January 2011

Prognostic Implications Of Patients With Mammographically Occult, Early Stage Breast Cancer

Tzu-I Jonathan Yang

PROGNOSTIC IMPLICATIONS OF PATIENTS WITH MAMMOGRAPHICALLY OCCULT, EARLY STAGE BREAST CANCER

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Tzu-I Jonathan Yang

2011

ABSTRACT

PROGNOSTIC IMPLICATIONS OF PATIENTS WITH MAMMOGRAPHICALLY OCCULT, EARLY STAGE BREAST CANCER

Tzu-I Jonathan Yang and Meena S. Moran

Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT.

Purpose: To compare mammographically occult (MamOcc) and mammographically positive (MamPos) early-stage breast cancer patients treated with breast-conservation therapy (BCT), to analyze differences between the two cohorts.

Methods: The 2 cohorts were comprised of 214 MamOcc and 2168 MamPos patients treated with BCT. Chart reviews were conducted to assess mammogram reports and method of detection. All clinical–pathologic and outcome parameters were analyzed to detect differences between the two cohorts.

Results: Median follow-up was 7 years. There were no differences in final margins, T stage, nodal status, estrogen/progesterone receptor status, or "triple-negative" status. Significant differences included age at diagnosis ($p < 0.0001$), more positive family history ($p = 0.0033$), less HER-2+ disease ($p = 0.0294$), and 1° histology ($p < 0.0001$). At 10 years, the differences in overall survival, cause-specific survival, and distant relapse between the two groups did not differ significantly. The MamOcc cohort had more breast relapses (15% vs. 8%; $p = 0.0357$), but on multivariate analysis this difference was not significant (hazard ratio 1.0, 95% confidence interval 0.993–1.007, $p = 0.9296$). Breast relapses were more commonly not picked up on mammography in the MamOcc cohort (32% 12% $p = 0.0136$).

Conclusions: Our study suggests that there are clinical–pathologic variations for the MamOcc cohort vs. MamPos patients that may potentially affect management, but that breast relapse rates after BCT are ultimately not significantly different for these 2 cohorts. Breast recurrences were more often mammographically occult in the MamOcc cohort; consideration should be given to closer follow-up and alternative imaging strategies (ultrasound, breast MRI) for routine post-treatment examination. To our knowledge, this represents the largest series addressing the prognostic significance of MamOcc cancers treated with BCT.

ACKNOWLEDGEMENTS

I would like to thank:
Dr. Meena Moran, my thesis advisor, for her guidance and mentorship in the past four years and for continuing to help me grow in the field of breast oncology.

Dr. Lynn Wilson for welcoming to the department five years ago, for his patience and mentorship, and for helping me achieve on an international level.

The International Journal of Radiation Oncology, Biology, Physics for accepting our manuscript for publication.

TABLE OF CONTENTS

INTRODUCTION

For early-stage breast cancer, mammography is an integral part of the workup before definitive treatment. Although diagnostic mammography is the standard breast imaging method used preoperatively to verify the location and extent of disease and to determine whether a patient is eligible for breast-conservation therapy (BCT), 9–26% of patients with breast cancer present with false-negative mammograms (1-4) at the time of diagnosis. A list of previous studies examining the rate of false-negative mammogram in women with breast cancer is provided in Table 1. Whether the cause of the negative result is dense breast tissue, diffuse disease, poor quality of the mammogram, or oversight of the primary tumor, the prognostic implications of a false-negative mammogram at presentation are generally unknown.

Table 1: Prevalence of mammographically occult breast cancer in literature.

Author	Total Breast Cancer Patients (n)	Mammographically Occult Breast Cancer Patients (n)	Percentage of Mammographically Occult Brest Cancer Patients (%)
Wallis *et al.* (1)	75	871	9
Feig *et al*. (2)	138	20	14
Edeiken *et al.* (3)	108	499	22
Niloff *et al.* (4)	160	41	26
Samuels *et al.* (5)	55	542	10
Morrow *et al.* (6)	52	269	19
Voogd *et al.* (7)	30	165	18

This thesis provides a summary of current common breast cancer screening imaging modalities, the clinical benefit of mammography, and predictive values of abnormalities on mammogram. It also provides an introduction to the concept of mammographic sensitivity, mammographically occult breast cancer, and the utilization of breast conservation therapy (BCT). Lastly, it details our investigation on the clinical and pathologic features and long-term outcome of patients with mammographically occult breast cancer.

Screening for Breast Cancer

Approximately 207,090 women in the United States are diagnosed with invasive breast cancer annually (8), with the majority of the breast cancers diagnosed as a result of an abnormal screening study. A variety of imaging modalities have been used for detection of breast cancer. Although Mammography has been and remains the primary imaging modality for the screening of breast cancer in the United States, a percentage of cancers are not visible mammographically, and it has a lower sensitivity for cancer detection in dense breast tissues (9). Furthermore, mammographic sensitivity seems to decrease and is insufficient for early diagnosis of breast cancer in women who are at increased familial risk with or without documented BRCA mutation (10). These issues have led to ongoing investigations for alternate imaging modalities in screening for breast cancer in specific patient populations, such as younger women with dense breast, or women with strong familial history of breast cancer.

Ultrasound is primarily used for diagnostic follow-up and further clarification of a questionable lesion and for visual guidance during a needle biopsy. Furthermore, it is

considered the first line imaging modality for breast imaging in pregnant women or in women less than 30 years of age with focal breast symptoms. A large, multi-center prospective study by Berg *et al.* evaluated the effectiveness of breast cancer screening using ultrasound in addition to mammography in elevated risk women with heterogeneously dense breast tissue in at least one quadrant. The authors found that of the 41 patients who were diagnosed with cancer, 8 demonstrated lesions on both ultrasound and mammography, 12 were detected by lesions on ultrasound alone, and 12 by mammography alone. The authors concluded that adding a screening ultrasound to mammography would lead to an additional 1.1-7.2 cancers per 1000 women (11). Interestingly, in addition to the 29% of the tumors which were mammographically occult, an additional 20% of participants diagnosed of cancer (8 patients) demonstrated no abnormality on either the mammogram or ultrasound.

Magnetic resonance imaging (MRI) is an emerging imaging modality for the screening of breast cancer that is under investigation. Currently MRI, in addition to mammography, is more commonly utilized among patients who are at high-risk for developing breast cancer. MRI relies on the increased vascularity of neoplasms and has been found to have higher sensitivity in detecting breast cancer when compared to mammography. The sensitivity has been demonstrated to be less dependent on breast density (12). This makes MRI an attractive screening tool for women with an elevated risk of developing breast cancer. In 2008, Warner and colleagues published their findings of a systemic review on studies after 1994 examining the use of MRI and mammography for screening of women at very high risk for breast cancer (13). From the 11 prospective studies included in their review, the authors found the sensitivity of

mammography varied from 14-59% when a positive mammogram was defined as a Breast Imaging Reporting and Data System (BI-RADS) 4 or 5 score, while the sensitivity of MRI ranged from 51-100%. The downside of using MRI routinely to screen all patients is the lower specificity and higher false positive rate, often warranting additional work-up (i.e. biopsies). A recent study by Riedl *et al.* compared mammography, ultrasound, and MRI of the breast used for the surveillance of women at high risk for breast cancer concluded specificities of 98%, 98%, and 92% for mammography, ultrasound and MRI, respectively. This study also documented the higher false positive rate of MRI compared to mammography and ultrasound (81% vs. 64%, 68%, respectively) (14).

Origin and the Clinical Benefit of Mammography

The first x-ray of the breast tissue was obtained in 1913 by Dr. Albert Salomon, a surgeon who reported the use of radiography of mastectomy specimens that demonstrated the primary tumors as well as spread to axillary lymph node (15). In 1949, Dr. Raul Leborgne was the first to report the significant association of radiographically detectable microcalcifications and breast carcinoma, reported finding radiographically visible microcalcifications in 30% of patients with breast cancer and thus setting the stage for screening mammography. In 1960, Dr. Robert L. Egan described a kilovoltage mammographic technique that was easily reproducible, which led to the development and widespread use of mammography. In 1963, the Cancer Control Program of the U.S. Public Health Service sponsored a conference at the M.D. Anderson Hospital, reporting on the usefulness and reproducibility of mammography (15). The results of a 24

institutions nationwide mammography study were presented at the conference: the true-positive rate for mammography was 79%, and the false-negative rate was 21% (16). The results of this study established that other radiologists could learn the technique of mammography developed by Dr. Robert Egan, that mammography could enable differentiation between benign and malignant lesions, and that mammography could be used to screen for cancer in asymptomatic women. Interestingly, despite the more recent advancements in mammographic techniques, the false-negative rate of mammography appears to be relatively consistent through the years (see Table 1), indicating the continuing need for patient selection and investigations of emerging imaging modality in breast cancer screening.

Mammography became the standard for breast cancer screening in the 1970s. In 1973, Strax and colleagues published their results of a randomized mass screening program using mammography as well as clinical examination in a group of 62,000 women aged 40 to 60. The authors found that mammography contributed substantially to the detection of breast cancer. Of 132 breast cancers detected through screening, 44 (33%) were found on mammography only and would have been missed if it were omitted. At 7-year follow-up, a 33% reduction in mortality rate was attributed to the use of mammography (17). In a 2002 Lancet publication, Nyström and colleagues demonstrated the advantageous effect of breast screening using mammography on breast cancer mortality after long-term follow-up (15.8 years) of the Swedish randomized controlled trials. The authors showed a 21% reduction in breast cancer mortality when comparing women who underwent mammography screening (164,770 patients) to those who did not (1,688,440 patients). They demonstrated that the benefit in terms of

cumulative breast cancer mortality reduction started to emerge at 4 years after randomization and continued to increase to approximately 10 years. Thereafter, the benefit in absolute reduction was maintained throughout the period of observation (18). In a recent Cochrane Database Systemic Review article, Gøtzsche *et al.* published their assessment of randomized trials comparing mammographic screening with no mammographic screening to determine the effect of screening for breast cancer with mammography on mortality and morbidity. The authors identified seven eligible trials and included 600,000 women in the analyses and concluded that mammographic screening is likely to reduce breast cancer mortality with an estimate 15%-20% reduction corresponding to an absolute risk reduction of 0.05% (19). From these studies, it is reasonable to conclude that the implementation of mammography has proven beneficial in reducing breast cancer related death worldwide.

Recently, there has been a great deal of controversy regarding changes in breast cancer screening recommendations released by the US Preventive Services Task Force (USPSTF) in 2009, and one of the recommendations made by the Task Force was to delay in the initial mammographic screening of asymptomatic women from age 40 to age 50 (20). Although the analysis of the Task Force included eight randomized trials and demonstrated an estimate relative risk for breast cancer-associated mortality of 0.85 (95% CI, 0.75-0.96), or 15% average breast cancer mortality reduction, for women of 39-49 years of age who undergo screening mammography, the Task Force also found that nearly 1 in 10 women in their 40s had a false-positive result per round of screening. Eighty percent of the false-positive screening resulted in additional imaging, and 10% of women with false-positive screenings resulted in biopsy (21). The USPSTF analysis

recognized the benefits of routine mammography starting at age 40, but the farms in terms of false-positive results are real as well. Clearly, there is a need of investigations that can help us better delineate the best imaging modalities in breast cancer screening for women younger than age 50.

Abnormalities on Mammogram

When mammographic findings that may be associated with breast cancer are identified at screening, further diagnostic work-up is required. These abnormal findings often include masses, calcifications, architectural distortion, and asymmetry. The accuracy of mammography is directly related to the positive predictive values of the findings. A large analysis of the positive predictive value associated with specific mammographic findings in screening and diagnostic examinations using the San Francisco Mammography Registry was published by Venkatesan and colleagues in 2009 (22). The study included 10,641 mammograms performed in 20 facilities between 1998 and 2002. The purpose of the study was to evaluate the risk of cancer associated with specific abnormal findings in mammographic examinations, to determine the distribution and prevalence of these findings, and to analyze positive predictive value variation according to user and patient factors. The authors found that masses and calcifications were the most commonly recording findings. While masses were much more prevalent (69%) in diagnostic examination, in screening examinations masses, calcifications, and asymmetry were equally common. Architectural distortion was an uncommon finding for both screening and diagnostic mammograms. The positive predictive values of specific mammographic findings are listed in Table 2. The authors concluded that overall, one in

twenty invasive cancers was identified with asymmetry, one in sixteen invasive cancers was identified with architectural distortion, one in five invasive cancer was identified with calcification, and two in three invasive cancers were identified with a mass.

Table 2: Prevalence and positive predictive value of mammographic abnormalities in breast cancer detection (22).

Screening Examination (n=4025)	**Mass**	**Calcifications**	**Architectural Distortion**	**Asymmetry**
Incidence (n)	1417	1345	265	998
Prevalence (%)	35.2	33.4	6.6	24.8
Positive Predictive Value (%)	9.7	12.7	10.2	19.6
Diagnostic Examination (n=6616)	**Mass**	**Calcifications**	**Architectural Distortion**	**Asymmetry**
Incidence (n)	4534	1741	108	233
Prevalence (%)	68.5	26.3	1.6	3.5
Positive Predictive Value (%)	19.6	24.1	60.2	14.6

Mammographic Sensitivity

Although mammography remains the primary imaging modality for breast cancer screening, it remains limited in its ability to detect all cancers; its sensitivity ranges from 60-98% and has been reported to be as low as 30% in women with dense breasts (23-26).

In 1996, Kerlikowske and colleagues published a large cross-sectional study on mammography and the effects of patient's age and breast density on its sensitivity(25). The study, with over 20,000 women aged 30 years and older who underwent mammographic screening from 1985 to 1992, had 238 women who were subsequently diagnosed with breast cancer. The authors found that the sensitivity of screening mammography was the highest for women ages 50 or older with primarily fatty breasts compared to dense breasts (98.4% vs. 83.7%). For women less than 50 years of age, the study suggested that breast density did not seem to affect the sensitivity of mammography (81.8% for women with primarily fatty breast, 85.4% for women with dense breast). When the patients were further stratified by age, mammographic sensitivity was lower in women of younger age (see Table 3).

Table 3: Sensitivity of screening mammography of all breast cancer (25).

Age Range (y)	**30-39**	**40-49**	**50-59**	**60-69**	**≥ 70**
Mammographic Examinations (n)	7306	8833	4631	3402	1885
Breast Cancer Incidence (n)	22	45	47	51	34
Sensitivity (%)	77.3	86.7	83.6	94.1	91.2

The authors concluded that the lower sensitivity of mammography in younger women was due primarily to the more aggressive tumors in younger women, and was not due to denser breast tissue as the sensitivity of screening mammography decreased with increasing size of tumor, and a lower sensitivity for detecting large tumors is more

pronounced in younger than in older women. But contradicting these results, other studies have suggested that breast density is, in fact, a significant predictor of mammographic detections (26, 27). In Kolb and colleagues' investigation comparing screening mammography, physical examination, and breast ultrasound, the authors found that mammographic sensitivity declined significantly with increasing density and in younger women with dense breast, and these effects were independent. The sensitivity of mammography for women 49 years or younger and 50 years or older were 58% and 83%, respectively. The sensitivity of mammography for women with breast density decreased from densities less than 25% having 98% sensitivity, versus 25-50% breast density with 83% sensitivity; 51-75% breast density with 64% sensitivity, and more than 75% breast density with 48% sensitivity (27).

More recently, Ernster *et al.* analyzed 653,833 mammograms of 540,738 women between 40 and 84 years of age screened between 1996 and 1997 from the mammography registries of the Breast Cancer Surveillance Consortium (28). The purpose of their study was to determine mammography's role and ability in the screening and detection of ductal carcinoma in situ (DCIS), a non-invasive form of breast cancer. While doing so, the authors also provided findings for invasive breast cancer. They determined that the sensitivity of screening mammography for all patients was higher for DCIS than it was for invasive breast cancer (86% vs. 75%, respectively). Table 4 details the percentages of positive screen stratified by patients' age in their investigation. The authors concluded that approximately 1 in every 1300 screening mammograms leads to a diagnosis of DCIS. The increased sensitivity in detecting DCIS when compared to invasive breast cancer could be attributed to the microcalcifications associate with DCIS.

In dense or heterogeneously dense breast tissue, microcalcifications are easier to detect on mammograms and the DCIS may never become clinically apparent, thus potentially biasing the sensitivity for detecting DCIS upward.

Table 4: Mammographic sensitivity in detecting DCIS and invasive cancer (28).

Age Range (y)	**40-49**	**50-59**	**60-69**	**70-84**
Mammographic Examinations (n)	211551	200255	135376	106651
DCIS Cases Diagnosed (n)	134	155	165	137
DCIS Sensitivity (%)	88	88	84	83
Invasive Cancer Cases diagnosed (N)	450	792	709	724
Invasive Cancer Sensitivity (%)	67	72	76	83

From the above studies, it is reasonable to conclude that mammography is effective in screening for both DCIS and invasive breast cancer, however, its sensitivity for the detection of invasive cancer correlates positively with patient's age and negatively with breast density. Breast density itself is a major independent risk factor for breast cancer that cannot be explained by the masking of cancers by dense breast tissue (29), and previous studies suggested that younger patients who presented with false negative mammograms could represent a more aggressive form of cancer (25, 30). Therefore it is necessary to understand the pathology of mammographically occult breast cancer and to

evaluate its prognostic indication and to determine the most suitable treatment for patients diagnosed with mammographically occult tumors.

Other Factors Associated with Mammographically Occult Breast Cancer

Although false negative mammogram is often attributed to dense breast parenchyma in younger patients, inadequate radiographic technique, observer error, and diffuse tumor histology have also been suggested (1, 31, 32). In an early study by Holland *et al.,* the authors suggested that tumors of diffuse invasive type with poorly outlined mass, such as invasive lobular carcinomas with poor desmoplastic reaction, may lead to false negative mammograms, even in an advanced stage (33). This same finding of diffuse histology leading to a highly risk of false negative mammographic screening was also reported by Hollingsworth et al. (32). Morrow and colleagues in 1997 showed that particular histological tumor types, such as tubular carcinoma (13.5% of mammographically occult tumors and 1.8% of mammographically evident tumors), are more often associated with mammographically occult breast carcinoma (6). In another investigation, Wallis *et al.* noted that 5.5% of mammographically occult carcinomas had medullary histology compared with 0.8% of their mammographically evident cohort (1).

Breast Conservation Therapy

To be able to evaluate the appropriate treatment for patients diagnosed with early stage mammographically occult breast carcinoma, the current standard of care for early stage breast cancer patients must be understood. Surgery today remains an integral part of early stage breast cancer management. As an alternative to mastectomy, breast-

conserving therapy (BCT) has been found to be the therapeutic equivalent of total mastectomy in early breast cancer patients through many randomized trials (34-39). In BCT, the tumor is first removed with a margin of normal tissue, followed by whole breast irradiation (WBI). Radiotherapy (RT) has been proven to be effective in improving local control and long-term survival (40-45). Several key randomized studies are shown in Table 5. In 2002, Fisher and colleagues published their twenty-year follow up of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 randomized trial comparing total mastectomy, wide local resection, and wide local resection plus breast radiation (36). Between 1976 and 1986, a total of 2163 patients with stage I or II breast carcinoma were assigned to one of the three arms: mastectomy, lumpectomy, or lumpectomy plus 50 Gy of radiation to the whole breast. The authors at twenty-year follow up concluded that lumpectomy followed by breast irradiation continues to be an appropriate treatment for women with early stage breast cancer. Some of the significant findings of the recent publication included a significantly higher ipsilateral breast recurrence rate for women who underwent lumpectomy and without WBI (39.2% vs. 14.3% in women who underwent lumpectomy and breast irradiation), demonstrating the benefit of local control with radiotherapy to the intact breast. There were no significant differences in disease-free survival, distant-disease-free survival, or overall survival amongst the three groups of women. The hazard ratio for death among the women who underwent lumpectomy followed by breast irradiation as compared to mastectomy was 0.97 (95% CI, 0.83-1.14; p=0.74).

Table 5: Selected randomized trials of breast-conserving therapy versus mastectomy

Authors	Patients (n)	Average Length of Follow-up (y)	Local Recurrence With Radiation Therapy (%)	Local Recurrence Without Radiation Therapy (%)
Veronesi *et al.* (39)	567	10	5.83	23.5
Liljegren *et al.* (46)	381	10	8.5	23
Fisher *et al.* (36)	930	20	14.3	39.2

More recently, the addition of a boost to the tumor bed was found to further decrease local recurrence rate (47, 48). Bartelink and colleagues published their ten-year follow up of the randomized boost versus no boost European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 trial in 2007 (49). The study included 5318 patients who underwent lumpectomy followed by WBI to 50 Gy and were randomly assigned to receive either a boost of 16 Gy or no boost. At 10 years, the incidence of local recurrence for the patients who did not receive boost irradiation was 10.2%, and for the patients who received boost irradiation it was 6.2%. Subsequent sub-set analysis revealed that while the absolute risk reduction was the greatest in young women (<40 years of age) and high-grade tumors, a statistically significant benefit existed in all patients. Furthermore, the number of salvage mastectomies was reduced by 41% with the use of a boost.

Table 6: Selected randomized trials of boost versus no boost following whole breast irradiation

Authors	Patients (n)	Boost (Gy)	Average Length of Follow-up (y)	Local Recurrence With Boost (%)	Local Recurrence Without Boost (%)
Bartelink *et al.* (49)	2661	16	10	6.2	10.2
Romestaing *et al.* (48)	521	10	5	3.6	4.5

From these investigations, breast conservation therapy has become a standard alternative to mastectomy in patients with early stage breast cancer. Contraindications to a breast conserving approach include: persistent positive resection margins, multicentric disease defined as two or more tumors in separate breast quadrants, diffuse malignant–appearing microcalcifications, history of prior radiation therapy to a field that includes the affected breast, or pregnancy. It is important to note that there is no consensus on whether mammographically occult breast carcinoma should be not considered as a contraindication to breast-conserving therapy at this point.

BCT for Patients with Mammographically Occult Breast Cancer

For patients who present with mammographically occult primary tumors (MamOcc) who opt for a breast conserving approach, it is unclear whether the presentation of MamOcc disease confers a worse outcome in terms of local control. Data

on outcomes after BCT are limited, with some studies suggesting that patients with palpable disease and false-negative mammograms have a higher risk of diffuse or extensive disease and implying that these MamOcc patients may be poor candidates for BCT (32) while other studies suggest that MamOcc patients remain candidates for BCT (5, 6, 50). Furthermore, issues regarding how to conduct long-term follow-up and detect future breast recurrences for patients initially undetected by mammography have evoked concern physicians and patients alike.

In 1992, Samuels and colleagues published their experience with 542 patients with breast cancer treated with breast conserving therapy, of which 55 presented with MamOcc disease (5). The local recurrence, 5-year actuarial survival, and 5-year disease-free survival rates did not differ significant between the mammographically occult and mammographically evident cohorts (see Table 7). The authors concluded that BCT is an appropriate treatment for patients with palpable but mammographically negative early stage breast cancer. Similar conclusions were reached by Rajentheran *et al.* in their cohort of patients with 18-month follow up (50). Finally, Morrow *et al.* found in their series of MamOcc cases that mammographically occult tumors were not associated with factors such as size, unfavorable histology, or multicentrity and therefore concluded that patients with mammographically negative early stage breast cancers are still candidates for BCT (6).

The above studies suggest that BCT is suitable for patients with mammographically negative early stage breast cancer. However, a histologic study of patients presenting with MamOcc disease by Hollingsworth *et al.* reported that a principal finding of patients presenting with false-negative mammograms is the diffuse

histology of the primary tumors (32). Voogd *et al.* reported in their series that mammographically occult breast cancers are associated with higher local recurrence rate after breast conserving therapy (7). These studies indicate that BCT may be contraindicated in patients with mammographically occult tumors.

Table 7: Local recurrence and survival of patients with mammographically occult and mammographically positive early stage breast cancers after BCT (6).

	Patients (n)	Local Recurrence (%)	5-year Actuarial Survival (%)	5-year Disease Free Survival (%)
Mammographically Occult Patients	55	10.9	79	94
Mammographically Positive Patients	219	10.5	79	84

STATEMENT OF PURPOSE

In this study, we examined our large institutional experience of early-stage breast cancer patients treated with BCT who initially presented with MamOcc disease, compared with patients who presented with positive mammograms (MamPos), to examine the clinical and pathologic features and long-term outcomes of these two groups of patients. Magnetic resonance imaging of the breast was not used in any of our patients as a method of detection in this study. In addition, we analyzed the recurrence patterns of these two cohorts of patients to determine the implications for follow-up for MamOcc patients who are treated with BCT.

METHODS AND MATERIALS

Patient Selection

Between the years of 1974 and 2003, 214 MamOcc and 2168 MamPos patients with early-stage breast carcinoma underwent BCT at the Yale University School of Medicine, Department of Therapeutic Radiology. These two groups of patients constituted our study and reference cohorts, respectively, and were the focus of our study. After approval from the Human Investigations Committee was obtained, a chart review was conducted for assessment of mammogram reports and method of tumor detection for all available patients within our database, to confirm the MamOcc cohort. In addition, clinical parameters (method of tumor detection, age of diagnosis, family history), pathologic factors (T stage, nodal status, margin status, histology, expression of estrogen, progesterone, and HER-2 receptors) and outcomes (local–regional relapse, distant relapse, and overall survival) were recorded. Because of the era in which these patients were treated, the vast majority had axillary lymph node dissection. For those who did not have axillary lymph node dissection, axillary radiotherapy was delivered to treat the axillary contents. All patients received a median dose of 48 Gy to the whole breast, followed by a boost, for a median total dose of 64 Gy. Regional nodal radiation was delivered as clinically indicated and has been previously described (51-53). Systemic therapy was delivered at the discretion of the treating physicians. All patients who were non-Caucasian were excluded from our outcomes analysis to ensure that race would not confound results, because the frequency of non-white vs. white patients was different for the MamOcc cohort (5.6% vs. 11.32%; $p = 0.0354$). Of the 2 cohorts, the white population was comprised of 202 MamOcc and 1918 MamPos patients.

Statistical analysis

All clinical and pathologic features of the two cohorts were entered into a database and analyzed using SAS 9.1 (SAS Institute, Cary, NC). All tests of statistical significance were two-sided, and p values of <0.05 were considered statistically significant. Bivariate analyses for the association between covariables and MamOcc/MamPos were performed using $\chi 2$ and Fisher exact tests. The outcome parameters analyzed included breast relapse–free survival (defined as time from diagnosis to recurrent disease within the breast), distant recurrence–free survival (time of diagnosis to disease failure outside the local–regional area), cause-specific survival (interval from the date of diagnosis to the date of death from breast cancer or to the last follow-up date), and overall survival (interval between date of diagnosis and death). Comparison of clinical and pathologic characteristics between the MamOcc and MamPos groups was done using $\chi 2$ analysis. The outcome endpoints were calculated using standard life-table methods, and the differences were compared using Cox regression models. The outcome parameters were analyzed by multivariate analysis incorporating method of tumor detection, age at diagnosis, T stage, nodal status, margin status, HER-2/neu status, and triple-negative status into the regression model.

RESULTS

Median follow-up was 8.4 years for MamOcc patients and 6.6 years for MamPos patients. The method of presentation for the 202 MamOcc patients was a palpable mass in all cases; there were no patients with T0 N+ (completely occult primary tumors presenting with lymph node involvement) in this analysis. The incidence of MamOcc over the study period in 4-year increments from 1975 to 2003 is shown in Fig. 1. The highest incidence occurred in the mid-1980s and then seems to have decreased over time. There were no significant differences in final margin status, T stage, or nodal status for the MamOcc vs. MamPos groups. The age at diagnosis differed significantly for the two cohorts; specifically, more patients in the MamOcc group presented at a young age (age ≤40 years) than in the MamPos group (31% vs. 11%, $p < 0.0001$). The MamOcc group reported positive family history more often than patients in the MamPos cohort (46% vs. 35%, $p = 0.0033$). Although all patients had invasive carcinoma, the primary histology of the tumor differed between the two cohorts, with the MamOcc patients having a higher incidence of infiltrating lobular carcinoma (12% vs. 5%) and a lower association with ductal carcinoma in situ (2% vs. 17%) when compared with the MamPos group ($p < 0.0001$). Although the percentages of patients who were estrogen receptor positive, progesterone receptor positive, and triple negative (estrogen, progesterone, and HER-2/neu negative) did not differ significantly between the two groups, the MamOcc patients were HER-2 positive less often (14% vs. 29%, $p = 0.0294$). Table 2 summarizes the clinical and pathologic tumor characteristics of the MamOcc and MamPos cohorts.

Table 7: Clinical and pathologic characteristics of MamOcc vs. MamPos.

Parameter	MamOcc n (%)	MamPos n (%)	*p* value
Age at diagnosis			<0.0001
≤ 40 years	66 (31)	246 (11)	
> 40 years	148 (69)	1922 (89)	
Family History			0.003
Positive	87 (46)	682 (35)	
Negative	101 (54)	1250 (65)	
Primary Histology			<0.0001
IDC	160 (76)	1495 (78)	
ILC	26 (12)	112 (5)	
Associated DCIS	5 (2)	322 (15)	
Margin			0.975
Positive	36 (26)	384 (26)	
Negative	102 (74)	1095 (74)	
Stage			0.818
T1	153(81)	1512 (80)	
T2	36 (19)	372 (20)	
Node			0.999
Positive	43 (26)	334 (26)	
Negative	125 (74)	971 (74)	
ER			0.215
Positive	95 (57)	995 (62)	
Negative	71 (43)	606 (38)	
PR			0.379
Positive	74 (48)	758 (52)	
Negative	79 (52)	697 (48)	
HER-2			
Positive	7 (14%)	128 (29%)	0.029
Negative	44 (86)	320 (71%)	
Triple Negative			0.060
Yes	14 (15)	87 (9)	
No	82 (85)	907 (91)	

Abbreviations: MamOcc= mammographically occult cohort; MamPos= mammographically positive cohort; ILC= infiltrating lobular carcinoma; DCIS= ductal carcinoma in situ; ER= estrogen receptor; PR= progesterone receptor; HER-2= human epidermal growth factor receptor 2.

Treatment parameters for the two cohorts were as follows: median dose to tumor bed was 64 Gy in both cohorts. All patients in the two cohorts underwent either axillary nodal dissection or radiation to the full axilla. There were differences in the percentages of patients who received chemotherapy (35% vs. 26%; p = 0.007) and adjuvant hormonal therapy (25% vs. 33%; p = 0.0135) for the MamOcc vs. MamPos cohorts, respectively. At 10 years there were no significant differences in survival outcomes between the two cohorts (overall survival, p = 0.693; cause-specific survival, p = 0.183). The distant metastasis rate between the two cohorts did not differ significantly (16% vs. 12%; p = 0.586).

Patients of the MamOcc cohort had a significantly higher breast relapse rate (15% vs. 8%; p = 0.036) compared with the MamPos patients and more nodal relapse (4% vs. 1%; p = 0.008). The clinical outcomes of the MamOcc and MamPos cohorts at 10 years are detailed in Table 3, and the survival curves are shown in Fig. 2.

Table 8: Clinical outcomes at 10 Years.

Outcome Parameter	**MamOcc (%)**	**MamPos (%)**	***p value***
Breast Relapse Free Survival	85	92	0.036
Nodal Relapse Free Survival	96	99	0.008
Distant Disease Free Survival	84	88	0.586
Cause Specific Survival	85	91	0.183

Abbreviations: abbreviations as in Table 7.

When method of detection, age at diagnosis, T stage, nodal status, margin status, and HER-2 and triple-negative status were incorporated into the multivariate regression model, MamOcc disease was not an independent predictor of breast relapse–free survival (hazard ratio 1.0, 95% confidence interval 0.993–1.007, p = 0.9296) but remained an independent predictor of nodal relapse–free survival (hazard ratio 0.987, 95% confidence interval 0.975–1.000, p = 0.0483), as shown in Table 4 and Table 5.

Table 9: Results of multivariate Cox regression analysis for local control- Breast relapse-free survival.

Variables	Hazard ratio (95% CI)	*p* value
Mammography		0.9296
Positive	1.0 (referent)	
Negative	1.0 (0.993-1.007)	
Age		0.8359
≤ 40	0.935 (0.494-1.768)	
> 40	1.0 (referent)	
Tumor Size		0.1184
T1	1.0 (referent)	
T2	1.666 (0.878-3.163)	
Nodal Status		0.9977
Negative	1.0 (referent)	
Positive	1.0 (0.858-1.166)	
Surgical Margin		0.0079
Negative	1.0 (referent)	
Positive	1.203 (1.050-1.378)	
HER2		0.3702
Negative	1.0 (referent)	

	Positive	1.366 (0.691-2.702)	
Triple Negative			0.9014
	Negative	1.0 (referent)	
	Positive	0.953 (0.444-2.046)	

Abbreviations: HR= hazard ratio; CI= confidence interval; other abbreviations as in Table 7.

Table 10: Results of multivariate Cox regression analysis for local control- Nodal relapse-free survival.

Variables		Hazard ratio (95% CI)	*p* value
Mammography			0.0483
	Positive	1.0 (referent)	
	Negative	0.987 (0.975-1.000)	
Age			0.1433
	≤ 40	2.677 (0.716-10.004)	
	> 40	1.0 (referent)	
Tumor Size			0.0326
	T1	1.0 (referent)	
	T2	4.525 (1.133-18.074)	
Nodal Status			0.1836
	Negative	1.0 (referent)	
	Positive	1.278 (0.890-1.279)	
Surgical Margin			0.3907
	Negative	1.0 (referent)	
	Positive	0.840 (0.563-1.251)	
HER2			0.8750
	Negative	1.0 (referent)	
	Positive	0.866 (0.144-5.205)	
Triple Negative			0.3152
	Negative	1.0 (referent)	
	Positive	0.460 (0.101-2.095)	

Abbreviations: abbreviations as in Table 9 and Table 7.

Of the MamOcc patients who sustained a breast recurrence, 32% (8 of 25) had a false-negative/mammographically occult tumor at the time of relapse. This contrasted with the MamPos patients, of whom only 13% (19 of 150) had false-negative/mammographically occult tumors at local relapse. This difference in false-negative mammograms at time of recurrence for the MamOcc and MamPos cohorts achieved statistical significance ($p = 0.0136$).

DISCUSSION

Although mammography is the current standard method for breast imaging before definitive treatment for early-stage breast cancer, a fraction of patients will have primary tumors that are mammographically occult. The actual percentage of patients presenting with mammographically occult primary tumors at diagnosis has been stated to be as high as 35% in younger women (54) but generally is quoted to be in the range of 9–22% (1-4). Unfortunately, the long-term prognostic implications for early-stage breast cancer patients who present with mammographically occult tumors and who choose BCT is largely unknown. Most studies on MamOcc disease have focused on radiographic analysis, concentrating on retrospectively reviewing mammograms after the diagnosis of breast cancer to discern whether the primary tumor was initially missed. Although several smaller studies have attempted to address recurrence after BCT for MamOcc patients, to the best of our knowledge our study represents the largest series of MamOcc patients treated with conservative surgery and radiotherapy and characterizes differences in long-term outcomes, as well as clinical and pathologic characteristics between MamOcc and MamPos patients.

Several smaller studies have attempted to analyze clinical–pathologic characteristics, outcomes, and recurrence patterns in MamOcc patients after BCT. In 1992, Samuels *et al.* (5) reported on outcomes and recurrences after BCT for MamOcc patients by analyzing 55 MamOcc and 487 MamPos patients who had undergone conservative surgery and radiotherapy. Consistent with our findings, they found that MamOcc patients presented at a younger age, with no difference in T stage and nodal status. They did not find any significant differences in local–regional control, distant

metastasis, or overall survival, and concluded that BCT is a suitable treatment option for MamOcc patients. Furthermore, in direct contrast to our findings, evaluation of mammograms at recurrence led them to conclude that "negative mammograms at the time of diagnosis are not predictive of a negative mammogram at recurrence." It is possible that the differences in our findings are due to the significantly larger sample sizes of our two cohorts. Because our study had four times as many subjects as that of Samuels et al., we had greater statistical power to detect a difference.

In 1999, Voogd et al. (7) took another approach to address the topic of BCT and MamOcc patients. They identified 39 patients who had local recurrence after BCT and 126 randomly chosen patients without recurrence after conservative therapy, and reviewed all the reports from the initial and recurrence mammograms. They demonstrated that patients who presented initially with mammographically occult primary tumors had a higher risk of local recurrence after BCT, although the difference was only significant for patients aged <50 years. Again, the sample size for the MamOcc group was small (30 patients), and there were only 4 patients in the cohort who were older than 50 years. They attempted to find an explanation for the association between mammographic findings and local recurrence by performing a central pathology review but did not find any factors that could potentially explain the increase in relapse for the MamOcc cohort.

In a 2008 study, Weinstein et al. (55) characterized mammographic finding in patients who had undergone BCT and sustained a local relapse. Of their 26 patients who initially presented with MamOcc disease and developed a breast relapse, 23.1% had mammographically occult recurrences, which did not differ significantly from their cohort of recurrent patients who were initially MamPos. They concluded that "the

mammographic appearance of the original tumor does not always correlate with the recurrent tumor." In contrast, Burrell et al. (56) retrospectively reviewed 31 patients with recurrent tumors and found a high concordance with the characteristics of the original mammogram. Because of the differences in design of these studies, neither of these publications spoke directly to the question of the characteristics of MamOcc patients who had undergone BCT but instead looked to characterize mammographic features of patients with recurrence.

In the present study we found a younger age at presentation, more invasive lobular histology, and less association with ductal carcinoma in situ in our MamOcc cohort, consistent with findings in other studies (2, 6, 31, 57). We also found a significant difference in the incidence of self-reported positive family history between our MamOcc and MamPos cohort, and less HER-2/neu–positive disease. It is notable that we did not find a difference in primary T stage of the tumor (i.e. T1 vs. T2 disease) or more nodal involvement in the MamOcc cohort.

In addition, the negative margin rate between the two cohorts was comparable, a finding of particular importance because mammography has been the standard tool used by surgeons to delineate the location and extent of disease to determine whether a patient will be a candidate for successful breast-conserving surgery. In our series, the percentage of patients with positive margins in both cohorts was exactly equal, which suggests that false-negative mammograms at presentation are not a predictor for positive margins (or inability to completely excise the primary tumor). It is important to note that our two cohorts were treated over a span of nearly 3 decades, in an era in which MRI of the breast was not available for routine use at our institution. Our mammographically occult cohort

generally went directly to biopsy (with or without ultrasound). With the frequent use of MRI in our current practices, contemporary workup for a MamOcc patient seen in our clinics today would likely result in positive MRI findings. Furthermore, with the current widespread use of breast MRI, it is even more unlikely that there would be any differences in outcomes for patients treated today.

We did note that the delivery of systemic therapy differed for the MamOcc and the MamPos cohorts. The MamOcc patients received more chemotherapy, and the MamPos patients received more adjuvant hormone therapy. This is likely explained by the fact that the MamOcc patients were younger and were therefore given chemotherapy more frequently and received hormones less frequently, although we did not find a difference in the estrogen/progesterone receptor status of the two study cohorts. Our outcomes analysis suggests there is no difference in distant disease–free survival, cause-specific survival, or overall survival between the two cohorts at 10 years. Although the differences we noted in breast relapse–free survival were statistically significant on univariate analysis, mammographically occult primary tumors at diagnosis were not an independent predictor of local relapse on multivariate analysis when taking into account the other confounding factors. MamOcc disease remained an independent predictor of nodal recurrence on multivariate analysis, but because the numbers of nodal relapses overall were very small, no firm conclusions can be drawn from these data as to the cause of increased nodal relapses in MamOcc patients.

An important finding of our study is the lower mammographic detectability of the recurrent cancers in the MamOcc cohort after BCT. These results lead us to conclude that clinical and pathologic differences in the MamOcc and MamPos patients ultimately result

in more false-negative mammograms at recurrence for the MamOcc cohort, suggesting that this population of patients should be considered for closer clinical follow-up and alternative imaging strategies, such as ultrasound and breast MRI after BCT.

There are several limitations to our study that warrant further discussion. Intrinsic to the nature of all retrospective studies, selection biases cannot be entirely accounted for. Furthermore, although the number of patients in our cohorts was relatively large, it is possible that the differences in outcomes did not achieve statistical significance owing to the study being underpowered. Most importantly, although a review of all mammogram reports was conducted to verify the MamOcc cohort, we did not conduct a central review of the actual mammograms to determine what percentage of these mammographically occult tumors were due to "radiological oversight." In addition, the use of other imaging modalities (i.e., breast ultrasound) was not evaluated in this study.

Finally, our study is based on a single-institution experience, and multi-institutional evaluation of larger patient population is needed to eliminate biases based on differences that may exist in patient demographics, diagnostic procedures, and therapeutic interventions from one institution to the next.

In conclusion, our series suggests that there are clinical–pathologic differences in MamOcc vs. MamPos patients that may ultimately affect management and outcomes. MamOcc patients present at a younger age, have invasive lobular histology more often, are less often associated with ductal carcinoma in situ, and have less HER-2/neu–positive disease. Although local control does not seem to be compromised in MamOcc patients undergoing BCT, these patients have a higher tendency to have false-negative mammograms at the time of breast recurrence and therefore should be considered for

closer clinical follow-up and alternative imaging strategies, such as ultrasound and breast MRI, as part of their routine post-treatment examination.

REFERENCES

1. Wallis, M.G., Walsh, M.T., and Lee, J.R. 1991. A review of false negative mammography in a symptomatic population. *Clin Radiol* 44:13-15.
2. Feig, S.A., Shaber, G.S., Patchefsky, A., Schwartz, G.F., Edeiken, J., Libshitz, H.I., Nerlinger, R., Curley, R.F., and Wallace, J.D. 1977. Analysis of clinically occult and mammographically occult breast tumors. *AJR Am J Roentgenol* 128:403-408.
3. Edeiken, S. 1988. Mammography and palpable cancer of the breast. *Cancer* 61:263-265.
4. Niloff, P.H., and Sheiner, N.M. 1981. False-negative mammograms in patients with breast cancer. *Can J Surg* 24:50, 52.
5. Samuels, J.R., Haffty, B.G., Lee, C.H., and Fischer, D.B. 1992. Breast conservation therapy in patients with mammographically undetected breast cancer. *Radiology* 185:425-427.
6. Morrow, M., Schmidt, R.A., and Bucci, C. 1998. Breast conservation for mammographically occult carcinoma. *Ann Surg* 227:502-506.
7. Voogd, A.C., van, d.H.F., Crommelin, M.A., Peterse, J.L., van, B.M.W., Repelaer, v.D.O.J., van, d.H.L.H., and Coebergh, J.W. 1999. The relationship between findings on pre-treatment mammograms and local recurrence after breast-conserving therapy for invasive breast cancer. *Eur J Surg Oncol* 25:273-279.
8. Jemal, A., Siegel, R., Xu, J., and Ward, E. Cancer statistics, 2010. *Ca* 60:277-300. Epub 2010 Jul 2017.
9. Pisano, E.D., Gatsonis, C., Hendrick, E., Yaffe, M., Baum, J.K., Acharyya, S., Conant, E.F., Fajardo, L.L., Bassett, L., D'Orsi, C., et al. 2005. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med.* 353:1773-1783. Epub 2005 Sep 1716.
10. Kuhl, C.K., Schrading, S., Leutner, C.C., Morakkabati-Spitz, N., Wardelmann, E., Fimmers, R., Kuhn, W., and Schild, H.H. 2005. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol.* 23:8469-8476.
11. Berg, W.A., Blume, J.D., Cormack, J.B., Mendelson, E.B., Lehrer, D., Bohm-Velez, M., Pisano, E.D., Jong, R.A., Evans, W.P., Morton, M.J., et al. 2008. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *Jama.* 299:2151-2163.
12. Morrow, M. Magnetic resonance imaging for screening, diagnosis, and eligibility for breast-conserving surgery: promises and pitfalls. *Surg* 19:475-492. Epub 2010 May 2015.
13. Warner, E., Messersmith, H., Causer, P., Eisen, A., Shumak, R., and Plewes, D. 2008. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med.* 148:671-679.
14. Riedl, C.C., Ponhold, L., Flory, D., Weber, M., Kroiss, R., Wagner, T., Fuchsjager, M., and Helbich, T.H. 2007. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and

premalignant lesions during surveillance of women at high risk for breast cancer. *Clin Cancer Res.* 13:6144-6152.

15. Gold, R.H., Bassett, L.W., and Widoff, B.E. 1990. Highlights from the history of mammography. *Radiographics.* 10:1111-1131.
16. Clark, R.L., Copeland, M.M., Egan, R.L., Gallager, H.S., Geller, H., Lindsay, J.P., Robbins, L.C., and White, E.C. 1965. REPRODUCIBILITY OF THE TECHNIC OF MAMMOGRAPHY (EGAN) FOR CANCER OF THE BREAST. *Am J Surg.* 109:127-133.
17. Strax, P., Venet, L., and Shapiro, S. 1973. Value of mammography in reduction of mortality from breast cancer in mass screening. *Am J Roentgenol Radium Ther Nucl Med.* 117:686-689.
18. Nystrom, L., Andersson, I., Bjurstam, N., Frisell, J., Nordenskjold, B., and Rutqvist, L.E. 2002. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet.* 359:909-919.
19. Gotzsche, P.C., and Nielsen, M. 2006. Screening for breast cancer with mammography. *Cochrane Database Syst Rev.*:CD001877.
20. 2009. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 151:716-726, W-236.
21. Nelson, H.D., Tyne, K., Naik, A., Bougatsos, C., Chan, B.K., and Humphrey, L. 2009. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med.* 151:727-737, W237-742.
22. Venkatesan, A., Chu, P., Kerlikowske, K., Sickles, E.A., and Smith-Bindman, R. 2009. Positive predictive value of specific mammographic findings according to reader and patient variables. *Radiology.* 250:648-657. Epub 2009 Jan 2021.
23. Burhenne, H.J., Burhenne, L.W., Goldberg, F., Hislop, T.G., Worth, A.J., Rebbeck, P.M., and Kan, L. 1994. Interval breast cancers in the Screening Mammography Program of British Columbia: analysis and classification. *AJR Am J Roentgenol.* 162:1067-1071; discussion 1072-1065.
24. Robertson, C.L. 1993. A private breast imaging practice: medical audit of 25,788 screening and 1,077 diagnostic examinations. *Radiology.* 187:75-79.
25. Kerlikowske, K., Grady, D., Barclay, J., Sickles, E.A., and Ernster, V. 1996. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *Jama.* 276:33-38.
26. Mandelson, M.T., Oestreicher, N., Porter, P.L., White, D., Finder, C.A., Taplin, S.H., and White, E. 2000. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst.* 92:1081-1087.
27. Kolb, T.M., Lichy, J., and Newhouse, J.H. 2002. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology.* 225:165-175.
28. Ernster, V.L., Ballard-Barbash, R., Barlow, W.E., Zheng, Y., Weaver, D.L., Cutter, G., Yankaskas, B.C., Rosenberg, R., Carney, P.A., Kerlikowske, K., et al. 2002. Detection of ductal carcinoma in situ in women undergoing screening mammography. *J Natl Cancer Inst.* 94:1546-1554.

29. Boyd, N.F., Martin, L.J., Yaffe, M., and Minkin, S. 2009. Mammographic density. *Breast Cancer Res.* 11:S4. Epub 2009 Dec 2018.
30. Brekelmans, C.T., Collette, H.J., Collette, C., Fracheboud, J., and de Waard, F. 1992. Breast cancer after a negative screen: follow-up of women participating in the DOM Screening Programme. *Eur J Cancer.* 28A:893-895.
31. Moran, M.S., Yang, Q., and Haffty, B.G. 2009. The Yale University experience of early-stage invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) treated with breast conservation treatment (BCT): analysis of clinical-pathologic features, long-term outcomes, and molecular expression of COX-2, Bcl-2, and p53 as a function of histology. *Breast J.* 15:571-578.
32. Hollingsworth, A.B., Taylor, L.D., and Rhodes, D.C. 1993. Establishing a histologic basis for false-negative mammograms. *Am J Surg* 166:643-647; discussion 647-648.
33. Holland, R., Hendriks, J.H., and Mravunac, M. 1983. Mammographically occult breast cancer. A pathologic and radiologic study. *Cancer* 52:1810-1819.
34. Jacobson, J.A., Danforth, D.N., Cowan, K.H., d'Angelo, T., Steinberg, S.M., Pierce, L., Lippman, M.E., Lichter, A.S., Glatstein, E., and Okunieff, P. 1995. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 332:907-911.
35. Blichert-Toft, M., Rose, C., Andersen, J.A., Overgaard, M., Axelsson, C.K., Andersen, K.W., and Mouridsen, H.T. 1992. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr*:19-25.
36. Fisher, B., Anderson, S., Bryant, J., Margolese, R.G., Deutsch, M., Fisher, E.R., Jeong, J.H., and Wolmark, N. 2002. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 347:1233-1241.
37. Sarrazin, D., Le, M.G., Arriagada, R., Contesso, G., Fontaine, F., Spielmann, M., Rochard, F., Le Chevalier, T., and Lacour, J. 1989. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol* 14:177-184.
38. van Dongen, J.A., Voogd, A.C., Fentiman, I.S., Legrand, C., Sylvester, R.J., Tong, D., van der Schueren, E., Helle, P.A., van Zijl, K., and Bartelink, H. 2000. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 92:1143-1150.
39. Veronesi, U., Marubini, E., Mariani, L., Galimberti, V., Luini, A., Veronesi, P., Salvadori, B., and Zucali, R. 2001. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 12:997-1003.
40. Overgaard, M., Jensen, M.B., Overgaard, J., Hansen, P.S., Rose, C., Andersson, M., Kamby, C., Kjaer, M., Gadeberg, C.C., Rasmussen, B.B., et al. 1999. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 353:1641-1648.

41. Fisher, B., Dignam, J., Wolmark, N., Mamounas, E., Costantino, J., Poller, W., Fisher, E.R., Wickerham, D.L., Deutsch, M., Margolese, R., et al. 1998. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 16:441-452.
42. Halverson, K.J., Perez, C.A., Kuske, R.R., Garcia, D.M., Simpson, J.R., and Fineberg, B. 1990. Isolated local-regional recurrence of breast cancer following mastectomy: radiotherapeutic management. *Int J Radiat Oncol Biol Phys* 19:851-858.
43. Ragaz, J., Jackson, S.M., Le, N., Plenderleith, I.H., Spinelli, J.J., Basco, V.E., Wilson, K.S., Knowling, M.A., Coppin, C.M., Paradis, M., et al. 1997. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 337:956-962.
44. Solin, L.J., Kurtz, J., Fourquet, A., Amalric, R., Recht, A., Bornstein, B.A., Kuske, R., Taylor, M., Barrett, W., Fowble, B., et al. 1996. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. *J Clin Oncol* 14:754-763.
45. Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans, E., Godwin, J., Gray, R., Hicks, C., James, S., et al. 2005. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366:2087-2106.
46. Liljegren, G., Holmberg, L., Bergh, J., Lindgren, A., Tabar, L., Nordgren, H., and Adami, H.O. 1999. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 17:2326-2333.
47. Bartelink, H., Horiot, J.C., Poortmans, P., Struikmans, H., Van den Bogaert, W., Barillot, I., Fourquet, A., Borger, J., Jager, J., Hoogenraad, W., et al. 2001. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 345:1378-1387.
48. Romestaing, P., Lehingue, Y., Carrie, C., Coquard, R., Montbarbon, X., Ardiet, J.M., Mamelle, N., and Gerard, J.P. 1997. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 15:963-968.
49. Bartelink, H., Horiot, J.C., Poortmans, P.M., Struikmans, H., Van den Bogaert, W., Fourquet, A., Jager, J.J., Hoogenraad, W.J., Oei, S.B., Warlam-Rodenhuis, C.C., et al. 2007. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol.* 25:3259-3265. Epub 2007 Jun 3218.
50. Rajentheran, R., Rao, C.M., Lim, E., and Lennard, T.W. 2001. Palpable breast cancer which is mammographically invisible. *Breast* 10:416-420.
51. Pejavar, S., Wilson, L.D., and Haffty, B.G. 2006. Regional nodal recurrence in breast cancer patients treated with conservative surgery and radiation therapy (BCS+RT). *Int J Radiat Oncol Biol Phys* 66:1320-1327.
52. Grills, I.S., Kestin, L.L., Goldstein, N., Mitchell, C., Martinez, A., Ingold, J., and Vicini, F.A. 2003. Risk factors for regional nodal failure after breast-conserving

therapy: regional nodal irradiation reduces rate of axillary failure in patients with four or more positive lymph nodes. *Int J Radiat Oncol Biol Phys* 56:658-670.

53. Reed, D.R., Lindsley, S.K., Mann, G.N., Austin-Seymour, M., Korssjoen, T., Anderson, B.O., and Moe, R. 2005. Axillary lymph node dose with tangential breast irradiation. *Int J Radiat Oncol Biol Phys* 61:358-364.
54. Joensuu, H., Asola, R., Holli, K., Kumpulainen, E., Nikkanen, V., and Parvinen, L.M. 1994. Delayed diagnosis and large size of breast cancer after a false negative mammogram. *Eur J Cancer.* 30A:1299-1302.
55. Weinstein, S.P., Orel, S.G., Pinnamaneni, N., Tchou, J., Czerniecki, B., Boraas, M., Rosato, E., and Solin, L.J. 2008. Mammographic appearance of recurrent breast cancer after breast conservation therapy. *Acad Radiol* 15:240-244.
56. Burrell, H.C., Sibbering, D.M., Evans, A.J., and Nottingham Breast, T. 1996. Do mammographic features of locally recurrent breast cancer mimic those of the original tumour? . *Breast* 5:233-236.
57. Ma, L., Fishell, E., Wright, B., Hanna, W., Allan, S., and Boyd, N.F. 1992. Case-control study of factors associated with failure to detect breast cancer by mammography. *J Natl Cancer Inst* 84:781-785.

FIGURES

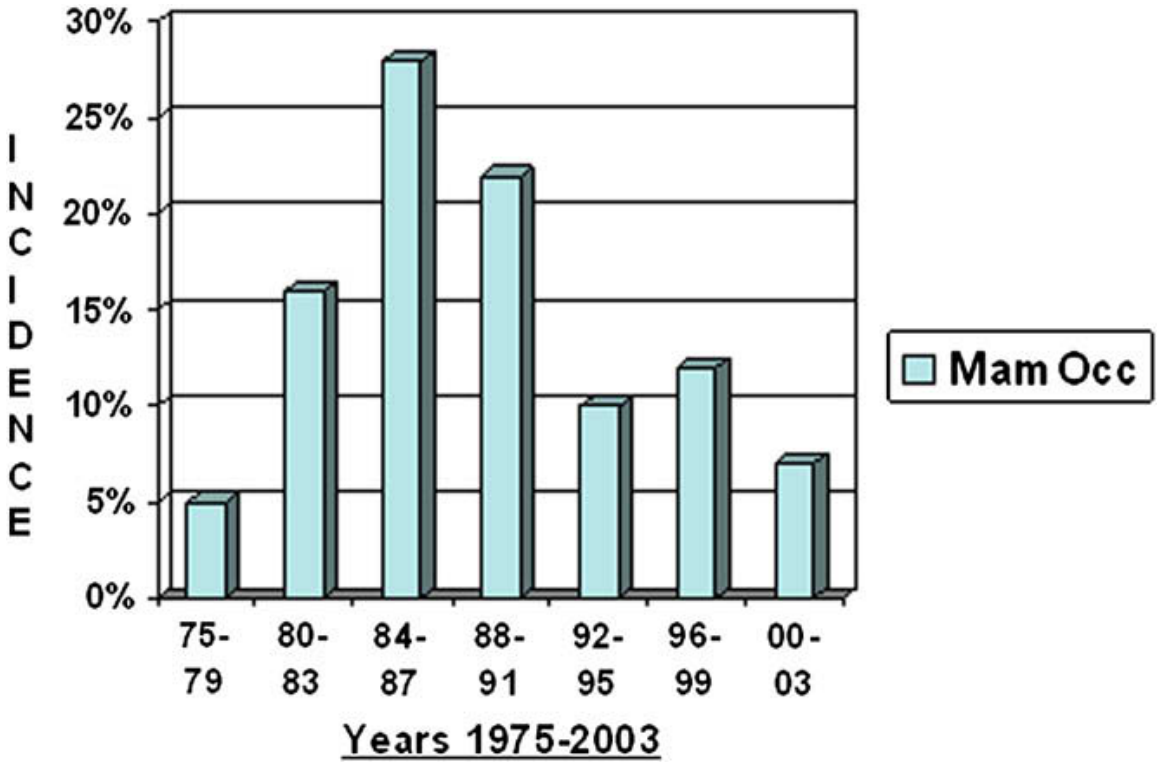

Fig. 1. Incidence of mammographically occult (MamOcc) patients over the study period 1975–2003 as a percentage of the total.

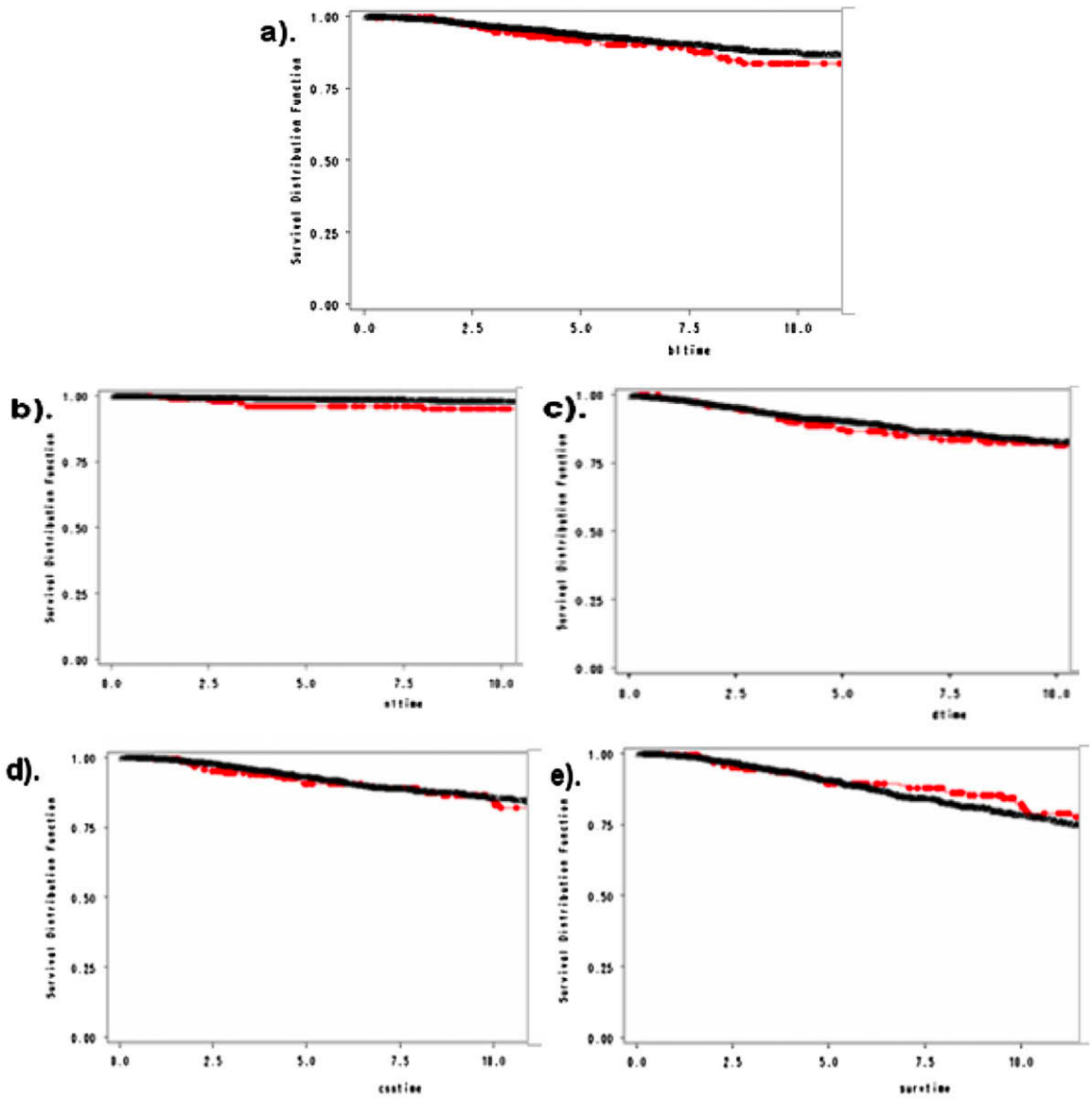

Fig. 2. Ten-year clinical outcomes of mammographically occult (red) and mammographically positive (black) cohorts. (a) Breast relapse–free survival; (b) nodal relapse–free survival; (c) disease-free survival; (d) cause-specific survival; (e) overall survival.