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● *Original Contribution*

THE NATURAL HISTORY OF BREAST CANCER: IMPLICATIONS FOR A SCREENING STRATEGY

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In the data base of the Institut Gustave-Roussy, the clinical courses of over 7000 patients treated since 1951 are registered. For 3000 of them treated prior to the introduction of adjuvant chemotherapy, the follow-up ranges from 15 to 32 years. For all patients, the size of the primary tumor, its histologic grade, and the number of involved axillary nodes at the time of initial treatment were registered prospectively. This series of patients was used to analyze the relationship between the size of the primary tumor and the probability of distant metastatic spread, taking into account other prognostic variables. A simulation model of the natural history of breast cancer was built which satisfactorily fits the available data on breast cancer screening. The aim of this paper is to use this model to assess the influence of: a) the time interval between mammographies and b) the diagnostic ability of the screening program, on the proportion of patients with distant metastases. The results show that the proportion of patients with distant metastases at the time of diagnosis increases gradually from approximately 25% for an interval of 1 year to 40% for an interval of 5 years. Moreover, the proportion of patients with metastases is critically influenced by the size of the tumors which can be detected; for example, for a 2-year interval the proportion of patients with metastases increases from 32% for tumors screened of 1 cm in diameter to 40% for tumors of 1.7 cm in diameter.

Breast cancer, Size of primary tumor, Distant metastic spread.

INTRODUCTION

Prior to metastatic spread, breast cancer is a regional disease which is easily cured either by surgery or radiotherapy. After the initiation of the first distant metastasis, it becomes a generalized disease, and even during the period when the metastases are too small to be detectable, the most aggressive regimens of multiple chemotherapy can cure only a small proportion of the patients. A better understanding of the natural history of human breast cancer could help us to design an optimal strategy for breast cancer screening.

During the past 2 decades, numerous investigations have shown that the growth rate of human cancer throughout its clinical course is either constant or slowly decreasing. The first attempts to modelize the natural history of breast cancer assumed a constant growth rate of the primary tumor (exponential growth pattern) and an equal growth rate for the primary tumor and its metastases. This model predicted that the metastases had been initiated long before the clinical emergence of the primary tumor. Therefore, with this model it was predicted that the detection of the tumor 1 or 2 years earlier should not have any significant impact on long-term survival. However, when the growth rates of the primary tumor and of its distant metastases were measured, it was found that they were related but that the latter were more rapid (1).

METHODS AND MATERIALS

The time course changes of breast tumor volume have been assessed on sequential mammographies in several hundred patients. The growth rates of these tumors were characterized by the tumor doubling time (TDT). In over 500 patients, the mean TDT was found to be equal to 7 months (confidence interval: 4–12 months).

In order to fit the data it was necessary to assume that the growth rate is more rapid during the initial phase of tumor growth corresponding to approximately the first 10 TDT (5). Hence the mean duration of the occult phase of the tumor history (during which the tumor is not clinically detectable) is about 12 years (confidence interval: 6–20 years). The doubling time of the metastasis is significantly shorter than that of the primary tumor; thus, the mean tumor volume at which the first distant metastasis is initiated is relatively large. An early diagnosis of breast cancer by mammography can therefore avoid a large proportion of distant metastatic spread (5).

To quantify this proportion, one must study the relationship between the size of the breast tumor and the

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dissemination probability. This study was carried out without any assumption as to the pattern of tumor growth (4). The study of experimental tumors had shown that a threshold volume at which the first metastasis is initiated exists for each tumor type. By analogy, the increase in the incidence of metastasis as a function of the clinical diameter of the tumor in a series of patients can be interpreted as the increasing proportion of tumors which are larger than their threshold volume.

The analysis of the data registered at Villejuif on approximately 3,000 patients with breast cancer, with a follow-up ranging from 15 to 32 years, shows that the proportion of metastases appearing at more than 25 years post-treatment is negligible. We subdivided the population of patients into eight classes according to the volume of the tumor at surgery, and plotted for each class the actuarial cumulated proportion of patients with metastases as a function of time after treatment up to the 25th year. This proportion at 25 years is assumed to be equal to the probability of distant dissemination before initial treatment in this class of patients. The patients with distant metastasis at initial work-up were included in this cumulated proportion. The volume at the time of detection (in logarithmic coordinates) and the metastasis initiation probability (in probit coordinates) show a remarkable linear relationship. Thus, in the whole population of patients (including patients with detectable distant metastases at time of initial treatment), the threshold distribution is lognormal with a median (termed V_{50}) of 23.6 ml (diameter = 3.56 cm) and a 95% confidence range of individual values from 0.14 to 4,000 ml (4). Thus, in clear contrast with experimental tumors in which most metastatic disseminations occur within a small range of tumor sizes, the range in human tumors is much wider. This illustrates their heterogeneity.

Table 1 gives the proportion of patients with metastatic occult dissemination as a function of tumor diameter among patients *without detectable distant metastases* at the time of initial treatment.

Several prognostic factors such as the number of involved axillary nodes, the histopathological grade of the tumor (2), its hormonal receptor content, the proportion of tumor cells in the proliferative cycle or the tumor growth rate all have an independent impact on the probability of distant dissemination (7, 8, 9). We have shown that the prognostic significance of the number of involved axillary lymph node varies with the size of the primary tumor (3). Table 2 shows the computed percentage of patients with distant metastases as a function of the variation in the number of involved lymph nodes and the histologic grade. Thus, for tumors of a given size, the proportion of patients with occult metastases may vary from one series of patients to another depending on the distribution of each of the prognostic variables.

However, for tumors of a given size, the differences in the distribution of prognostic variables should not be large from series to series and Table 1 gives a fair estimation of the influence of tumor diameter on the likelihood of distant spread.

Table 1. Proportion of patients with occult distant metastases among patients without detectable metastases at initial work-up

Tumor diameter	% of pts with occult distant met.
4.5 cm	50%
2.5 cm	32%
1.2 cm	10%
0.75 cm	4%

Note: Estimation based on the data registered at Villejuif.

Table 2. Percentage of patients with distant metastases, for tumors of 1 or 2 cm in diameter, as a function of the number of involved axillary lymph nodes and the histologic grade

	T = 1 cm		T = 2 cm	
Axillary node	Grade 1 %	Grade 2 + 3 %	Grade 1 %	Grade 2 + 3 %
0	4	12	8	19
1–3	11	36	17	44
4–9	16	51	24	59
≥10	19	58	29	67

RESULTS AND DISCUSSION

These data show very clearly that the best means for diminishing the proportion of deaths among patients with breast cancer is an earlier diagnosis because this will lead to a reduction in the average tumor size at initial treatment. Moreover, if the tumors are treated earlier the average size of distant metastases will be small. We have previously shown that adjuvant chemotherapy is effective mainly on small metastases. The analysis of the metastasis appearance curve in patients having received adjuvant CT and in controls suggested that the threshold below which chemotherapy is effective is about 1 mm^3. This value is consistent with experimental data. Thus, early diagnosis should result in a higher efficacy of adjuvant CT. The main problem will be to identify the criteria which will help us to delineate the subsets of patients for whom CT is justified.

Three methods have been instrumental in reaching a smaller tumor volume at initial treatment. They can be used concurrently.

The first is *informing* the general public and the practitioners. Women who are aware of both the risk of breast cancer and of the value of early treatment will consult their physician with smaller tumors. The median size of the breast cancer referred to the Institut Gustave-Roussy for treatment varied from 5 cm in 1955 to 3 cm in 1982, and 2.5 cm in 1987. Moreover, the proportion of women with a breast tumor of ≤1 cm in diameter was 2% in 1955, 5% in 1982, and 19% in 1987. This clearly illustrates the impact of information campaigns.

The second method is *breast self examination.* This method has been widely publicized in several countries with varying results. Several studies in particular in Canada are ongoing with the aim of assessing the cost-effectiveness of this method, which has not yet been properly evaluated. However, some preliminary data are encouraging.

The third method is *mass breast screening* by mammography. The validity of this approach has been demonstrated by several controlled and non-controlled clinical studies.

However, several questions remain unanswered (6). The main one is related to the optimum time interval between mammographic screening examinations. In the various studies, this interval has ranged from 1 to 3 years. A shorter interval increases the effectiveness of the screening and results in a smaller average size of the treated tumors, and therefore, in a small proportion of patients with distant metastases; however, this benefit has not yet been quantified. On the other hand, the shorter the interval, the higher the cost. A controlled clinical trial comparing a 1-year interval to a 3-year interval is ongoing in the U.K., but its results will only become available in a decade. In the meanwhile, it would be helpful to estimate the benefit which can be expected from various intervals. This is why we have used the previously reported simulation model of the natural history of breast cancer (5) to estimate the proportion of patients with distant metastases as a function of time interval between mammographies. The preliminary results of this study are given in Table 3.

The threshold size of the primary tumors detected is related to the quality of the mammography and of its interpretation. This size was found to have a critical impact of the effectiveness of the screening program (Fig. 1). This emphasizes the need for systematic quality insurance programs.

These simulations assume that all women are examined and that there is no false negative mammography (above the threshold size specified). Since the cost is inversely proportional to the interval, the results suggest that a 2-

Table 3. Influence of interval between mammography on the proportion of patients with distant metastases (10 yrs)

	% of patients with distant metastases	
Interval between mammographies	Women 40–49 yrs %	Women 50–70 yrs %
1 yr	23.3	26.9
2 yrs	28.8	32.5
3 yrs	32.9	36.9
4 yrs	35.9	40.2
5 yrs	38.3	42.5
No screening	50.5	54.4

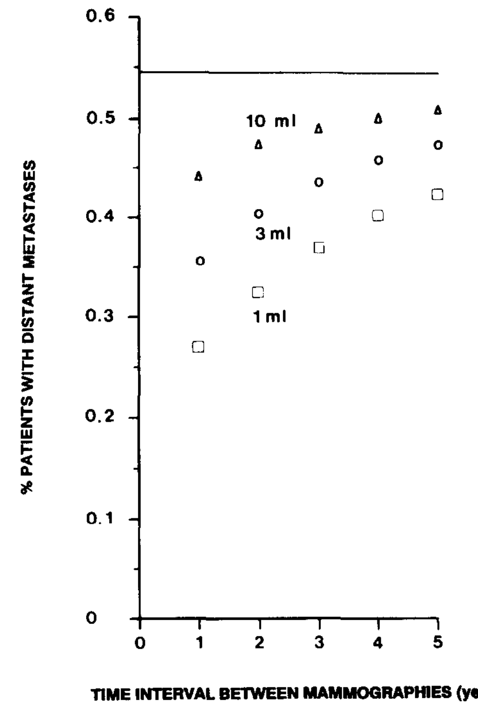

Fig. 1. Proportion of patients (age range 50–69 years) with distant metastases at the time of diagnosis, as a function of the time interval between screening and of the size of the primary tumor at diagnosis. These data illustrate the role of the mammographic technique. It is more important to be able to detect a small tumor than to shorten the delay between mammographies.

to 3-year interval is acceptable from a cost-effectiveness point of view. The results further show that there is no reason to have a shorter interval for women between 40 and 50 years than for older women. For women below 40 years of age, the shorter TDT is associated with a higher dissemination probability (3, 9) but in this age range screening is not warranted. However, one question remains open: that of women at high risk (familial history, young age at menarche, or late first pregnancy).

Another problem which has been a matter of debate is that of the carcinogenic risk induced by breast irradiation. A working party has recently reviewed this question. The report concludes that when a mammography is performed with proper techniques and equipment, and when it is well interpreted, the benefit should be a hundred times higher than the eventual detrimental effect. This review once again emphasized the necessity of an effective quality control program.

CONCLUSIONS

Our current knowledge on the natural history of breast cancer supports the validity of breast screening, and the predictions of a simulation model built with available data are consistent with the published results of the controlled screening programs. This model can be used to assess the influence of the interval between mammographies on the effectiveness of screening.

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