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Prognostic impact of the early detection of metachronous contralateral breast cancer

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Abstract

The study aimed to assess whether the early detection of asymptomatic metachronous contralateral breast cancer (MCBC) improves the prognosis of the patient compared with a diagnosis at symptomatic onset. We reviewed 339 MCBC cases that were consecutively diagnosed from 1970 to 2001, for which reliable information on subjective symptoms was available. The association of early (asymptomatic vs. symptomatic) detection with mortality from breast cancer was studied by univariate and multivariate analyses, adjusting for potential confounders. A more favourable stage at diagnosis was evident for asymptomatic vs. symptomatic MCBC (pT1 = 84.2% vs. 58.1%, pN0 65.0% vs. 52.4%). The hazard ratio (HR) of breast cancer death was approximately half (0.49%, 95% Confidence Interval (CI) 0.29–0.83, $P = 0.008$) for asymptomatic vs. symptomatic MCBC. Although length bias may have occurred (symptomatic MCBC had a shorter free interval from the first cancer), the present evidence supports the practice of active follow-up aimed at the early detection of asymptomatic MCBC.

Keywords: Breast; Second primary neoplasm; Metachronous; Symptoms; Diagnosis; Follow-up

1. Introduction

One aim of the periodic follow-up of breast cancer patients is the early detection and treatment of metachronous contralateral breast cancer (MCBC). This is not a rare event and is significantly more frequent in patients than in healthy women [1–4]. Although periodic follow-up allows for the detection of MCBC in its asymptomatic phase, and at an earlier stage compared with the detection of the first breast cancer [5], the question remains as to whether the early detection of MCBC has a favourable impact on mortality from breast cancer and is not commonly addressed: while most follow-up tests aimed at the early diagnosis of distant metastases have been shown to be ineffective in improving prognosis [6], detecting cancer in the other breast is currently part of a minimalist follow-up approach for a patient with breast cancer.

A previous study from our institution of 175 consecutive cases of MCBC assessed the impact of early detection of MCBC on prognosis: early detection in the asymptomatic phase was associated with an average diagnostic anticipation of 2.6 years compared with diagnosis in presence of symptoms, but no significant difference was observed for breast cancer mortality when this was measured from the first cancer diagnosis, a necessary measure to avoid lead time bias [5]. Such a study might be criticised as it involved a limited series, followed up for a limited period of time.

In the present study, we considered a larger consecutive series of MCBC, observed over a long period at a major breast clinic in Florence. Cases detected by periodic follow-up in the asymptomatic phase were compared with cases diagnosed in the presence of subjective symptoms as to their stage at diagnosis and disease-free interval from the first breast cancer to the MCBC diagnosis. The association of early (asymptomatic vs. symptomatic) detection with mortality from breast cancer was also studied using univariate and multivariate analyses.

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1.1. Patients and methods

Since 1970, the Centro per lo Studio e la Prevenzione Oncologica (CSPO) has managed both a population-based mammographic screening programme [7] and a breast clinic for symptomatic women, as well as the regular follow-up of breast cancer patients: approximately 800 new cases of breast cancer are diagnosed every year. From January 1970 to December 2001, 429 cases of MCBC (invasive breast cancer occurring at least 6 months after the first invasive breast cancer) were diagnosed in (a) breast cancer patients accrued and invited to regular follow-up (palpation every 6 months for 5 years, then yearly, and mammography yearly for 5 years, then biennally), or (b) breast cancer patients self-referring for mammographic examination. Average patient age was 54.7 years (range 30–90 years).

Data retrieved from the clinical records for the study purpose were: (a) date of birth, (b) date of diagnosis, pathological T and N category of first breast cancer, (c) date of diagnosis, pathological T and N category of MCBC, (d) presence or absence of subjective symptoms (lump, skin or nipple abnormalities, enlarged axillary nodes) at MCBC diagnosis, and (e) date and status at last observation. The presence of breast pain alone was not considered a symptom of cancer, although it may result in self-referral: symptomatic status at MCBC diagnosis was clearly reported in 339 cases (234 asymptomatic, 105 symptomatic), whereas it was questionable (not or inconstantly reported in records relating to single diagnostic tests – i.e., palpation, ultrasonography, mammography) for the remaining 90 cases: subjects with non-palpable pT1a–b tumours were assumed to be asymptomatic as symptoms, if present, were likely not cancer-related, and subjects with palpable pT2> tumours were assumed to be symptomatic. A separate analysis was performed for subjects with known or questionable symptomatic status.

MCBC detected in the asymptomatic phase at the periodic follow-up examination ($N = 312$, 274 with known symptomatic status) were assumed as "early" detected, and were compared with MCBC cases diagnosed as self-referring to clinical mammography ($N = 117$, 65 with known symptomatic status). In order to confirm that detection in the asymptomatic phase was associated with earlier detection, we compared MCBC detected as asymptomatic or symptomatic in terms of (a) stage at diagnosis and (b) disease-free interval (DFI), calculated as the time elapsing from the date of histological diagnosis of first breast cancer to the date of histological diagnosis of MCBC. When comparing paired data (e.g.: characteristics of first and contralateral breast cancers), McNemar's Chi square for frequencies was used; if data were not paired (e.g.: characteristics of symptomatic and asymptomatic MCBC), Chi square for frequencies and unpaired t test for the continuous variables were used. The unpaired t test was used to test the statistical significance of DFI differences by symptomatic status, time elapsing from first breast cancer to MCBC being known for all cases.

The impact of early detection in the asymptomatic phase was determined by Cox regression, including the following covariates in the model: (a) age at first diagnosis (<50, 50–69, $\geqslant 70$ years), (b) pT and pN category of first breast cancer, (c) symptomatic status at MCBC diagnosis, (d) time elapsing from first breast cancer to MCBC diagnosis, and (e) year of incidence of MCBC. Survival since the date of the histological diagnosis of first cancer was considered. Breast cancer-specific mortality was the considered event: subjects alive at the end of follow-up (August 2003), lost to follow-up or dying from other causes were censored at the date of their last observation. Vital status was assessed directly for those subjects regularly followed-up at the CSPO or according to the Regional Mortality Registry for cases lost to active follow-up. Last linkage with the Mortality Registry was done in December 2001. All the statistical analyses were performed using the STATA software, release 8.0 [8].

2. Results

Tables 1 and 2 show the distribution of first breast cancers and MCBC by pT and pN category at diagnosis. A more favourable stage at diagnosis was evident for MCBC compared with first breast cancers: pT1a–b or pT1 frequency was 31.9% vs. 11.4% (McNemar $\chi^2 = 53.8$, $P < 0.001$) or 72.5% vs. 47.8% (McNemar $\chi^2 = 58.5$, $P < 0.001$). pN0 frequency was 59.0% vs. 69.2% (McNemar $\chi^2 = 11.4$, $P < 0.001$). A significant difference persisted when Tx and Nx cases were excluded (data not reported). The proportion of stage I (pT1pN0) cases was 38.7% for first cancers and 49.2% for MCBC (McNemar $\chi^2 = 10.9$, $P < 0.001$), and the difference was even more evident when pTx and pNx cases were censored (45.1% vs. 64.4%, McNemar $\chi^2 = 24.8$, $P < 0.001$). Downstaging of MCBC compared with first cancer (first cancer stage II, MCBC stage I) occurred in 100 of 326 (30.7%) cases in which stage could be determined, whereas upstaging of MCBC compared with first cancer (first cancer stage I, MCBC stage II) occurred only in 43 cases (13.2%).

Tables 3 and 4 show the distribution of MCBC by symptomatic status and pT and pN category at diagnosis. A more favourable stage at diagnosis was evident for asymptomatic compared with symptomatic cancers: pT1a–b or pT1 frequency was 42.7% vs. 16.2% ($\chi^2 = 22.6$, $P < 0.001$) or 84.2% vs. 58.1% ($\chi^2 = 27.1$, $P < 0.001$). pN0 frequency was 65.0% vs. 52.4% ($\chi^2 = 4.8$, $P = 0.028$). A significant difference persisted when the Tx and Nx cases were excluded (data not reported). The proportion of stage I (pT1pN0) cases was

Table 1
Distribution of first breast cancers or MCBC by pT category at diagnosis

1st cancer	MCBC					
	pT1a–b	pT1c	pT2	pT3–4	pTx	Total
pT1a–b (row %)	21 (42.9)	22 (44.9)	4 (8.1)	1 (2.0)	1 (2.0)	49 (100.0)
(column %)	(15.3)	(12.6)	(6.0)	(5.0)	(3.2)	(11.4)
pT1c	63 (40.4)	56 (35.9)	24 (15.4)	3 (1.9)	10 (6.4)	156 (100.0)
	(46.0)	(32.2)	(35.8)	(15.0)	(32.3)	(36.4)
pT2	32 (20.9)	74 (48.4)	29 (19.0)	7 (4.6)	11 (7.2)	153 (100.0)
	(23.4)	(42.5)	(43.3)	(35.0)	(35.5)	(35.7)
pT3–4	6 (18.8)	9 (28.1)	7 (21.9)	6 (18.8)	4 (12.5)	32 (100.0)
	(4.4)	(5.2)	(10.4)	(30.0)	(12.9)	(7.5)
pTx	15 (38.5)	13 (33.3)	3 (7.7)	3 (7.7)	5 (12.8)	39 (100.0)
	(10.9)	(7.5)	(4.5)	(15.0)	(16.1)	(9.1)
Total	137 (31.9)	174 (40.6)	67 (15.6)	20 (4.7)	31 (7.2)	429 (100.0)
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)

MCBC, metachronous contralateral breast cancer.

Table 2
Distribution of first breast cancers or MCBC by pN (number of involved nodes) category at diagnosis

1st cancer	MCBC					
	pN0	pN+ (1–3)	pN+ (4–10)	pN+ (>10)	PNx	Total
pN0 (row %) (column %)	190 (64.0)	35 (11.8)	10 (3.4)	8 (2.7)	54 (18.2)	297 (100.0)
	(75.1)	(67.3)	(45.5)	(50.0)	(62.8)	(69.2)
pN+ (1–3)	30 (47.6)	11 (17.5)	5 (7.9)	1 (1.6)	16 (25.4)	63 (100.0)
	(11.9)	(21.2)	(22.7)	(6.3)	(18.6)	(14.7)
pN+ (4–10)	17 (50.0)	4 (11.8)	4 (11.8)	5 (14.7)	4 (11.8)	34 (100.0)
	(6.7)	(7.7)	(18.2)	(31.3)	(4.7)	(7.9)
pN+ (>10)	3 (18.8)	2 (12.5)	2 (12.5)	2 (12.5)	7 (43.8)	16 (100.0)
	(1.2)	(3.8)	(9.1)	(12.5)	(8.1)	(3.7)
pNx	13 (68.4)	0 (0.0)	1 (5.3)	0 (0.0)	5 (26.3)	19 (100.0)
	(5.1)	(0.0)	(4.5)	(0.0)	(5.8)	(4.4)
Total	253 (59.0)	52 (12.1)	22 (5.1)	16 (3.7)	86 (20.0)	429 (100.0)
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)

Table 3
Distribution of asymptomatic or symptomatic MCBC by pT category at diagnosis

	Symptomatic	Asymptomatic	Total
pT1a–b	17	100	117
	16.2%	42.7%	34.5%
pT1c	44	97	141
	41.9%	41.5%	41.6%
pT2	30	22	52
	28.6%	9.4%	15.3%
pT3–4	10	7	17
	9.5%	3.0%	5.0%
pTx	4	8	12
	3.8%	3.4%	3.5%
Total	105	234	339
	100%	100%	100%

Table 4
Distribution of asymptomatic or symptomatic MCBC by pN (number of involved nodes) category at diagnosis

	Symptomatic	Asymptomatic	Total
pN0	55	152	207
	52.4%	65.0%	61.1%
pN+ (1–3)	14	25	39
	13.3%	10.7%	11.5%
pN+ (4–10)	12	7	19
	11.4%	3.0%	5.6%
pN+ (>10)	5	8	13
	4.8%	3.4%	3.8%
pNx	19	42	61
	18.1%	17.9%	18.0%
Total	105	234	339
	100%	100%	100%

59.0% for asymptomatic and 40.0% for symptomatic MCBC ($\chi^2 = 10.5$, $P = 0.001$), and the difference was even more evident when pTx and pNx cases were censored (73.8 vs. 49.4%, $\chi^2 = 15.5$, $P < 0.001$). When the analysis was extended to subjects with questionable symptomatic status a significant difference was still evident (data not shown).

Average DFI was 81.4 months (range 6–339 months). Corresponding values for asymptomatic or symptomatic MCBC were 86.5 months (range 6–321 months), or 81.7 months (range 6–339 months), a non-significant difference (unpaired t test, $P = 0.527$). Corresponding figures after the inclusion of questionable symptomatic subjects were 85.6 months (range 6–321 months) for asymp-

tomatic, or 75.6 months (range 6–339 months) for symptomatic, still a non-significant difference (unpaired t test, $P = 0.105$).

MCBC in the present series were detected in subjects undergoing regular follow-up or in subjects self-referring for clinical mammography: the proportion of MCBC detected as asymptomatic was higher in the former (200/274 = 73.0%) compared with the latter group (34/65 = 52.3%, $\chi^2 = 10.5$, $P = 0.001$). When the average DFI was determined in the regularly followed-up subjects, the difference (shorter DFI for symptomatic cases) was even more evident (85.6 vs. 63.6 months) and statistically significant (unpaired t test, $P = 0.008$). Such a difference was concentrated in the first 1–3 years after the first breast cancer, with a steeper slope for symptomatic MCBC occurrence, and curves were parallel thereafter (see Fig. 1).

Table 5 shows the results of the multivariate analysis of the association of the different variables with survival. The Hazard Ratio (HR) of death measured from the date of the first breast cancer diagnosis correlates with the MCBC asymptomatic status, which is associated with

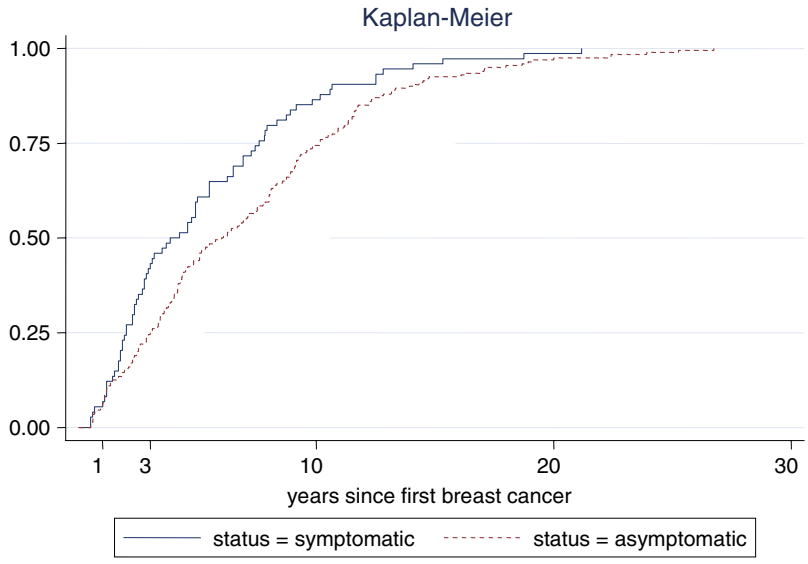

Fig. 1. Time elapsing from first breast cancer to metachronous contralateral breast cancer (MCBC) diagnosis, by symptomatic status. Patients with regular follow-up only ($N = 274$).

Table 5
Multivariate analysis of the association of different variables to risk (Hazard Ratio = HR) of death from breast cancer since the date of first breast cancer diagnosis

Variable	HR	95% CI	P value
Age (years)			
<50	1.00		
50–69	0.64	0.35–1.16	0.139
>69	1.97	0.94–4.14	0.073
1st cancer			
pT1	1.00		
pT2+	1.25	0.71–2.20	0.436
pTx	0.69	0.22–2.17	0.535
1st cancer			
pN0	1.00		
pN+	2.29	1.28–4.10	0.005
pNx	2.65	0.73–9.61	0.137
Free interval from first breast cancer to MCBC (by incremental year)	0.96	0.89–1.03	0.309
Year of MCBC diagnosis (by incremental year)	0.88	0.83–0.93	<0.001
MCBC status			
Symptomatic	1.00		
Asymptomatic	0.49	0.29–0.83	0.008

95% CI, 95% Confidence Interval.

approximately half risk of death compared with the symptomatic status, and with the year of MCBC diagnosis, which is associated with a 12% reduction in the risk of death for each additional year. Women who were 50–69 years old had a better survival than younger or older women, but the finding was not statistically significant. The association of survival with pT and pN of the first tumour were in the expected direction, although only the second one was statistically significant. DFI was not associated with survival in the multivariate model.

When the analysis was extended to subjects with questionable symptomatic status, a significant difference was still evident (HR 0.58, 95% Confidence Interval (CI) = 0.37–0.92, $P = 0.019$).

The association of asymptomatic status with prognosis did not become any more statistically significant (HR = 0.72, $P = 0.246$) when the pT and pN categories of MCBC were entered in the model (data not shown), confirming that downstaging through anticipated detection was the main determining mechanism of the improved prognosis in the asymptomatic MCBC patients.

3. Discussion

The present study is based on a relative large series and therefore allows a number of observations to be made regarding the impact of early detection of MCBC through periodic follow-up.

Our findings confirm that periodic examination of the contralateral breast allows for detection MCBC to be detected before its symptomatic onset (73.0% among regular attenders to mammographic follow-up). Detection in the asymptomatic phase, as expected, was also associated with a significantly lower stage. Both findings are consistent with the current experience with mammographic screening for first breast cancers [9].

A fair proportion of pTx (first cancer = 9.1%; MCBC = 7.2%) and pNx (first cancer = 4.4%; MCBC = 20.0%) cases was observed. The higher frequency of pNx cases among MCBC might be explained by the adoption of less aggressive surgery in older patients (average DFI was 81.4 months). The proportion of pTx and pNx was almost the same among symptomatic or asymptomatic MCBC (pTx: 3.8% or 3.4%; pNx 18.1% or 17.9%) and does not suggest any major selection biases.

Although downstaging was evident for asymptomatic compared with symptomatic MCBC, no difference was observed as to the free interval from first breast cancer to MCBC. In the subset of regular attenders to mammographic follow-up, a shorter free interval for symptomatic than for asymptomatic patients was observed. These findings were somewhat unexpected, as detection prior to symptomatic onset and at a less advanced stage implies diagnostic anticipation, as observed in mammographic screening studies for primary breast cancer, with a lead time estimated to be around 2–3 years [9]. The absence of a shorter DFI in cases of asymptomatic detection may be explained by a length bias in the sampling, that is a selection of fast-growing MCBC in the symptomatic subgroup and of slow-growing MCBC in the asymptomatic one. A length bias is expected when comparing screen-detected to interval cancers: in the present experience, data suggest that fast-growing MCBC escaped mammographic detection and occurred mostly symptomatically in the first three years of follow-up, whereas the occurrence of slow-growing MCBC was more constant over time and the longer preclinical detectable phase allowed for the asymptomatic detection in most of them: the proportion of MCBC occurring in the first 5 years following the first breast cancer was 61.8% among cases detected as symptomatic and 44% among cases detected as asymptomatic.

Survival of MCBC was measured from the date of the first breast cancer diagnosis, that is from the start of periodic follow-up of the contralateral breast. This was inorder to avoid a lead time bias due to diagnostic anticipation, which would have occurred if survival had been measured from the date of MCBC diagnosis. The survival analysis showed a significant impact of the detection of MCBC in the asymptomatic phase on the risk of death from breast cancer. Such an effect is unbiased by lead time and is likely to be due to early detection and downstaging, as it is reduced and no longer significant if adjusted for MCBC stage.

The HR of death from breast cancer also correlates with the year of MCBC diagnosis, an effect which is independent of the length of the DFI. Such an effect may be explained by progressive improvements in breast cancer management due to the availability of better treatments (the study covered a 32 years period from 1970 to 2001). Nevertheless, when the calendar year covariate is excluded, the HR changes from 0.49 to 0.52 and therefore seems to have no confounding effect on the association of an asymptomatic diagnosis on prognosis.

The present study design could not avoid a length bias in the sampling, with slow-growing cancers that are associated with a better prognosis being more likely to be picked up by periodic mammography when the patient is asymptomatic. Thus, periodic examination of the contralateral breast may have acted, at least to some extent to simply select the slow-growing cancers, rather than modifying the natural history of the disease by downstaging and earlier treatment, and the observed survival improvement associated with detection in patients were asymptomatic might be, at least partially, explained by such a bias. Nevertheless, a length bias, which has been claimed to affect case-control studies of mammographic screening efficacy [7], is certainly absent in prospective randomised studies, which have shown that a real reduction in breast cancer mortality may be

achieved by the early detection of asymptomatic breast cancer [10].

MCBC is known to negatively affect prognosis [2,11,12]. At the same time there is evidence, also seen in this study, (a) that periodic mammography of the contralateral breast allows for the detection in the asymptomatic phase of most MCBC cases occurring over time, and (b) that detection in the asymptomatic phase is associated with a less advanced stage. As both of these occurrences are associated with a real improvement in prognosis for screen-detected first primary breast cancers: the same is likely to be true for MCBC cases.

Our experience shows that the detection of MCBC in the asymptomatic phase is associated with a better prognosis, and our findings support the current practice of periodic screening of the contralateral breast in breast cancer patients. The presence of a length bias in retrospective studies, like the present one, and the real prognostic impact of screening for MCBC may be proved and measured only by means of a randomised prospective trial, comparing mammographic follow-up of the contralateral breast to simple breast self-examination, but ethical and psychological implications are likely to make such a study unlikely.

References

1. Horn PL, Thompson WD, Schwartz SM. Factores associated with the risk of second primary breast cancer: an analysis of data from the Connecticut Tumor Registry. *J Chron Dis* 1987, **40**, 1003–1011.
2. Rosselli Del Turco M, Ciatto S, Perigli G, Borrelli D, Carcangiu ML, Santucci M. Bilateral cancer fo the breast. *Tumori* 1982, **68**, 155–160.
3. Storm HH, Jensen OM. Risk of contralateral breast cancer in Denmark: 1943–1980. *Br J Cancer* 1986, **54**, 483–492.
4. Buiatti E, Crocetti E, *et al*. Incidence of second primary cancers in three Italian population based cancer registries. *EJC* 1997, **33**, 1829–1834.
5. Ciatto S, Ambrogetti D, Bonardi R, Bravetti P, Rosselli Del Turco M. Prognostic impact of early detection of contralateral primary breast cancer. *Tumori* 1990, **76**, 370–373.
6. Palli D, Russo A, Saieva C, Ciatto S, Rosselli Del Turco M, Distante V, *et al*. Intensive vs. clinical follow-up after treatment of primary breast cancer: 10-year update of a randomized trial. National Research Council Project on Breast Cancer Follow-up. *JAMA* 1999, **281**, 1586.
7. Palli D, Rosselli Del Turco M, Buiatti E, Carli S, Ciatto S, Toscani L, *et al*. A case-control study of the efficacy of a non-randomized breast cancer screening program in Florence (Italy). *Int J Cancer* 1986, **38**, 501–504.
8. Heron DE, Komarnicky LT, Hyslop T, Schwartz GF, Mansfield CM. Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. *Cancer* 2000, **88**, 2739–2750.
9. Paci E, Ciatto S, Buiatti E, Cecchini S, Palli D, Rosselli Del Turco M. Early indicators of efficacy of breast screening programmes. Results of the Florence District Programme. *Int J Cancer* 1990, **46**, 198–202.
10. Wald NJ, Hackshaw A, Chamberlain J. The efficacy and safety of periodic mammographic breast cancer screening: summary of report of the European Society of Mastology. *Clin Radiol* 1994, **49**, 592–593.
11. Holmberg L, Adami HO, Ekbom A. Prognosis in bilateral breast cancer. Effects of time interval between first and second primary tumors. *Br J Cancer* 1988, **58**, 191–194.
12. Wanebo HJ, Senofsky GM, Fechner RE, Kaiser D, Lynn S, Paradise J. Bilateral breast cancer. *Ann Surg* 1985, **201**, 667–677.