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PATIENT'S AND DOCTOR'S DELAY IN PRIMARY BREAST CANCER

Prognostic implications

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In a study of 7 608 patients with primary breast cancer patient's and doctor's delay were examined in relation to age, tumour size, grade of anaplasia, and number of positive lymph nodes. The delays were arbitrarily divided into the following intervals: Short (0–14 days), intermediate (15–60 days) and long (>60 days). The well-established patient and tumour characteristics were shown to have prognostic significance. Similarly the delays showed significant influence on survival. A long patient's delay was associated with an unfavourable outcome, as compared with a short delay. On the contrary, the prognosis was superior for patients with a long doctor's delay compared to those with a short doctor's delay. Overall, when corrected for age, the prognostic value of delay in terms of mortality increased by 24% for a long patient's delay compared to a shorter and by 13% for a short doctor's delay compared to a longer. This indicates that doctors are capable of distinguishing between more and less aggressive malignancies. The study also suggests that all sources of delays should be kept at a minimum.

It is generally assumed that the greater the delay in seeking treatment for breast cancer the worse the prognostic outcome (1). The available data, however, from studies analyzing this relationship remain controversial. Some investigators have found a general reduction in survival rate with increasing treatment delay (2–7). Others have reported a better prognosis for patients with symptoms suggestive of breast cancer that have extended over several months or years, compared to women with a shorter delay in seeking medical advice (8, 9). Some studies show no difference in survival rate when comparing patients with short and long delay (10–13). The conflicting results may to some extent be ascribed to selection bias. Thus, patients who survive many years with symptoms from a primary breast cancer are likely to have a slowly growing tumour with a relatively favourable prognosis.

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In the present prospective nation-wide study we have analyzed the prognosis in relation to known and well-established prognostic factors, such as number of positive lymph nodes, tumour size, histological malignancy grade of ductal-type carcinomas, and age in female patients with breast cancer. Furthermore, we have examined the relation between prognosis and delay and compared groups with short and long delay with regard to known prognostic factors.

Material and Methods

The present study included all patients with primary breast cancer who were registered in the DBCG (Danish Breast Cancer Cooperative Group) treatment programmes from August 1977 to November 1982.

Primary surgery was total mastectomy with lower axillary dissection, with a median of 5 lymph nodes examined. Tumour size was measured by the pathologist by gross examination. The histological diagnosis of a breast tumour followed the International Histological Typing of Breast Tumours, WHO, Geneva, 1968. Ductal type carcinomas, 82% of all newly diagnosed cases, were histologically graded according to Bloom & Richardson (14).

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All patients were evaluated for protocol inclusion. The following criteria excluded the patients from entering protocol: surgical recommendations not followed, medical contraindications for treatment according to protocol, previous breast cancer, distant spread, protocol recommendations not followed, previous or concurrent malignant disease other than breast cancer, synchronous bilateral breast cancer, refusal to participate, primary tumour inoperable, etc.

Patients who were eligible for protocol inclusion were divided into two risk groups: 1) The low-risk group included patients with tumours 5 cm or less in diameter, negative nodes, and no invasion to skin or deep fascia. No adjuvant treatment was given to this group of patients (protocol DBCG 77 A (15)). 2) The high-risk group included patients with tumours more than 5 cm in diameter, positive nodes, or invasion to skin or deep fascia. These patients received adjuvant radiotherapy to the chest, and parasternal, clavicular, and axillary lymph nodes. In addition, the patients were randomized to receive no further therapy or to receive adjuvant systemic treatment, which differed for premenopausal (protocol DBCG 77 B, (15)) and postmenopausal patients (protocol DBCG 77 C, (15)).

Age and menopausal status were recorded for all patients. Prior to surgery the time of first symptoms or signs of breast cancer, and first visit to the doctor due to these complaints were recorded.

Patient's delay was defined as the interval between the first symptom or sign of breast cancer recorded by the patient and first visit to the doctor. Doctor's delay was defined as the interval between the first visit and the time of definitive surgery or biopsy if this was the only intervention. The delays were arbitrarily divided into the following intervals: short: (0–14 days), intermediate: (15–60 days), and long: (> 60 days). To facilitate the interpretation of the data, only the groups with the shortest and the longest delays were compared in the univariate analyses.

Regular clinical follow-up was carried out for 10 years or until recurrence, loss to follow-up, death, or patient refusal to continue. Clinical end-point was death. The time of death was obtained from the Central Personal Registery, CPR. Duration of survival was defined as the time between biopsy/surgery and death. All data were controlled, stored, and processed on computer. Data analysis was performed using a statistical software package (SAS computer package version 6).

Comparisons of characteristics between groups of patients were performed by χ^2-test in the relevant contingency tables.

The survival has been evaluated by the life-table analysis and compared using the log-rank test. The p-values given are those for a two-tailed test of a significance level of 5%.

Numerous prognostic variables may affect survival of women with breast cancer. We used the Cox's regression model for survival data to test the strength of delay as an independent prognostic factor. Since we expected that tumour size, grade of malignancy, and number of positive nodes depended upon delay, these factors were not included in the model. The assumption of proportional hazards effect was fulfilled. We studied whether the prognostic value of the delay was the same in all age groups. This was performed by including the interaction terms; age by patient's delay and age by doctor's delay in this model. All data refer to the patient status as of August 1st 1993, when the median observation time, defined as the period between the primary operation and the date of evaluation for this study, was 157 months (range 124–193 months).

Results

A consecutive series of 9 873 pre- and postmenopausal women with breast cancer, age range 19 to 96 years (median age 60 years), were registered by DBCG during the entry period. Of these, 6 209 patients entered the DGCG protocols 77 A, 77 B and 77 C. A total of 3 664 patients did not meet the criteria to enter the protocols (Table 1).

A total of 7 608 (86%) patients discovered by themselves the first sign or symptom of breast cancer. In 1 202 cases the cancer was found incidentally by the doctor. As to the remaining 1 063 patients no information was available whether the patient herself or the doctor first detected the tumour.

In our study, evaluation of the prognostic factors is based on the total series of 9 873 patients. The interpretation of the delay is based on the 7 608 patients only who discovered their tumour by themselves. The characteristics of these two patient groups are shown in Table 2. The distribution with regard to age, tumour size, number of metastatic nodes, and degree of anaplasia was similar in the groups. In Table 3 the relationship between the known prognostic factors and the delay is shown.

Table 1

Distribution of patients according to predeterminant exclusion criteria

Cause	Patients n	(%)
Surgical recommendations not followed	941	(26)
Medical contraindication	798	(22)
Previous breast cancer	333	(9)
Distant spread	325	(9)
Protocol recommendations not followed	271	(7)
Previous or concurrent malignant disease	243	(7)
Synchronous bilateral breast cancer	187	(5)
Refusal to participate	169	(5)
Primary tumour inoperable	53	(2)
Others	344	(9)
Total	3 664	

Table 2

Patient and tumour characteristics of the total patient series (group A, n = 9 873) and of those with self-discovered breast cancer (group B, n = 7 608)

Variable	Group A n	(%)	Group B n	(%)
Age (years)				
-39	659	(7)	575	(8)
40-49	1 716	(17)	1 402	(18)
50-59	2 215	(22)	1 780	(23)
60-69	2 393	(24)	1 861	(25)
70-79	2 040	(21)	1 451	(19)
⩾80	850	(9)	539	(7)
Total	9 873		7 608	
Tumor size (cm)				
0-2	2 794	(42)	2 226	(42)
3-5	3 133	(47)	2 467	(47)
>5	773	(12)	581	(11)
Total	6 700		5 274	
Positive lymph nodes (no)				
0	5 424	(60)	4 248	(59)
1-3	2 421	(27)	1 944	(27)
⩾4	1 270	(14)	1 029	(14)
Total	9 115		7 221	
Grade of anaplasia				
I	2 393	(32)	1 845	(31)
II	3 981	(53)	3 157	(53)
III	1 129	(15)	943	(16)
Total	7 503		5 945	

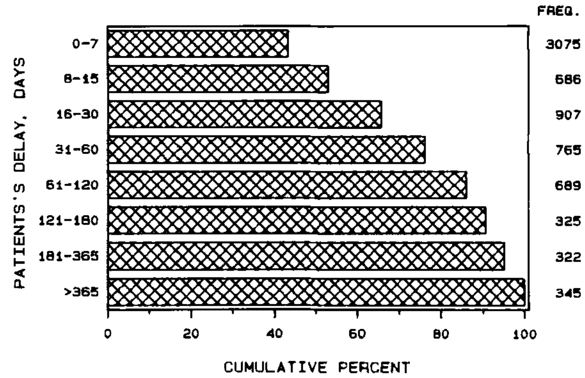

Fig. 1. Cumulative patient's delay, i.e. interval between first symptom or sign of breast cancer recorded by the patient and first visit to the doctor.

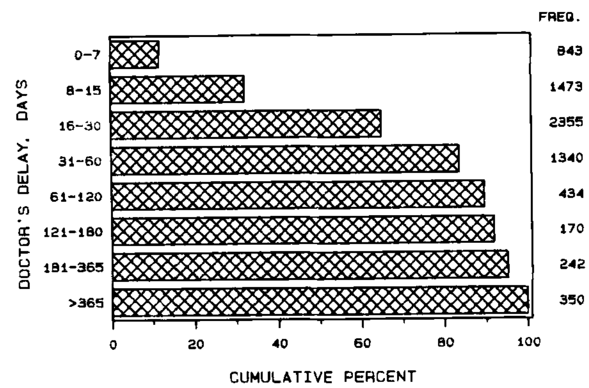

Fig. 2. Cumulative doctor's delay, i.e. interval between first visit and time of definitive surgery or biopsy if this was the only intervention.

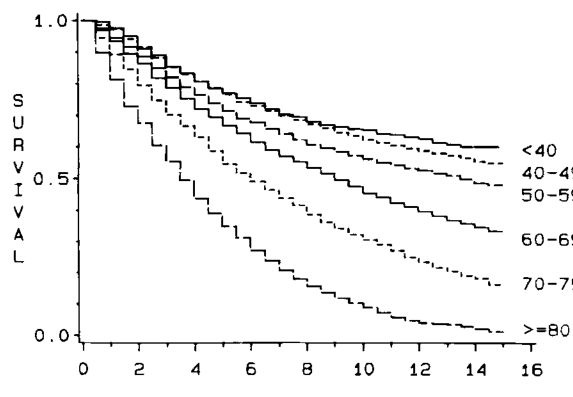

Fig. 3. Survival in patients with primary breast cancer according to age.

Cumulative percentages of patient's and doctor's delay are seen in Figs 1 and 2. Median patient's delay was 13 days (2.5 percentile 0 days and 97.5 percentile 365 days). Patient's delay was significantly shorter in the calendar year 1982 than in the calendar year 1977 ($p = 0.002$).

The younger patients sought medical advice earlier than did the older patients ($p < 0.0001$, Table 3). The median patient's delay was 10 days in patients younger than 40 years compared to 20 days in patients older than 80 years.

The median doctor's delay was 22 days (2.5 percentile 4 days and 97.5 percentile 364 days). There was no change in doctor's delay during the observation period. The doctor's delay decreased with patient age ($p < 0.0001$, Table 3). Thus, a median of 31 days in patients younger than 40 years was recorded compared to 19 days in patients aged 80 years or more.

Patients with a long patient's delay had larger tumours than patients with a short delay ($p < 0.0001$) and more positive nodes ($p < 0.0001$). Grade of anaplasia did not differ significantly in patients with short and long patient's delay (Table 3).

Patients with a long doctor's delay had tumours that were smaller ($p = 0.002$) and less anaplastic ($p = 0.02$) than those with a shorter doctor's delay. The number of positive nodes did not differ significantly between groups ($p = 0.12$, Table 3).

The survival figures for various known prognostic factors are demonstrated in Figs 3–6. A significant reduction

Table 3

Comparison of patient and tumour characateristics in patients with short (0–14 days) and long (> 60 days) delay

Variable	Patient's delay				Doctor's delay			
	short		long		short		long	
	n	(%)	n	(%)	n	(%)	n	(%)
Age (years)	n = 7 114				n = 7 207			
–39	300	(8)	93	(6)	113	(5)	159	(13)
40–49	769	(22)	245	(15)	374	(16)	300	(25)
50–59	916	(24)	363	(22)	549	(24)	263	(22)
60–69	898	(24)	423	(25)	584	(25)	256	(21)
70–79	652	(17)	398	(24)	493	(21)	160	(13)
≥80	226	(6)	159	(10)	203	(9)	58	(5)
	3 761		1 681		2 316		1 196	
	p < 0.0001				p < 0.0001			
Tumour size (cm)	n = 4 938				n = 4 990			
0–2	1 239	(47)	350	(32)	552	(36)	349	(44)
3–5	1 220	(46)	548	(50)	768	(50)	350	(44)
>5	198	(8)	205	(19)	216	(14)	103	(13)
	2 657		1 103		1 536		802	
	p < 0.0001				p = 0.002			
Positive lymph nodes (no)	n = 6 776				n = 6 852			
0	2 254	(62)	780	(51)	1 195	(55)	664	(59)
1–3	929	(26)	461	(30)	612	(28)	294	(26)
≥4	434	(12)	302	(20)	362	(17)	171	(15)
	3 617		1 543		2 169		1 129	
	p < 0.0001				p = 0.12			
Grade of anaplasia	n = 5 584				n = 5 646			
I	875	(30)	430	(33)	527	(29)	284	(32)
II	1 585	(54)	663	(51)	1 014	(55)	485	(55)
III	468	(16)	200	(16)	309	(17)	116	(13)
	2 928		1 293		1 850		885	
	p = 0.09				p = 0.02			

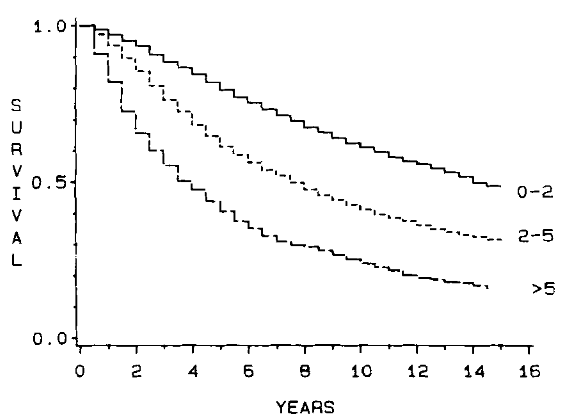

Fig. 4. Survival in patients with primary breast cancer according to tumour size (cm).

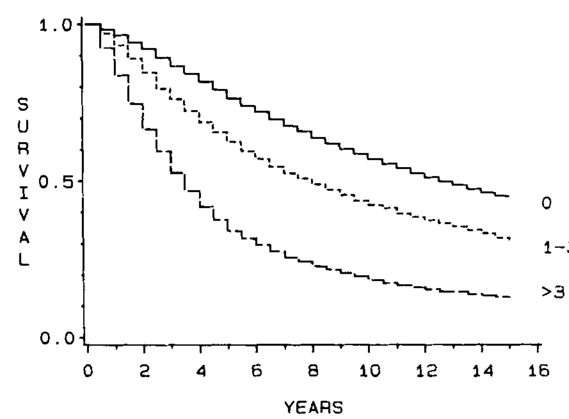

Fig. 5. Survival in patients with primary breast cancer according to number of positive lymph nodes.

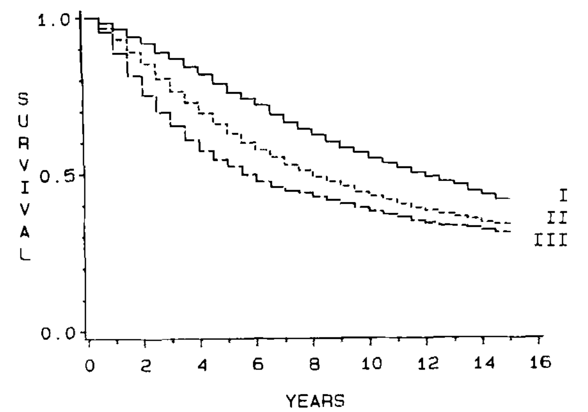

Fig. 6. Survival in patients with primary breast cancer according to grade of anaplasia.

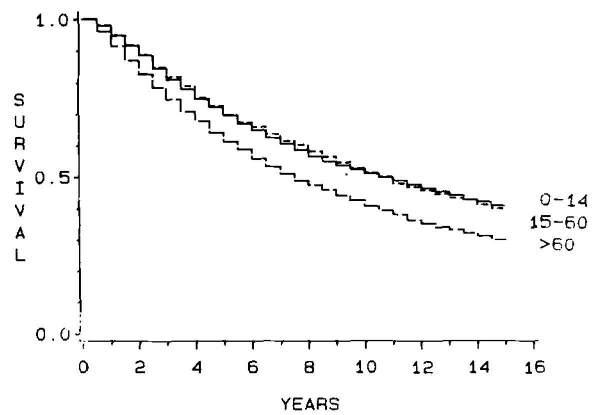

Fig. 7. Survival according to patient's delay (days).

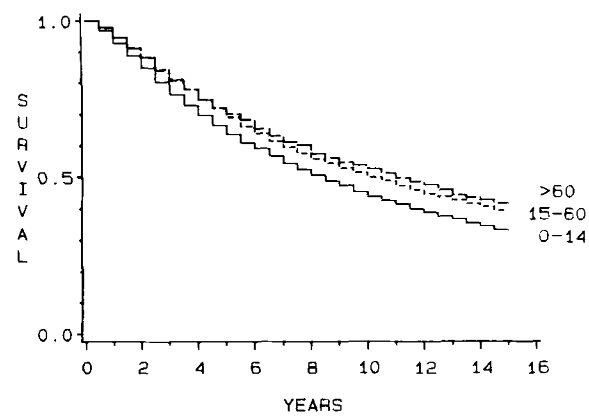

Fig. 8. Survival according to doctor's delay (days).

in survival with increasing age ($p < 0.0001$, Fig. 3), increasing tumour size ($p < 0.0001$, Fig. 4), increasing number of positive lymph nodes ($p < 0.0001$, Fig. 5), and increasing degree of anaplasia ($p < 0.0001$, Fig. 6) was found. Figs 7 and 8 illustrate survival in relation to patient's delay and doctor's delay. A short patient's delay was correlated to the longest survival ($p < 0.0001$) and the opposite relation was seen concerning doctor's delay ($p < 0.0001$).

Table 4

Cox regression analysis with age and delay as prognostic covariates in the DBCG registered patients

Covariate	Scoring
Age	
<50 years	1
Otherwise	0
⩾70 years	1
Otherwise	0
Patient's delay, short	
⩽14 days	1
Otherwise	0
Patient's delay, long	
>60 days	1
Otherwise	0
Doctor's delay, short	
⩽14 days	1
Otherwise	0
Doctor's delay, long	
>60 days	1
Otherwise	0

Estimates:

Covariate	Regression coeff. β	SD	exp(β)	p-value
Age < 50 years	−0.42	0.0043	0.66	<0.00001
Age > 70 years	0.64	0.035	1.90	<0.00001
Patient's delay, short	0.22	0.035	1.24	<0.00001
Doctor's delay, long	0.12	0.033	1.13	0.0002

Cox regression analysis demonstrated that besides age both patient's and doctor's delay had prognostic value (Table 4). If the patient's delay was more than 60 days the mortality was 24% higher than for a short or intermediate delay ($p < 0.0001$). Concering a doctor's delay of less than 15 days the mortality was 13% higher than for longer delays ($p = 0.0002$). These findings were seen irrespectively of age. When omitting age from this model the prognostic value of delay in terms of excess mortality increased to 34% for a long patient's delay compared to a shorter and to 19% for a short doctor's delay as compared to a longer.

Discussion

It is generally accepted that cancer should be detected as early as possible. Studies have shown that survival and cure rates are higher in patients diagnosed in early stages. A tumour in its early growth may differ only slightly from its tissue of origin, but with increasing size the tumour becomes less differentiated and more difficult to treat (16–18) with a greater probability of metastatic dissemination (17–19).

It is difficult to compare our data with those of others due to different definitions of delays; one study defined delay as two weeks or more (20), but most report in categorical blocks by months or describe continua ranging from days to years. In this presentation the delays are also arbitrarily divided into intervals of short and long delays to better elucidate interpretation of data.

Earlier studies mark the beginning of the patient's delay as the time of self-discovery of symptoms, but end-points of the delay vary from first consultation with a doctor until biopsy, diagnosis, or until first treatment. We have chosen to define patient's delay as the interval between first symptom recorded by the patient and first consultation with a doctor to avoid interference with doctor's delay. Only few studies have defined a doctor's delay (3, 5, 11, 12, 20–22). In this study doctor's delay was defined as from first visit until definitive surgery, or until biopsy if this was the only intervention. However, doctor's delay might still include a patient's delay since patients may contribute to delays that occur after consultation with a doctor by not following advice given. On the other hand, delay before consultation was solely the patient's responsibility.

The present study demonstrates for the first time that delay has a significant prognostic value even when differences in age distribution are taken into account. Cox's regression analysis indicates that both patient's and doctor's delay had significant independent prognostic value. The prognosis of younger patients was better than that of older patients and younger patients had a significantly shorter patient's delay and a longer doctor's delay. This explains why exclusion of age in the Cox's model leads to increased excess mortality in patients with long compared to short patient's delay. Thus, age must be taken into account when evaluating delay as an independent prognostic factor.

In agreement with the literature survival was significantly reduced with increasing age, tumour size, grade of anaplasia and number of positive lymph nodes (13, 14, 19, 23–26). A long patient's delay was associated with larger tumours, more positive lymph nodes, and reduced survival. In contrast, a long doctor's delay was associated with tumours that were smaller and less anaplastic, and with longer patient survival. These findings indicate tumour progression during the patient's delay and the physician's apparent capability to identify the more malignant cases.

The reason for the shorter delay of younger patients in seeking medical advice could be a tendency of younger women to have a more rapid progression of the disease (26, 27) or a higher awareness of breast disorders. The reduction of patient's delay during the period of patient accrual can probably be ascribed to the increased public attention to breast cancer that occurred after the introduction of the nation-wide breast cancer programme in 1977. The long delay in older patients may be ascribed to a cohort effect, which at any age would lead to a delay in this age-group. The long delay may also be ascribed to an age-effect. Thus, older patients may be less inclined to seek medical advice for breast disorders, especially in the presence of other concurrent diseases related to ageing. Doctor's delay was longer in younger patients. The reason may be that the diagnostic work-up is more difficult in younger patients due to a higher frequency of dense and lumpy breast tissues in this age-group. The information about first symptom or sign of breast cancer, and thus patient's delay, is generally not as accurate as the information of doctor's delay. The time of first symptom may be difficult to establish since patients usually make no record of the exact date and, therefore, many patients might misjudge the delay.

The true causal relationship between delay as a prognostic factor and the study end-point can be established only through a randomized study. We believe, however, that the validity of the delays as independent prognostic factors is well-established by the statistical model set up in the present prospective study. Therefore, it is important to emphasize that all sources of delay are kept at a minimum. This implies a well-functioning health care system, high professional diagnostic work-up, and an efficient referral system.

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