#Mammographically Occult Cancers (%)
All Patients Having Mammography		
<40	50	10 (20)
41–50	118	18 (15.3)
51–60	99	11 (11.1)
61–70	90	6 (6.7)
>70	80	7 (8.8)
Patients with Clinical Abnormalities		
<40	39	10 (25.6)*
41–50	70	18 (25.7)†
51–60	55	11 (20.0)
61–70	58	6 (10.3)
>70	46	7 (15.2)

* p = 0.002 *versus* women age 61–70
† p = 0.055 *versus* women age 61–70

dent breast carcinomas (and underwent mammography before the biopsy) are the subject of this report.

In 142 of the 268 patients (53%), mammography was performed at the University of Chicago as a diagnostic examination that included the placement of skin markers on palpable abnormalities and compression and microfocal spot magnification views of the area of clinical concern. In the remaining 126 patients, mammography was performed at other institutions using a variety of protocols that did not always include extra views of the area of clinical abnormality. All outside mammograms were reviewed by a dedicated mammographer at the University of Chicago before a determination was made indicating whether a tumor was mammographically occult. The tumor size was defined as the largest tumor diameter on the surgical pathology report. Statistical comparisons among groups were made by Chi square analysis with the Bonferroni correction for multiple pair-wise comparisons.

RESULTS

Mammographically occult tumors were present in 52 patients, constituting 11% of the entire group. If only patients with clinical breast abnormalities are considered, the incidence of mammographically occult tumors is 19%. Mammographically occult tumors were seen in 16 of the 142 patients (11%) whose mammograms were performed at the University of Chicago compared with the 36 of 126 (29%) women whose mammograms were done elsewhere. While some of this difference may be because of differences in the imaging protocols used, it is also a reflection of referral bias, with younger women more frequently being referred for care than their older counterparts. Women with MO and ME tumors were compared to determine if differences in age, tumor size, tumor stage, histologic tumor type, or the incidence of nodal metastases were present. The relationship between patient age and mammographic tumor identification is shown in Table 1. The mean age of women with MO tumors was 52 years compared with 57 years for women with ME tumors (p = 0.009). The incidence of mammographically occult carcinoma varied from 8.8% of tumors in women more than 70 years of age to 25.6% of tumors in women less than the age of 40. Although the incidence of MO tumors appeared to decrease with each decade of age, analysis of variance did not reveal any significant differences. However, pairwise comparisons of false negative rates by age did reveal a significantly greater rate of false negative mammograms in women less than 40 than in those ages 61 to 70.

The MO tumors in this study ranged in size from 0.5 cm to 12.0 cm, while the size range of the ME tumors was 0.4 cm to 11 cm (Table 2). The median tumor size for MO tumors was 1.95 cm *vs.* 2.50 cm for ME tumors, and this difference was not significant. A comparison of tumor size between ME and MO tumors for each decade of age revealed no significant differences in size for any age group. When only patients with MO tumors were considered, no significant relationship between tumor size and patient age was noted. Axillary node metastases were present in 37% of patients with MO tumors and 45% of patients with ME tumors (p = NS). Tumor stage also did not differ between groups (Table 3).

Infiltrating ductal carcinoma was the most common histologic tumor type in both the MO and ME patients, present in 69% and 85% of cases, respectively. However, infiltrating ductal carcinoma accounted for a significantly lower proportion of MO tumors than ME tumors (p = 0.009).

No significant differences in the incidence of infiltrating lobular carcinoma and ductal carcinoma *in situ* were noted between the MO and the ME groups (Table 3). However, "special" histologic tumor types were more frequent in the MO than in the ME group (13.5% *vs.* 1.8%; p < 0.001). Four of the 7 mammographically occult tumors of special

Table 2. COMPARISON OF TUMOR SIZE IN PATIENTS WITH MAMMOGRAPHICALLY OCCULT AND EVIDENT TUMORS

	Median Size (cm), (Range)	
Age	Occult	Evident
<40	2.35 (0.7–5.0)	2.50 (0.8–9.0)
41–50	1.80 (0.5–6.0)	2.10 (0.4–11)
51–60	1.30 (1.8–12)	2.0 (0.5–7.0)
61–70	1.30 (0.6–5.0)	1.95 (0.7–6.0)
>70	1.95 (0.7–2.5)	2.30 (0.9–6.5)

Table 3. TUMOR HISTOLOGY AND STAGE *VERSUS* MAMMOGRAPHIC FINDINGS

Histologic Type	No. of Patients (%) Occult n = 52	Evident n = 217	p Value
Infiltrating ductal	36 (69.2)	184 (85)	0.009
Infiltrating lobular	3 (5.8)	16 (7.1)	NS
DCIS	6 (11.5)	13 (6.0)	NS
Special type	7 (13.5)	4 (1.8)	<0.001
Stage			
0	6 (8.4)	13 (6.6)	NS
1	25 (35)	66 (33.5)	NS
2	33 (46.5)	103 (53.8)	NS
3	7 (9.9)	12 (6.1)	NS

DCIS, ductal carcinoma *in situ;* NS, not significant.

histology were pure tubular carcinomas, that ranged in size from 6 mm to 5 cm, 2 were colloid carcinomas, and 1 was an adenoid cystic carcinoma.

Eligibility for breast conserving therapy (BCT) was compared between patients with MO and ME tumors. The contraindications to BCT in this study were multiple primary tumors in separate quadrants of the breast, diffuse malignant or indeterminate microcalcifications on mammogram, pregnancy, a history of prior irradiation to the breast region, and the inability to excise the tumor to histologically negative margins with two surgical procedures. A large tumor to breast ratio that was felt to preclude a cosmetically acceptable lumpectomy also was considered a contraindication to BCT. Thirty-five of the 52 (67%) patients with MO tumors were candidates for BCT compared with 151 of the 217 (70%) women with ME tumors. A large tumor to breast ratio was the most common contraindication to BCT in both groups. Multifocality or multicentricity, as evidenced by the presence of multiple gross primary tumors or the inability to achieve negative margins of resection, was observed with equal frequency among MO and ME tumors. Diffuse indeterminate microcalcifications on mammogram as a contraindication to BCT did not occur in the MO group, but were found in 13 patients (20%) in the ME group. These results are summarized in Table 4. Not all patients eligible for BCT opted to have the procedure. Breast conserving therapy was selected by the patient and successfully carried out in 30 of 52 (58%) women with MO tumors *versus* 114 of 217 (53%) women with ME tumors.

DISCUSSION

The failure to detect a clinically evident cancer on a mammogram may be because of poor mammographic technique, the density of the normal breast tissue, growth characteristics of the tumor, or an observer error in the interpretation of the images. The reported incidence of mammographically occult carcinoma varies widely. Table 5 summarizes the incidence of mammographically occult carcinoma in women with palpable breast abnormalities. Obviously, calculation of the rate of mammographically occult cancer from patient populations that include screen detected cancers will artificially lessen the incidence because screen detected cancers are by definition mammographically visible. It is noteworthy that even in studies that employ modern mammographic technology, the incidence of mammographically occult tumors ranges from 10% to 20%. In our study the mean age of patients with mammographically occult tumors was significantly less than that of women with mammographically evident tumors (53 *vs.* 57 years), a finding that has been reported by others.[7,9] However, when patient age was divided by decade mammographically occult carcinoma was noted to be a problem for all age groups.

Table 4. CONTRAINDICATIONS TO BREAST CONSERVING THERAPY

Contraindications	Mammographically Occult n = 17 (%)	Evident n = 66 (%)
Multifocal/centric	6 (35)	20 (30)
Large tumor/breast ratio	8 (47)	27 (41)
Diffuse mammographic microcalcification	0	13 (20)
Other	3 (18)	6 (9)

The presence of mammographically occult carcinoma was not found to have a negative impact on patient eligibility for breast conserving therapy. This is not surprising, in light of our observations regarding tumor size and histology. The median size of mammographically occult and evident tumors did not differ. This finding is in contrast to the report of Ma et al.,[12] who used a case control methodology to compare mammographically occult and evident tumors. Using size cut offs of less than 2 cm, 2 to 5 cm or greater than 5 cm, small size was found to be significantly associated with mammographically occult tumors. However, because small tumors are most amenable to lumpec-

Table 5. INCIDENCE OF NEGATIVE MAMMOGRAMS IN PALPABLE BREAST CANCER

Author	#Cancers	#Mammographically Occult	%
Feig[6] 1977	78	30	38
Niloff[7] 1981	146	41	28
Cahill[8] 1981	288	30	10
Edeiken[5] 1988	499	108	22
Wallis[4] 1991	871	75	9
Hollingsworth[9] 1993	100	9	9
Present Study	268	52	19

tomy, this finding supports our thesis that patients with mammographically occult carcinomas are appropriate candidates for breast conserving therapy. Studies of the relationship of histologic tumor type and failure to detect breast cancer by mammography have yielded conflicting results. Ma et al.[12] observed that tumors of lobular histology were significantly less likely to be visualized than other histologic types (OR = 7; 95% CI 2.2–22.1). This finding was based on 16 cases of lobular carcinoma, 9 of which were mammographically occult. We did not find infiltrating lobular carcinoma to be more frequent among mammographically occult carcinomas. There were 19 lobular cancers in our study, and 16 (84%) were visualized mammographically. This incidence of mammographically occult lobular carcinoma is consistent with the 16% incidence reported by Hilleren et al.[13] in a review of 137 cases of infiltrating lobular carcinoma. However, as noted by Sickles[14] and Hilleren et al.[13] the radiographic signs of lobular carcinoma are often subtle, and the extent of radiologic workup and the experience of the radiologist may influence the likelihood of detecting this lesion on a mammogram to a greater extent than for other histologic tumor types.

Tumors of special histologic type were found to be mammographically occult significantly more often than infiltrating ductal or lobular carcinomas or ductal carcinoma *in situ.* These tumors, primarily pure tubular carcinomas, accounted for 13.5% of the mammographically occult tumors, compared with 1.8% of the mammographically evident tumors. In the 169 patients whose tumors were detected only by screening mammography, the incidence of special histologic tumor types was 2.3%. Samuels et al.[15] noted that 7% of the 55 mammographically occult carcinomas in their series had tubular histology. Other reports of mammographically occult breast carcinoma[5–12] have not mentioned special histologic tumor types, with the exception of the report of Wallis et al.[6] In Wallis, it was noted that 5.5% of mammographically occult carcinomas had medullary histology, compared with 0.8% of tumors that were mammographically visualized.

Extensive intraductal carcinoma, a histologic finding that is important in determining the extent of surgery needed for breast conservation,[16] was seen in only 2 of the 36 patients with occult infiltrating ductal carcinoma. Healey et al.[17] have reported that the mammographic appearance of a mass or distortion without calcifications has a 92% predictive value for a cancer without an extensive intraductal component, a finding confirmed in our study. Of the six patients with pure intraductal carcinoma, three had nipple discharge and two had the skin changes of Paget's disease of the nipple.

These findings are the basis for our observation that the proportion of patients with mammographically occult carcinoma who were able to undergo breast preservation did not differ from that of women with mammographically evident tumors (67% *vs.* 70%). The most common contraindication to breast preservation in both groups was a large tumor to breast ratio, and this reflects the exclusion of patients with tumors detected by mammography alone from this study. Diffuse indeterminate or suspicious calcifications on mammogram, a contraindication to breast preservation in 20% of patients with mammographically evident tumors, were not seen in any patients with mammographically occult carcinoma. But, the incidence of multifocal or multicentric carcinoma did not differ between groups.

No other studies have examined the success of breast conserving surgery in patients with MO carcinoma. However, Samuels et al.[17] have data on the incidence and detection of local failure in patients with mammographically occult breast carcinoma after treatment with excision and irradiation. Of the 542 patients treated with lumpectomy and irradiation from 1962 to 1985, 10.1% (55) had a palpable breast mass that was not mammographically visible. The local failure rate for the patients with mammographically occult tumors was 10.9%, compared with 10.5% in the group with mammographically visible tumors. Four of the five local recurrences in the patients whose tumors were mammographically occult were visible on mammograms. While this study supports the use of breast conserving therapy in this patient group, it does not address the proportion of patients with mammographically occult carcinoma who are candidates for breast preservation.

Patients and physicians have expressed concern that patients with mammographically occult carcinoma are poor candidates for breast conserving therapy because of the intrinsic growth patterns of such carcinomas,[5] difficulty in determining the appropriate extent of the surgical resection, or inability to detect breast recurrence at an early stage. Our study demonstrates that clinical selection criteria, based on the history and a careful physical examination, will identify the majority of patients who require mastectomy. Although not routinely used in this study, ultrasonography provides an alternate means for defining the extent of the tumor when is not apparent from the physical examination.

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