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Non-palpable Lesions of the Breast Detected by Mammography — Review of 1182 Consecutive Histologically Confirmed Cases

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We report on 1182 consecutive histologically confirmed non-palpable breast lesions detected by mammography (infiltrating carcinoma 427, *in situ* carcinoma 121, benign 634). The proportion of cancer cases varied according to age (< 50 years = 33%; 50–59 years = 46%; > 59 years = 63%), mammographic pattern (regular opacities = 8%, parenchymal distortions = 20%, isolated calcifications = 42%, irregular opacities = 62%, stellate opacities = 73%), and calendar period (1970–1985 = 29%, 1986–1989 = 56%; 1990–1992 = 69%). A sharp decrease of the benign/malignant biopsy ratio was evident after routine fine-needle aspiration cytology (sonography-guided or stereotactic) was introduced in 1986. The independent significant association of cancer frequency to age, calendar period and mamographic pattern was confirmed by multivariate analysis. A significant trend over time in favour of conservative surgery was also observed for cancer cases (1970–1979 = 6%, 1980–1985 = 41%, 1986–1992 = 83%). Among invasive cancers, node involvement was observed in 11.5% of cases, being associated with tumour size (pT1a = 0%, pT1b = 7%, pT1c = 13%, pT2a = 33%). Five-, ten- and fifteen-year overall survivals of invasive cancers were 98.1, 95.7 and 87.3%, respectively.

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INTRODUCTION

SUSPICIOUS NON-PALPABLE lesions of the breast are increasingly detected due to the widespread use of mammography, performed either for screening or clinical purpose [1, 2]. Unfortunately, mammography is not very specific, and the detection of subclinical cancer results in a relatively high number of unnecessary biopsies for benign lesions [1, 3]. The use of stereotactic or sonography-guided cytology has greatly improved the accuracy

of preoperative diagnosis, and the benign/malignant biopsy ratio has been reduced considerably [3–6].

Non-palpable breast cancer may be managed by conservative surgery in the majority of cases, and has a very favourable prognosis in terms of survival [2, 7]. Although length biased sampling, lead time bias and overdiagnosis must be taken into account, preclinical detection is possibly the major benefit of mammographic screening, which has been shown to significantly reduce breast cancer mortality [8].

Table 1. Distribution of studied cases according to histological diagnosis and by patient's age, year of diagnosis and mammographic pattern

	(n)	Histological diagnosis			
		Infiltrating cancer (%)	<i>In situ</i> cancer (%)	Atypical hyperplasia (%)	Other benign (%)
Age					
< 40	(39)	13 (33.3)	1 (2.6)	—	25 (64.1)
40–49	(373)	90 (24.1)	32 (8.6)	9 (2.4)	242 (64.9)
50–59	(412)	145 (35.2)	43 (10.4)	11 (2.7)	213 (51.7)
> 59	(358)	179 (50.0)	45 (12.6)	2 (0.5)	132 (36.9)
Mammographic pattern					
Opacities					
Regular	(98)	7 (7.1)	1 (1.0)	—	90 (91.8)
Irregular	(234)	135 (57.7)	11 (4.7)	3 (1.3)	85 (36.3)
Stellate	(156)	112 (71.8)	2 (1.3)	2 (1.3)	40 (25.6)
Microcalcifications	(649)	164 (25.3)	107 (16.5)	13 (2.0)	365 (56.2)
Distortions	(45)	9 (20.0)	—	4 (8.9)	32 (71.1)
Year of diagnosis					
1970–1975	(45)	24 (53.3)	1 (2.2)	—	20 (44.4)
1976–1980	(100)	28 (28.0)	4 (4.0)	—	68 (68.0)
1981–1985	(415)	85 (20.5)	21 (5.1)	5 (1.2)	304 (73.2)
1986–1989	(344)	149 (43.3)	45 (13.1)	8 (2.3)	142 (41.3)
1990–1992	(278)	141 (50.7)	50 (18.0)	9 (3.2)	78 (28.1)
Total cases	(1182)	427 (36.1)	121 (10.2)	22 (1.9)	612 (51.8)

The present study reviews a consecutive series of non-palpable lesions of the breast, detected by mammography at the Centro per lo Studio e la Prevenzione Oncologica of Florence, and for which open biopsy for histological confirmation had been conducted. The aim of the study was to evaluate the predictive value of the different mammographic patterns of non-palpable lesions, its variation over time and the possible causes of such variation, and the association of mammographic and pathological features. Trends in surgical treatment over time and long-term prognosis were studied, and the benefits of early detection of non-palpable breast cancer, as well as possible related evaluation biases, are discussed.

MATERIALS AND METHODS

We reviewed 1182 consecutive, histologically confirmed, non-palpable breast lesions observed from January 1970 to June 1992, detected by mammography performed either for clinical or screening [9] purposes. Criteria for radiological suspicion have been described previously [1]. From 1986, stereotactic or sonography-guided fine-needle aspiration cytology was routinely performed to improve diagnostic accuracy [4].

For each case, the following data were drawn from clinical records: patient's age, mammographic pattern (opacity with sharp, irregular or stellate borders, parenchymal distortions, and isolated microcalcifications), data and type of surgery

(quadrantectomy + axillary dissection or mastectomy, either modified or radical), histological diagnosis [10], pT and pN (determined on an average of 18 nodes) UICC-TNM category [11], and final status.

The positive predictive value for cancer of the different mammographic patterns was investigated by univariate and multivariate analysis (multiple logistic regression), adjusting for potential confounders such as age or calendar period. Statistical significance of observed differences, determined by the χ^2 test, was set at $P < 0.05$.

Cancer cases were actively followed-up and final status was assessed in December 1992, when no cases had been lost to follow-up. Follow-up ranged from 6 months to 22 years, 6.9 years average. Survival curves were determined according to Kaplan and Meier [12], and statistical significance of observed differences was determined by the log rank test.

RESULTS

Table 1 shows the distribution of studied cases according to histological diagnosis and by patient's age, mammographic pattern or year of diagnosis. Overall, 427 infiltrating carcinomas, 121 carcinomas *in situ*, 22 atypical hyperplasias and 612 benign lesions were observed. Cancers were significantly less frequent among younger women (< 40 years = 36%, 40–49 years = 33%, 50–59 years = 46%, > 59 years = 63%; $P < 0.0001$). The mammographic pattern was significantly associated with the probability of cancer: the positive predictive values for cancer were 73%, 62% or 8% for stellate, irregular or regular opacities, 42% for microcalcifications and 20% for parenchymal distortions ($P > 0.0001$). A trend of decreasing benign/malignant biopsy ratios was observed from 1986 (overall = 0.9:1; 1970–1975 = 0.8:1; 1976–1980 = 2.1:1; 1981–1985 = 2.9:1; 1986–1989 = 0.8:1; 1990–1992 = 0.4:1; $P < 0.0001$).

Table 2 summarises the results of multiple logistic regression

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Table 2. Multivariate analysis of the association of age, calendar period or mammographic pattern to cancer diagnosis

	Relative risk	Standard error	χ^2	P
Age				
< 50	1.00	—	—	—
50–59	1.12	1.04 – 1.21	9.3	0.002
> 59	1.26	1.18 – 1.34	47.9	0.0001
Year				
1970–1985	1.00	—	—	—
1986–1989	1.36	1.26 – 1.46	48.3	0.0001
1990–1992	1.26	1.21 – 1.32	99.3	0.0001
Mammographic pattern				
Opacity, regular*	1.00	—	—	—
Distortion	1.15	0.69 – 2.24	0.5	0.47
Microcalcifications	2.55	1.74 – 3.75	22.8	0.001
Opacity, irregular	19.20	7.81 – 47.4	41.1	0.0001
Opacity, stellate	27.12	11.6 – 63.2	58.4	0.0001

* Relative risk has been set to 1.00 for reference categories.

analysis of the association of different variables to cancer diagnosis. Age and calendar period maintained independent and significant associations, but the magnitude of such associations was rather limited; mammographic patterns had the strongest association. Only regular opacities and parenchymal distortions did not differ significantly in their predictive value at multivariate analysis, whereas a significant difference was present for any other pattern combination. Results did not differ when age and calendar year were entered in the model as continuous variables (data not shown).

Table 3 shows the distribution of invasive cancers by histological subtype. Pure ductal carcinoma (NOS) was the most frequent type, accounting for 56.9% of cases. A higher frequency of "special" subtypes (tubular, mucinous, cribriform; 10.4%) and of the "comedo" subtype with extensive intraductal components (9.8%) was recorded with respect to what is currently reported for palpable cancer.

Mammographic pattern was associated with some histological cancer subtypes. Isolated microcalcifications were significantly more frequent among intraductal compared to infiltrating cancers (88 versus 38%; $P < 0.0001$). Among invasive cancers, only the comedo subtype with extensive intraductal components (isolated microcalcifications = 83 versus 38%, $\chi^2 = 39.7$, degrees of freedom = 1, $P < 0.001$) and the tubular subtype (stellate opacities = 47.8 versus 26%, $\chi^2 = 5.86$, degrees of

Table 3. Distribution of invasive cancers by histological subtype

Subtype	Cases	%
Pure ductal (NOS)	243	56.9
Comedo, extensive intraductal component	42	9.8
Pure lobular	36	8.4
Ductal and other	34	8.0
Tubular	23	5.4
Cribriform	17	4.0
Mucinous	4	1.0
Apocrine	2	0.5
Medullary	1	0.2
Not specified	25	5.8

freedom = 1, $P < 0.05$) showed pattern distributions different from the average (data not shown).

Conservative surgery [13] was performed in 370 of 548 cancer cases (intraductal = 92/121, infiltrating = 278/427). A significant trend in favour of conservative surgery was observed over time, as the frequency of mastectomy decreased from 94% in 1970–1979 to 59% in 1980–1985 to 17% in 1986–1992 ($P < 0.0001$).

Table 4 shows the distribution of 427 cases of infiltrating cancer by pT, pN and mammographic pattern. Overall node involvement was reported in 11.5% (46/401) of examined axillary specimens. Involved nodes were less than four in 68% of cases. Nodal status was significantly ($P < 0.0001$) associated with T category, being 0% in pT1a, 7% in pT1b, 13% in pT1c and 35% in pT2a cases. No significant association of nodal status and mammographic pattern was observed.

To date, death from breast cancer has been recorded in 12 subjects after 1 (2 cases), 5 (2 cases), 6 (1 case), 8 (2 cases), 11 (1 case), 12 (1 case), 15 (2 cases) and 16 (1 case) years. The features of these cases are reported in Table 5. In 5 cases, death might also be ascribed to metachronous or synchronous contralateral palpable infiltrating breast cancer. Among the remaining 7 cases, the reported features did not differ from the average except for the distribution by mammographic pattern (more stellate opacities, less isolated microcalcifications), a difference which did not reach statistical significance due to the small sample size.

Figure 1 shows the overall survival curves of invasive cancers. Five-, ten- and fifteen-year survival rates were 98.1% (standard error = 0.009), 95.7% (standard error = 0.02) and 87.3% (standard error = 0.06), respectively.

DISCUSSION

The present study is based on a large consecutive series and allows some considerations on the diagnostic features of non-palpable breast lesions, and on the prognosis of non-palpable breast cancer.

The study confirms the difficulties of the differential diagnosis of non-palpable cancer based on mammographic patterns [1]. Opacities with regular borders had a very low predictive value for cancer, and biopsy may be unnecessary in these cases

Table 4. Distribution of 427 cases of non-palpable infiltrating cancer according to pT, pN category and mammographic pattern

	Negative (%)	Nodal status		Total
		Positive (%)	Not determined (%)	
T category				
pT1a	31 (96.9)	—	1 (3.1)	32
pT1b	114 (87.0)	9 (6.9)	8 (6.1)	131
pT1c	135 (80.4)	22 (13.1)	11 (6.5)	168
pT2	17 (63.0)	9 (33.3)	1 (3.7)	27
Unknown	58 (84.1)	6 (8.7)	5 (7.2)	69
Mammographic pattern				
Opacities	7 (100)	—	—	7
Regular	110 (81.5)	16 (11.8)	9 (6.7)	135
Irregular	87 (77.7)	14 (12.5)	11 (9.8)	112
Stellate	143 (87.2)	15 (9.1)	6 (3.7)	164
Microcalcifications	8 (88.9)	1 (11.1)	—	9
Distortions				
Total cases	355 (83.1)	46 (10.8)	26 (6.1)	427

Table 5. Features of 12 of 427 cases of non-palpable invasive cancer for which death from breast cancer has been recorded to date

Age	Histological subtype	Mammographic pattern	pT	Nodal status	Contralateral invasive palpable cancer
70	Ductal NOS	Irregular op.	1c	Unknown	—
62	NOS + other	Stellate op.	1c	Negative	—
45	Ductal NOS	Irregular op.	1c	Negative	—
52	Not specific	Stellate op.	1b	Unknown	—
51	Ductal NOS	Stellate op.	1b	Negative	—
63	Ductal NOS	Stellate op.	1c	Positive	—
67	Ductal NOS	Microcalcif.	2	Negative	—
65	Tubular	Stellate op.	1c	Negative	Metachronous
70	Ductal NOS	Irregular op.	1b	Unknown	Metachronous
70	Ductal NOS	Microcalcif.	x	Unknown	Synchronous
62	Ductal NOS	Stellate op.	1c	Negative	Metachronous
61	Ductal NOS	Stellate op.	1c	Unknown	Metachronous

NOS, pure ductal carcinoma; op, opacity; Microcalcif, Microcalcifications; x, unknown.

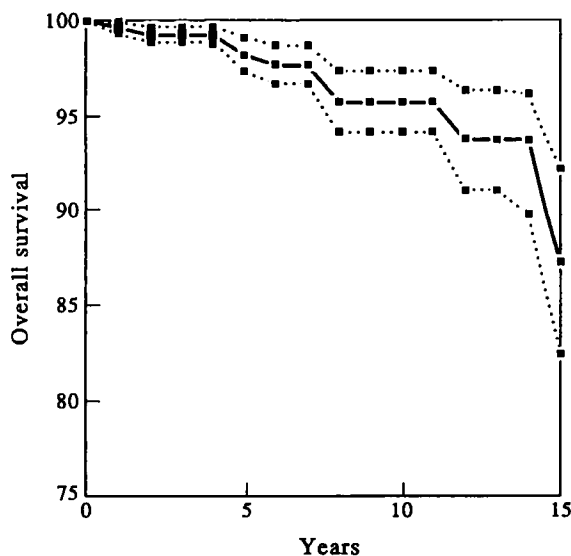


Fig. 1. Overall survival observed for 427 non-palpable invasive breast cancers. Standard errors of survival rate estimates are indicated (dotted lines).

when no other "suspicious" criteria are present (advanced age, previous negativity or rapid growth). For the remaining mammographic patterns, the predictive value for cancer (range 20–73%) was high enough to recommend open biopsy, although this results in a large number of unnecessary biopsies. This finding is consistent with most studies on the subject, reporting an average benign/malignant biopsy ratio of 3:1, when the final decision was based only on the mammographic appearance of the lesion [1, 2, 14–16].

The benign/malignant biopsy ratio varied over time in the present study. The increase observed until 1985 may be ascribed both to the increasing skill and experience of radiologists, and to the improvement of mammographic imaging, in addition to the effort to detect more cancers through a more aggressive use of open biopsy, even in cases of low suspicion at mammography. The sharp decrease in the benign/malignant biopsy ratios

observed after 1985 was most likely due to the introduction of the routine use of stereotactic or sonography-guided fine-needle aspiration cytology. The diagnostic accuracy of cytology is high, and when suspicion at mammography is low, a negative cytological report may be reassuring, and follow-up may be advised rather than open biopsy. Such policy allowed a major reduction in benign/malignant biopsy ratios without apparently affecting cancer detection rates [3, 4]. This finding is confirmed by other studies of stereotactic cytology, reporting a benign/malignant biopsy ratio lower than 1:1 [5, 6], and encourages the routine use of cytology in the diagnostic assessment of non-palpable breast lesions.

Non-palpable breast cancer is the ideal candidate for conservative surgery which, in fact, was increasingly adopted in this series, confirming a trend which has also been reported for palpable breast cancer [17]. Conservative surgery was first adopted after the report of the Milan trial [13], and became the treatment of choice in the late 1980s. Approximately 20% of non-palpable cancers are still treated by mastectomy for several reasons, such as patient's refusal, previous contralateral mastectomy, poor expected cosmetic outcome, and multicentricity or histological positivity of the quadrantectomy resection margins [17]. The identification of preclinical cancer is the major goal of mammographic screening: the eligibility of non-palpable cancer to conservative surgery is an important aspect as it may encourage women to respond to screening invitations.

The higher frequency of "special" histological subtypes, commonly associated to a more favourable prognosis, and of the comedo subtype with the extensive intraductal component, is consistent with the hypothesis of a selection bias in favour of slow-growing cancers having a longer preclinical detectable phase (length biased sampling). However, this relates to a minority of cases, whereas the majority of non-palpable invasive cancers in this series did not differ significantly from palpable cancer as far as the histological subtype was concerned. The attribution of the histological subtype of invasive lesions was not retrospective in this study, as all specimens were not available for review. In fact, this series was collected over a long period of time, and different pathology departments were involved. This suggests the possibility of interobserver variations in reporting.

A subset of 210 cases observed at the Istituto di Anatomia Patologica of Florence University between 1970 and 1989 has been reviewed recently for this purpose, [18] and a higher frequency of special subtypes (tubular = 9%, mucinous = 4.7%, cribriform = 7%), as well as of comedo subtype with extensive intraductal component (15.7%) has been observed.

Nodal involvement was rather infrequent, and was evidently related to the size of the tumour. The observed frequency of nodal involvement was consistent with that reported in other series [14, 15, 19]. This finding indicates a favourable prognosis, but stresses the importance of careful pathological examination of the axillary nodes. Nevertheless, pT1a and pT1b cancers showed a very low frequency of nodal involvement. Considering that metastases evading the first nodal level are quite rare [20, 21], limited axillary dissection [22, 23] might be suggested at least for lesions measuring less than 1 cm in diameter.

The magnitude of diagnostic anticipation, with respect to clinical diagnosis, is indicated by the high relative frequency of *in situ* lesions. Survival of non-palpable, infiltrating cancers was much more favourable compared to what is currently observed for clinically detected breast cancer [7, 24]. The limited number of deaths from breast cancer did not allow the evaluation of prognostic factors, nor did the features of the deceased cases suggest any hypothesis about prognostic indicators. Although most of the reduction in breast cancer mortality, demonstrated by controlled screening studies, has been ascribed to early detection in the preclinical phase [8], prognosis may be greatly overestimated because of the lead time bias of the length biased sampling [25] and the actual gain in life expectancy by preclinical detection might be lower than it appears from observed survival.

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