The Rationale for Early Diagnosis of Cancer

The Example of Breast Cancer

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The main advantage of early diagnosis of cancer is the reduction of tumor size at initial treatment and thereby an increase in the proportion of patients without distant dissemination. This benefit is illustrated by the example of breast cancer. A model of its natural history was built using data extracted from the files of over 4000 patients followed in the same institution for 20 to 35 years. The model was used to quantify the impact of tumor size, histologic grade, and lymph node involvement on the probability of distant spread. The relationships were found to be highly significant. The model also and unexpectedly revealed that the tumors progress while they grow; avoiding histologic progression is therefore another advantage of early diagnosis. The model showed that residual tumor can be a nidus for distant dissemination, and that consistency between the prediction of the model and the results of post-operative radiotherapy is satisfactory. Conversely to what is often stated, the benefits of post-operative radiotherapy appear to be greater for small tumors, even in the absence of lymph node involvement, than for large ones. The model could be used to help improve screening strategies, but more data are required, in particular for the young age range.

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The main cause of cancer death is metastatic dissemination. Therefore the most effective way to reduce the cancer death toll is early diagnosis, which increases the proportion of patients treated prior to the occurrence of this dissemination, when cancer is a loco-regional disease easily cured by local treatment. Early diagnosis has several other benefits: it facilitates local control and enables conservative surgery, it reduces the local sequelae caused by surgery and/or radiotherapy, and helps avoid the stress of adjuvant chemotherapy.

However, in breast cancer, distant spread may have already occurred in some cancers < 5 mm in diameter, whereas it may not occur in some bulky tumors > 8 cm in diameter cured by local treatment alone. The selection of patients in whom the likelihood of distant dissemination is very small must therefore rely on a good knowledge of cancer natural history. This article will illustrate this point by taking the example of breast cancer.

In 1975, we decided to extract data from patient files, taking advantage of our hospital computerized cancer registry (1). The purpose was to study the relationship between tumor size and the probability of metastatic dissemination as well as the influence of the various tumor characteristics on this relationship. The aim of this paper is, first, to review briefly the quantitative information that was obtained during the past two decades and, second, to discuss certain aspects of breast cancer treatment and screening in the light of our current knowledge of its natural history.

RELATIONSHIP BETWEEN TUMOR SIZE AND PROBABILITY OF DISTANT SPREAD

The main event during the growth of a human tumor is metastatic dissemination (2). In patients with local relapse, the proportion of distant metastases appearing more than 25 years after treatment is negligible. The proportion after 25 years can therefore be assumed to be equal to the probability of distant dissemination before initial treatment in a group of patients (3).

The study that we performed was based on approximately 4000 breast cancer patients treated at the Institut Gustave Roussy in Villejuif prior to the use of adjuvant chemotherapy, with a follow-up ranging from 20 to 35 years (3–6). We subdivided the population of patients into eight classes according to the tumor diameter at surgery, and plotted for each class the actuarial cumulated proportion of patients with metastases as a function of time after treatment up to 25 years. The patients with distant metas-

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tasis at initial work-up were included in this study. The relationship between the volume at the time of diagnosis (in logarithmic coordinates) and the cumulative proportion of patients with distant metastases is sigmoid (Fig. 1). The curve becomes linear in PROBIT log coordinates (Fig. 2), which indicates that the relationship is log-normal in the whole population of patients (including patients with detectable distant metastases at the time of initial treatment). The proportion of patients with overt metastases at time of diagnosis increases also with tumor volume, and in PROBIT log coordinates the two curves are parallel.

The median volume (termed V50) is the volume for which a distant dissemination has occurred in half of the patients. In 1984, we reported (3) a value of V50 = 23.6 ml (diameter 3.6 cm). However, patients with local relapse had been included, which artefactually decreases the size of the V50 since (see below) residual tissue is a nidus for distant dissemination. Recently, we have recalculated the value of V50 and its variations with age (unpublished data). We found the following values for patients under 35 years of age at diagnosis: V50 = 11 ml (diam = 2.8 cm (confidence interval of volume 4–29 ml), between 35 and 45 years: V50 = 42 cm^3 (diam = 4.3 cm) (CI 31–59 ml) and for patients above 45 years: V50 = 35 cm^3 (diam = 4.1 cm) (CI 26–49 ml). The difference between the two latter values is far from being significant. However, the difference between patients under or above 35 years is highly significant and shows the great aggressiveness of breast tumors in that age period.

In 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. Fig. 1 also shows that for tumors > 1 cm in diameter, a small decrease in the size of the tumor at initial treatment results in a marked reduction in the proportion of patients with occult metastases.

IMPACT ON PROBABILITY OF DISSEMINATION OF HISTOLOGIC GRADES AND LYMPH NODE INVOLVEMENT

The average threshold volume (V50) at which dissemination occurs is inversely correlated with the histologic grade of the tumor (7). In order to quantify the influence of histologic grade on the probability of metastatic dissemination for tumors of all sizes, the patients were subdivided into three groups according to histologic grade. In each subgroup there was a significant correlation between tumor size and the probability of distant spread; the distributions were log-normal, and the median size V50 was markedly larger for grade 1 tumors (Fig. 3). The earlier occurrence of metastatic spread in high-grade tumors provides quantitative data on the influence of grade on the prognosis. The difference between the three curves is greater for small tumors than for large ones. Among low-grade tumors, the cumulative probability does not

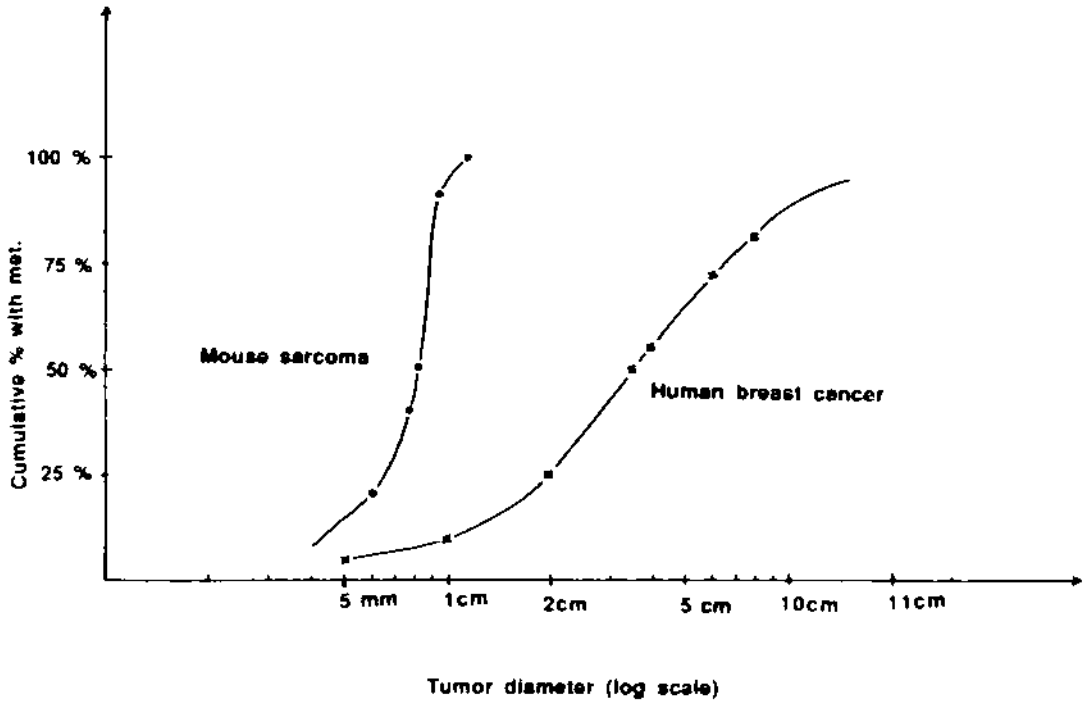

Fig. 1. Relationship between the diameter of human breast cancers and the probability of distant metastatic dissemination (crosses; from Koscielny et al. 1984). For comparison, on the left, relationship between the diameter of an experimental tumor and probability of distant dissemination (circles).

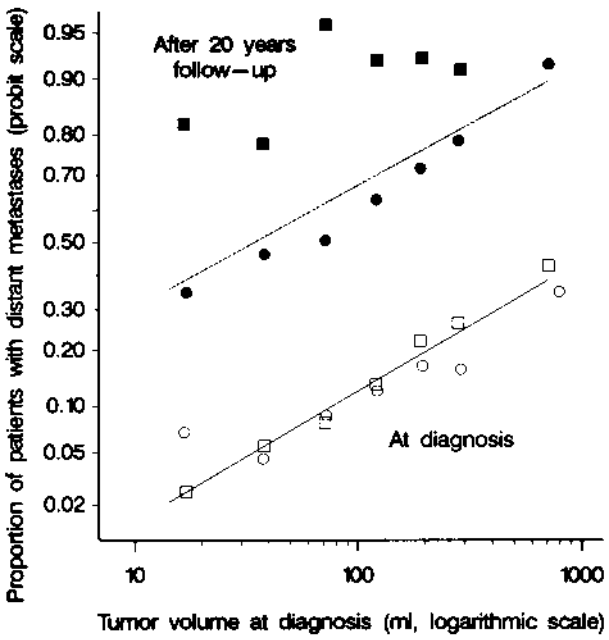

Fig. 2. Relationship between clinical volume (log-scale) and proportions of patients with metastases after a follow-up of 20 years (probit scale). Each symbol corresponds to a group of patients: circles to groups of patients without local recurrence and squares to patients with local recurrence. Patients with overt metastases at initial treatment (synchronous metastases) are not excluded. Lower curve (open circles and open squares): relationships between tumor volume and proportion of patients with synchronous metastases. The slopes of the curve corresponding to metastases detected during the follow-up of patients without local recurrence (upper curve) and of the lower curve are equal. In patients with local recurrence there is no significant relationship between initial size and proportion of metastases due to distant dissemination initiated from residual tissue (from Koscielny & Tubiana, in press).

reach 100% even for very large tumor sizes (7). These data are consistent with the time intervals which have been observed between the treatment of the primary tumor and the clinical emergence of metastases intervals, which are equal to 65, 44, and 21 months respectively for grade 1, 2, or 3 tumors (Fig. 3).

An observation made during the study is that the proportion of grade 1 tumors was higher in small tumors than in large ones, while the reverse was observed for grade 3 tumors; these data suggest that, during their growth, tumors progress towards higher grades (7). In effect, by plotting the proportion of tumors with each of the three grades as a function of tumor size (Fig. 4), it can be seen that the percentage of grade 2 tumors is constant, that of grade 3 tumors increases gradually from 20% to 40%, and that of grade 1 tumors decreases from 30% to 12%. This confirms that some tumors with grade 1 progress towards grade 2 during their growth, while some grade 2 tumors progress to grade 3. The constancy in the proportion of grade 2 tumors is compatible with an equality between the

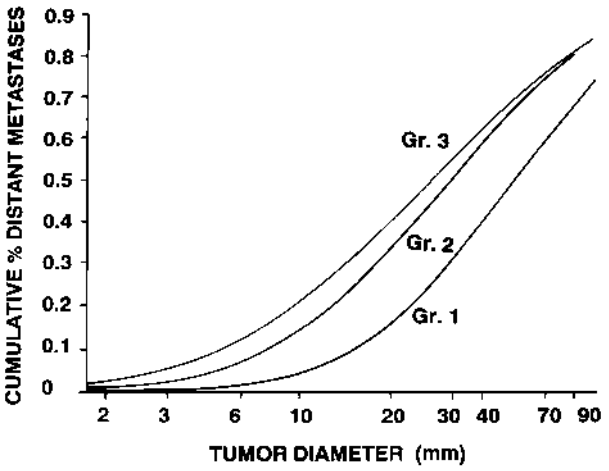

Fig. 3. Relationship between the diameter of breast cancers and the probability of metastatic dissemination in patients with histological grade (Gr.) 1, 2, or 3 tumors (From Tubiana & Koscielny 1991).

inflow from grade 1 to grade 2 and the outflow from grade 2 to grade 3. This observation is in keeping with a slow but constant rate of progression of breast tumors during their growth (7) and in accordance with the concept of tumor progression, which postulates that tumors evolve from 'bad to worse' (2).

These data show that an early diagnosis has the advantage of detecting tumors that are not only smaller, but also, on average, of lower grades. This conclusion is supported by the data subsequently reported by Tabar et al. (8). These authors compared tumors detected by screen-

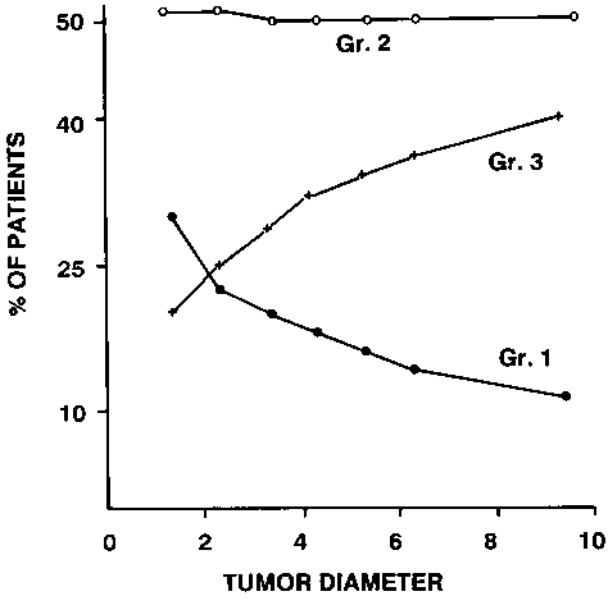

Fig. 4. Proportions of breast tumors with histological grade (Gr.) 1, 2, or 3 as a function of the diameter of the primary tumor (From Tubiana & Koscielny 1991).

ing with those of a control group. They found that tumors in the control group had higher malignancy grades than those of the screened group, i.e. advancing the time of diagnosis changed the grade distribution. These observations might be explained by the more rapid proliferation of the more malignant part of a tumor, which would lead to a change in tumor grade with time (2, 7, 9).

THE PATTERN OF AXILLARY LYMPH NODE INVOLVEMENT

Axillary lymph node involvement is probably the best prognostic indicator in patients with breast carcinoma. The invasion of axillary nodes is strongly correlated with the probability of distant hematogenous dissemination. However, the significance of the presence of a given number of involved axillary lymph nodes is probably different in a patient with a larger tumor of 5 cm in diameter than with a small tumor of 0.5 cm in diameter. Previous data suggested also that axillary lymph nodes are more frequently involved when the primary breast tumor is large than when it is small (10, 11). Other data showed that the likelihood of axillary node invasion is influenced by the histologic type of the cancer (12).

However, in order to assess fully the prognostic significance of the number of involved lymph nodes, the relationship between the primary tumor size and the probability of lymph node involvement had to be quantitatively studied in a large series of patients. We found that the proportion of patients without lymph node involvement diminishes rapidly as a function of tumor size, while the proportion of patients with four or more involved nodes increases markedly (Fig. 5). These observations are consistent with a model assuming the existence of a threshold volume for nodal invasion and gradual axillary node involvement during tumor growth (5). Thus, the constancy in the proportion of patients with one involved lymph node means that the inflow (progression from 0 to 1) is equal to the outflow (progression from 1 to 2). A classical statistical method was used to estimate the sizes at which 50% of the tumors have a number of involved lymph nodes ≥ 1 node, 2 nodes and so on. The results are given in Table 1. They suggest an orderly pattern of nodal involvement, which appears not to be a random process. Tumors involving one axillary node early on in their development are, on average, also those for which there is an early invasion of a second node and, subsequently, a third node and so on (5). Hence, there are tumors with high or low propensity for lymph node involvement. The data correspond to a unimodal distribution of the tumors, from those with the earliest to those with the latest nodal involvement, in clear contradiction with the model of Slack et al. (13) in which there are two subgroups of breast tumors. However, the size of the tumor at the time of axillary involvement varies with histologic grade; these

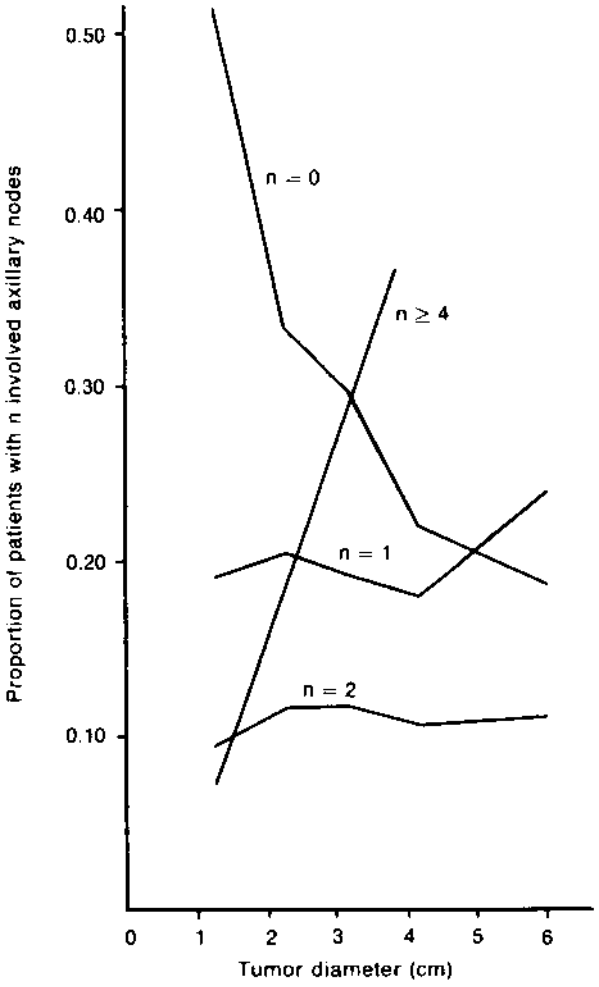

Fig. 5. Variations, as a function of tumor diameter, in the proportions of patients with 0, 1, 2, or more than 4 involved axillary nodes. With increasing tumor volume the proportion of patients without nodal involvement decreases and that of patients with several involved nodes increases (From Koscielny et al. 1989).

diameters are respectively 2.80 cm, 1.27 cm and 0.89 cm for grades 1, 2 and 3.

The orderly pattern of nodal involvement makes it possible to calculate the tumor size at invasion of the first axillary node in each subset of patients. Once the size of the tumor at initiation of distant metastasis and at invasion of the first lymph node was known, it was possible to show that a strong and highly significant correlation exists between these two sizes (5, 7).

As a consequence of this study, the prognostic significance of axillary lymph node involvement can be more adequately interpreted and assessed. Intuitively, clinicians knew that the prognostic significance of a given number of involved lymph nodes was not the same for small and large tumors. The relationship between the sizes of the tumor at first axillary node invasion and at distant dissemination makes it possible to compute the proportion of patients with occult metastases as a function of grade and

number of involved lymph nodes for various tumor sizes. Good agreement was found between the values calculated with this method and the observed ones. Results are given in Table 2.

The present results also show that, on average, during tumor progression the capacity for lymphatic spread is acquired much earlier than the capacity for hematogenous spread (5, 7). Thus, the assumption that all patients with involved axillary nodes are at high risk of distant metastasis is over-pessimistic. As can be seen in Table 2, for low-grade tumors of 1 cm in diameter the probability of distant spread remains small in patients with a small number of involved lymph nodes, while it is about twice as large in high-grade tumors of 2 cm in diameter without lymph node involvement. Even for low-grade tumors without lymph node involvement, the probability of metastatic dissemination becomes $>15\%$ when their diameter is >3 cm. These predictions are consistent with the data of Tabar et al. (8), which show that for small tumors of about 1 cm in diameter the probability of distant dissemination remains small, even when axillary nodes are involved.

CELL KINETICS AND NATURAL HISTORY

We shall only briefly summarize two observations we made during our tumor cell kinetic studies (14–17). First, there is a strong correlation between either growth rate or proportion of tumor cells in the S-phase and the probability of distant dissemination (17). Since growth rates are also significantly correlated with histologic grade or number of involved lymph nodes, multivariate studies had to be performed. They showed that the influence of growth rate or percentage of tumor cells in the S-phase on the probability of dissemination remained significant independently of the grade and of the lymph node involvement (17). Second, there is a correlation between the growth rate of a primary tumor and that of its metastasis, but the growth rate of metastasis is always faster than that of the primary tumor (14, 15).

INFLUENCE OF THE LOCATION OF THE TUMOR IN THE BREAST ON ITS NATURAL HISTORY

For tumors located in the inner or outer quadrants, the median size at first metastatic dissemination is not statistically different in the two subgroups (5). Conversely, the pattern of lymph node involvement is influenced by the tumor location. It has long been known that patients with inner quadrant tumors have a much higher probability of internal mammary chain (IMC) involvement than patients with outer quadrant tumors (18). The proportion of lymph that takes the medial route is somewhat larger in the central and medial parts of the breast compared with the lateral (19). The median volumes of the tumor at the initiation of the first, second, etc. axillary nodes were calculated for subgroups of patients with tumors located in the inner or outer quadrants of the breast. Tumor volumes at the invasion of the first axillary node are approximately 1.5 times larger in patients with tumors located in the inner quadrants than in those with tumors located in the outer quadrants (5). This observation remains valid for the second and third axillary nodes (5).

This discrepancy between axillary involvement and distant spread demonstrates that the correlation between the two is not causal (5, 7). Axillary involvement is a good index of the propensity of tumor cells to acquire the capacity for hematogenous spread, but it is not the cause of this spread. Furthermore, loco-regional recurrence rates are higher in patients with nodal involvement and are correlated with the number of invaded nodes (20). Hence, lymphatic spread is also a pointer of tumor cell migration and seeding into surrounding tissues.

The relationship between the size of the primary tumor and the proportion of patients with IMC involvement was established for the 646 patients with a tumor located in the inner quadrants who had undergone a dissection of this chain in controlled studies (5). The median tumor volume at the initiation of the first internal mammary nodes was 243 ml (CI 117–506) and, for the second node, 2031 ml (CI 699–5900), the corresponding diameters being 7.9 cm

Table 1

Mean tumor volume at initiation of axillary node involvement (from Koscielny et al. 1989)

No. of nodes	All patients (n = 2408)			Outer quadrants (n = 1880)		Inner quadrants (n = 926)	
	Mean volume (ml)	Corresponding diameter (cm)	95% CI (ml)	Mean volume (ml)	Corresponding diameter (cm)	Mean volume (ml)	Corresponding diameter (cm)
0<1	1.21	1.32	0.97–1.5	1.15	1.30	1.36	1.37
1<2	12.3	2.86	10.1–14.9	11.2	2.76	15.7	3.11
2<3	48.7	4.53	37.1–63.7	43.9	4.38	58.1	4.80
3<4	129	6.27	91.8–181	115	6.03	156	6.67
4<5	243	7.74	164–358	220	7.48	323	8.51
5<6	531	10	337–831	489	9.77	631	10.64
6<7	916	12	555–1500	904	12	1050	12.6

Table 2

Probability of metastatic dissemination as a function of histological grade and number of involved axillary nodes in patients with operable breast cancers of 1 or 2 cm in diameter (from Tubiana & Koscielny 1991)

No. axillary nodes	Tumor diameter (cm)			
	1		2	
	Grade 1(%)	Grades 2 and 3 (%)	Grade 1(%)	Grades 2 and 3 (%)
0	4	12	8	19
1–3	11	36	17	44
4–9	16	51	24	59
≥10	19	58	29	67

and 15.8 cm, respectively. Thus the volume of the primary tumor at involvement of the internal mammary nodes is approximately 100 times larger than the corresponding value for the axillary nodes. The average number of invaded axillary nodes is slightly <5 when the first internal mammary node is invaded. The ratios between the volumes of the primary tumor at the initiation of the first and second nodes are similar for axillary and internal mammary nodes. Moreover, the slope of the curve relating the proportion of nodal involvement to the size of the tumor is identical for the two lymphatic areas (5, 7).

There is a highly significant correlation between the propensity for axillary invasions and internal mammary node invasions. This confirms that the size of the tumor at first invasion of axillary nodes is a good index of the tumor's capacity to migrate and to seed in other tissues (5, 7). The proportion of patients with involvement of the IMC and without distant metastasis is slightly higher for small tumors (<2 cm in diameter) than for larger tumors, which suggests that IMC treatment should be more beneficial in patients with small tumors. This is, in effect, what has been observed.

IMPACT OF RESIDUAL TUMOR AND LOCAL RECURRENCE ON THE NATURAL HISTORY OF BREAST CANCER

It has long been known that in patients with local recurrence, the probability of metastatic dissemination is higher (21–28). However, the impact of residual tumor on the course of the disease is still debated for two reasons. The first is that there is, in most studies, a wide discrepancy between the important reduction in the incidence of locoregional recurrence achieved by post-operative radiotherapy (RT) and the modest reduction in the mortality rate, the reduction in mortality being caused by a decrease in the incidence of distant metastases (29). In some studies the survival advantage for irradiated patients is so small that it is not significant; sometimes RT even appears to be detrimental. It should be recalled that post-operative RT can be useful only in patients without occult distant dissemination. Thus, a large proportion of patients with large tumors do not benefit from it. Moreover, the lack of benefit may be due in part to inadequate irradiation techniques, but also to a lack of statistical power due to an insufficient number of patients, too short a follow-up (29–31) or statistical bias (32). The second reason is that some authors argue that the correlation between local recurrence and distant metastases is coincidental and not causal (33–35). For them, local recurrence is an indicator of tumor aggressiveness, which is the source of the higher likelihood of remote metastases. For example, Fisher et al. (34) recognized the association between ipsilateral breast tumor recurrence after lumpectomy and distant metastases, but stated that a recurrence 'indicates increased risk for, not a cause of, distant metastases'.

This debate is of great importance because if local residual tissue can be a nidus for distant dissemination, post-operative RT and treatment of IMC should be carried out in all patients without distant spread. Several data are in favor of this therapeutic strategy: the so-called 'Villejuif studies' (18, 22, 26, 29, 36), the Oslo and Stockholm trials (24, 37–40) and, more recently, the Danish trials (41, 42) and a Canadian study (43). The impassioned letters received by the *New England Journal of Medicine* after the publication of the two latter articles and the editorial by Hellman (44), which accompanied them, highlighted the extent of the controversy. This controversy prompted us to compare the natural history of patients with or without local recurrence (6). In short, the data showed that the proportion of metastasis-free patients was reduced by about 80% in all subsets of patients with local recurrence (Fig. 2). In patients without local recurrence, the monthly rate of distant metastases incidence decreases continuously with time after initial treatment. Conversely, in patients with local recurrence, this rate increases during the first year after initial treatment and the metastases in excess appear slightly later in patients without local recurrence. Using a mathematical model, it can be shown that in patients with local recurrence, nearly all of the metastases in excess had been initiated after initial treatment (6).

These conclusions satisfactorily explain the correlation observed between local recurrence and distant dissemination. They also support the usefulness of radiotherapy in

node-negative patients even when the tumor is small, in agreement with other studies (42, 45). However, for these patients the risk of local recurrence is small; therefore the potential gain expected from RT is limited (5%–10%) and the benefits will become significant only after a sufficiently long follow-up, viz. 10–20 years. These data suggest also that the benefit of post-operative radiotherapy should be greater in patients with tumors located in the inner quadrant. This is, in effect, what has been observed (18, 22, 24, 26, 29, 36).

SCREENING

All these data emphasize the benefit of screening, which is the most effective way to reduce the tumor size at treatment. We shall not discuss here the organization of mass screening and of the quality assurance which must be associated with it, nor its drawbacks, such as the diffuse anxiety mass screening may generate.

The knowledge of breast cancer natural history may help answer one of the main questions of screening: the time interval between mammographies as a function of age. It is possible to estimate the mean growth rate of the tumor and its variance at different ages. We have shown that the time interval between cancer treatment and the emergence of clinical metastasis is related to four parameters: the tumor sizes at metastatic dissemination and treatment, and the growth rate of the primary tumor and of the metastasis. In each subset of patients, we can measure or estimate the tumor sizes, and the ratio of tumor and metastasis doubling times (DT) is known. Thus, we can estimate the metastasis DT by fitting the appearance curve of metastasis after treatment. This method was proposed in 1985 (4) and developed recently (6). We have recently computed the DT of the primary tumor as a function of age. The results show clearly that the DT is shorter in women under 35 years than between 35 and 45 or between 45 and 55: they are, respectively, 5.2 months (CI 1.8–4.3), 7 (CI 3–4.6) and 7.2 months (CI 3.5–4.2). The difference between the last two is not significant (unpublished data). Knowing the Vo of the primary tumor and the DT, it becomes possible to compute the influence of the time interval between mammographies on the cumulated proportion of patients in whom metastasis will clinically emerge during the follow-up (Table 3). This table, which is slightly different from the one published earlier (46), predicts that for patients of 35 years, screening is less effective even if carried out every year. Is this the consequence of the two characteristics described above: a smaller tumor size at dissemination and a faster growth rate? Or are there other causes? Is the population of patients in this age range homogeneous or is there a subgroup of patients with a rapid growth rate? It has been reported that familial breast cancers associated with the gene BRCA have, more often than sporadic cancers, a histologic grade 3 and a higher proliferation rate (47, 48). Thus, cancer with genetic predisposition may constitute a special subgroup. We unfortunately do not have enough data regarding women under 40 years to be able to answer these questions. These are obviously controversial fields for which we need much more information.

CONCLUSION

The data extracted from patient files can be used to build a model of the natural history of breast cancer. This model quantifies the advantages of early diagnosis. Its predictions are consistent with the results of post-operative radiotherapy. They should be able to help improve screening strategy, but more data should be collected in young age groups.

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Table 3

Influence of interval between mammography on the proportion of patients with distant metastases (20 years)

Interval between mammographies (years)	Percentage of patients with metastases		
	Women <35 years	Women 35–45 years	Women 46+ years
1	35	20	22
2	42	25	28
3	47	29	31
4	50	32	34
5	52	34	36
No screening	66	47	52

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