THE NATURAL HISTORY OF BREAST CANCER AND THE LINK BETWEEN LOCAL RECURRENCE AND DISTANT METASTASES: IMPLICATIONS FOR THERAPY

Maurice Tubiana[1], Serge Koscielny[2]

[1]M.D. Honorary Director of the Institute Gustave Roussy, Villejuif – Professor Emeritus of Medicine at Paris – Sud University – President of the French National Academy of Medicine,
[2]PhD – Department of biostatistics and epidemiology of the Institute Gustave Roussy, Villejuif, France

Received July 30th, 2001; received in a revised form October 15th, 2001; accepted 24th October 2001

SUMMARY

This study had two aims:
1) to assess the tumour size at metastatic dissemination by analyzing the relationship between tumor diameter and incidence of distant metastases during the 25 years after initial treatment,
2) to investigate the impact of a residual tumor on the probability of distant dissemination.

An analysis of the data registered at the Institut Gustave Roussy in Villejuif was undertaken on about 4000 breast cancer patients treated prior to the use of adjuvant chemotherapy and followed-up for over 15 years.

The data show that the volume at which dissemination occurs in 50% of patients can be estimated in each subset of patients as defined by the size of the tumour, histopathologic grade and number of involved axillary nodes. This V_{50} varies widely but is inversely correlated with the histologic grade and the number of involved axillary nodes. Moreover, a gradual increase in the grade of the tumours was observed during their growth, confirming the usefulness of early treatment and breast screening.

The analysis of the delay between the initial treatment and clinical emergence of the metastases shows that the excess of distant metastases in patients with local recurrence corresponds to disseminations which are initiated after initial treatment, and therefore originated from the residual tumor. This finding emphasizes the importance of loco-regional treatment.

Whereas during the first 2 years after treatment the incidence of distant metastases was lower in the arm treated by chemotherapy (P=0.32, NS), from the third year on, the reverse was observed and the incidence of metastases was significantly lower in the group treated by post-op RT + poly A – poly U ($P<10^{-4}$). At 15 years, the incidence was significantly lower in the group treated by post-op RT + poly A – poly U (42% metastasis-free survival in the RT group and 29% in the CT group p=0.03). This result seems to be due mostly to lower incidence of local recurrence. But even in patients without local recurrence, the incidence of distant metastasis is not greater than that in patients treated by CMF, which might be due to the favourable effect of poly A – poly U. The results of this trial are consistent with those of other recent clinical trials, and emphasize the favourable impact of post-op RT and the paramount importance of local control on the long-term outcome of the disease.

INTRODUCTION

It was shown a few decades ago that post-operative radiotherapy (post-op RT) markedly reduced the incidence of local recurrence both after a mastectomy and as a conservative surgery; subsequently several controlled clinical trials reported a higher survival in patients having received post-op RT. Nevertheless, the usefulness of post-op RT in routine clinical practice is still controversial. The first reason is that the data are somewhat conflicting. The discrepancies appear to be mostly related to the quality of radiation therapy. In the first studies, the dose was often not sufficient to control residual disease [1,2,3,4], or the treatment duration was too long [5]. In order to prevent local recurrence, a sufficient dose of 40-50 Gy in 4-5 weeks has to be delivered [3,4]. After lower doses or longer protraction, the incidence of local recurrence is appreciable [3]. Moreover, the toxicity

Proceedings of the Conference "Advances in Radiation Oncology: Diagnosis-Treatment Planning-Clinical Outcome", Poznań, April 19th – 21st, 2001.

of RT is far from being negligible when the doses to the heart, the great vessels or the lungs are high [6]. Thus the signifycance of the first meta-analysis was limited because trials with poor or satisfactory radiation techniques and doses were pooled together [7]. Since it is difficult retrospectively to discard trials with unsatisfactory techniques (such as orthovoltages) only recent trials should be considered.

Secondly, the methodology of the statistical studies was often debatable. A five year follow-up is much too short to allow any conclusions to be drawn as we will show below. Moreover, statistical studies, in which only the first site of recurrence is monitored, are misleading: in patients submitted to post-op RT local recurrences are suppressed or delayed, consequently, the frequency of distant metastases, as the first site of recurrence, is artefactually increased [8]. Similarly, in patients who did not receive RT, the high incidence of locoregional recurrence conceals the actual frequency of distant metastases.

Thirdly, the interpretation of the data must take into account the natural history of breast cancer. For example, the growth rate of breast cancer is slower in older patients [9] *(Table 1),* therefore the delay between treatment and recurrence is longer, which may explain the difference between pre and postmenopausal patients. Similarly, the growth rate of histopathologic grade 1 tumors is slower, and the delay TM (time interval between initial treatment and detection of metastases) between treatment and recurrence, as well as the overall metastatic growth duration are longer *(Table 1).* In general, in patients with good prognostic indicators, such as the absence of nodal involvement, the delay is longer and therefore a longer follow-up is required to evidence the beneficial effect of post-op RT.

Table 1. The median growth duration (GD) is the time interval between the first proliferation of the first metastatic cell and the clinical detection of the metastasis. It was calculated in each subset of patients with the method previously described (8). GD is equal to the sum of IT (the part of the metastatic growth that has occurred before the treatment of the tumor) and TM (the time interval between initial treatment and detection of the metastases). IT is calculated and TM measured. TM values are given in parentheses after the GD value. GD is approximately equal to 20 doubling times (DT) (12). Therefore the mean DT appears to be about 3 months. The values indicated in parenthesis are the theoretical cumulated proportions of patients with distant metastases after a very long delay since treatment (23). The growth durations were computed assuming in (A) that metastases in excess were initiated before initial treatment and in (B) that they originated from residual tumor after initial treatment. As discussed in this paper, A values are not consistent with our knowledge of tumor cell kinetics, therefore in the table the values given are those calculated with the latter hypothesis.

	Median metastatic growth duration in months			**Proportion of pts with met at 20 y**	
Groups of patients	**in pts without LR**		**in pts with LR**	**pts without LR**	**pts with LR**
Overall population	67		45	0.45	0.86
Age £ 40	58		42	0.51	0.78
41 - 60	65		44	0.46	0.88
60	69		48	0.41	0.85
Tumor diameter					
0 – 3.9 cm	112		71	0.31	0.79
4 – 5.9 cm	71		72	0.47	0.86
> 6 cm	49		33	0.68	0.93
Nodal involvement					
0	100		67	0.22	0.70 (¥ 0.75)
1 - 3	103		71	0.43	0.85
> 4	71		48	0.64	0.95
Histol. Grade		A	B		
I	115	641	157	0.22	0.66 (¥ 0.85)
II	94		61	0.47	0.88
III	55		33	0.49	0.90

Based on data from reference 8.

This paper has two aims: the first one is to review our knowledge on the natural history of breast cancer and the link between local recurrence and distant dissemination, and the second one is to interpret the clinical results in the light of this knowledge.

Natural history of human breast cancer: Until recently, the description of the natural history of human cancers had remained purely qualitative. However, with the introduction of computerized cancer registries, we are now able to extract reliable quantitative information that otherwise could not have been obtained from the huge amount of data found in patient files [10,11,12,13,14,15,16].

The main event during the growth of a human tumour is metastatic dissemination [17]. Prior to its occurrence, the breast cancer is a locoregional disease which is easily cured by local treatment. The tumor size at metastatic dissemination varies widely [10,15]. Dissemination has already occurred in some breast cancers of less than 5 mm in diameter, whereas it has not occurred in some bulky tumors of more than 8 cm in diameter cured by local treatment alone.

A major goal of the study of the natural history of breast cancer is the analysis of the relationship between tumor size and the probability of metastatic dissemination as well as the influence on this relationship of the various tumor characteristics, such as the histologic grade and the number of involved axillary nodes [15]. In 1975, we undertook a study which was based on the analysis of the data registered at the Institut Gustave-Roussy in Villejuif on over 3000 breast cancer patients treated prior to the use of adjuvant chemotherapy, their follow-up ranging from 15 to 32 years [10]. The data showed that the proportion of distant metastases appearing more than 25 years after treatment is negligible. In patients without local recurrence, the cumulative proportion of patients with distant metastases after 25 years of follow-up can therefore be assumed to be equal to the probability of distant dissemination before initial treatment. We subdivided the population of patients into eight classes according to tumor volume and the tumour 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 metastasis at initial work-up were included in this cumulated proportion. The relationship between the volume at the time of diagnosis and the cumulative proportion of patients with distant metastases is sigmoid. The distribution of tumor size at initiation is log normal. For tumors larger than 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. This is the rationale behind screening procedures [10].

Moreover, it was found that the average threshold volume at which dissemination occurs is inversely correlated with the number of involved lymph nodes [13] and the histologic grade of the tumor [15]. 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 the histologic grade. In each subgroup, there was a significant correlation between tumor size and the probability of distant spread, but the median tumor size at dissemination was markedly larger for grade 1 tumors [15] *(Table 2).* An interesting observation made during the study was 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 [15]. *Table 5* shows that for a diameter of 0.35 cm half of the tumors have already a grade higher than 1. This prognosis of the grade was later confirmed by the Tabar et al. data [18]. The gradual increase in a tumor's malignant potential concurs with the concept of tumor progression, which postulates that tumors evolve from "bad to worse" [19].

Another finding was 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. 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 [13]. The data support a model in which there is an orderly pattern of nodal involvement from no lymph node involvement to involvement of one lymph node and subsequently of two lymph nodes and so on. The data strongly suggest that tumors with early first node involvement are also those which invade the second and the third node early. Each tumor progresses at its own pace. The propensity for lymph node involvement varies from tumor to tumor. However, the data correspond to a unimodal distribution of the tumors, from those with a high propensity and the earliest nodal involvement to those with the lowest and the latest involvement. These data are in clear contradiction to the model of Slack et al. [20], which assumed the existence of two subgroups of breast tumors, those with high and those with low propensity. It is possible to estimate the tumor diameter for which 50% of tumors have initiated distant metastases in patients with various histological grades and numbers of involved axillary lymph nodes *(Table 3).*

Table 2. Median tumor diameter (cm) at the time of the involvement of the first axillary node and at initiation of distant metastases, and median delay TM (months) between treatment and emergence of the first metastasis. (from ref. 10, 12, 13).

Grade	Lymph node involvement	Distant metastases	Delay TM treatment - - emergence of the first met
1	2.8	4.8	65 months
2	1.27	2.8	44 months
3	0.89	2.4	21 months

Table 3. Tumor diameter (cm) for which 50 % of tumors have initiated distant metastases as a function of the histologic tumor grade, and number of involved nodes (from ref. 10).

	Number of involved axillary nodes			
	0	1 - 3	4 - 10	> 10
Grade 1	9	4.8	3.1	2.5
Grade 2 or 3	3.7	2.6	2	1.8

Once the size of the tumor at initiation of distant metastasis and at invasion of the first lymph node had been estimated it was possible to show that there was a strong and highly significant correlation between these two sizes in the various subsets of patients, and therefore to calculate for a tumor of a given size the probability of distant dissemination as a function of histologic grade and number of involved axillary lymph nodes *(Table 4).*

Table 4. Proportion of patients with distant metastases as a function of diameter of the tumor, the histopatologic grade (Gr), and the number (N) of involved axillary nodes. (from ref. 15).

Tumor Diameter						
	1 cm		2 cm		4 cm	
N	Gr 1	2 + 3	Gr 1	2 + 3	Gr 1	2 + 3
0 -	4	12	8	19	16	35
1 - 3	11	36	17	44	35	58
4 - 9	16	51	24	59	45	68
10	19	68	29	67	59	79

The data also show that, during tumor progression, the capacity for lymphatic spread is on average acquired much earlier than the capacity for hematogenous spread [15] *(Table 5)*. Thus, the assumption that all patients with involved axillary nodes are at high risk of distant metastasis is overly pessimistic. Knowing the tumor diameter, the grade and the number of involved axillary nodes of a patient, it becomes possible to estimate the probability of distant spread *(Table 4).*

Tumor volumes at the invasion of the first axillary node are approximately 1.5 times larger in patients with a tumor located in the inner quadrants than in those with tumors located in the outer quadrants and patients with outer quadrant tumors have earlier axillary node invasion *(Table 6).* Nevertheless, for tumors located in the inner or the outer quadrants, the median size at first metastatic dissemination is not statistically different in the two subgroups, and, if anything, is slightly smaller for the inner quadrant tumors [13]. This discrepancy shows that the correlation between node involvement and distant spread is not causal. Distant dissemi-

nation is not a two-step process. 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.

Table 5. Tumor size and prognostic factors.

	Tumor diameter
1. Grade 1 Grade > 1	0.35 cm
2. Grade < 3 Grade 3	7 cm
3. Axillary lymph node 0 1	1.3 cm
4. Internal mammary chain 0 1 (inner quadrants)	3.9 cm
5. Distant metastases (pts without local recurrence) $_7$ M_O M_A	3.8 cm

The mean diameter of the tumor for which in 50 % of patients:
1. the histological grade becomes greater than 1
2. the histological grade becomes equal to 3
3. the first axillary lymph node is involved
4. the first internal mammary chain lymph node is involved for patients with breast tumor located in the inner quadrant
5. distant dissemination occurred.

(compiled from ref. 8, 13, 15)

Table 6. Median tumor diameter (cm) at the time of first and second axillary node involvement and at metastatic dissemination in inner and outer quadrant tumors. (from ref. 8 and 13).

	All pts	**Inner Quadrants**	**Outer Quadrants**
Involvement of first axillary node 0 1	1.32	1.36	1.15
Involvement of second axillary node 0 2	2.86	3.11	2.76
Metastatic dissemination	2.87	2.60	3.0

Locoregional recurrence rates are much higher in patients with nodal involvement and are correlated with the number of invaded nodes [4]. Lymphatic spread is therefore also a pointer of local tumor cell migration and invasion of the surrounding tissues.

Hence the studies of the cell kinetics of breast cancer and those of its natural history lead to several practical conclusions:

1 – The delay TM between the initial treatment and the clinical emergence of occult metastases depends on (a) The growth rates (i.e. their doubling time) of the metastases and of the primary tumor, (b) The size of the primary tumor at which distant dissemination occurred. (This critical size is smaller in tumors of high grade and/or with nodal involvement) and, (c) There is a strong correlation between the growth rate of distant metastases and the time interval between detection of metastases and death [9,15,21,22]. The growth rate of the primary tumor or its DNA labelling index are very strong independent prognostic factors, a high proliferatie rate being associated with a high probability of early distant dissemination [15,21].

2 – Early involvement of axillary lymph nodes is strongly correlated with early distant spread and with rapid growth rate of the tumor and its metastasis. However, despite this correlation, growth rate and early lymph node involvement have an independent and highly significant prognostic value [15].

3 – The growth rate of breast cancer is relatively slow, the mean tumor doubling time is about 9 months. The mean doubling time of metastases is much shorter, about 4 months. Both vary markedly and metastatic growth duration (GD) are shorter in patients under 40 and slightly longer in patients over 60 years *(Table 1).* They are also much shorter in patients with high grade tumors or nodal involvement.

The growth rate of tumor metastasis can be estimated in the various subsets of patients by analyzing the delay TM between initial treatment and clinical emergence of the metastasis [8]. The median metastasis growth duration (GD) is equal to IT (time interval between the initiation of metastases and treatment of the primary tumor) plus TM. TM can be measured and IT is evaluated in each subset of patients if the mean size of the primary tumor at the time of initial treatment and the primary tumor growth rate are known. The size at metastatic

initiation can be assessed if the histologic grade and the number of involved lymph nodes are known. The accuracy of the evaluation of the growth duration of the metastases can be improved by searching the best fit with the metastasis appearance curve [8]. GD is about equal to 20 doubling times. The value evaluated for GD corresponds to a mean doubling time of a few months (3 to 4 months), which is consistent with the doubling time measured on sequential chest X-rays of patients with lung metastases [23,24]. The results of these evaluations confirm the influence of the grade, the nodal involvement, and the age on the metastatic growth rate *(Table 1).* They also show that the metastases detected after treatment of large tumors have a more rapid growth rate [8], which is consistent with the concept of tumor progression [19], illustrated by the progression from hormone dependence to independence [25] and the progression of histologic grade [15,18].

The link between local recurrence and distant dissemination

Numerous data show that there is also a strong correlation between the existence of residual disease after initial treatment and distant dissemination [26,27,28,29,30, 31,32,33,34,35,36]. Two possible explanations have been proposed for the increased incidence of distant metastases observed in patients with locoregional recurrences (LR). Either LR is the signature of tumor aggressiveness, and then avoiding recurrences (i.e., by radiotherapy) is of little value. The alternative is that LR is a nidus for metastatic dissemination. In order to investigate this problem, four thousand patients consecutively treated in the same institution from 1954 to 1975 were studied [8]. None of them had received adjuvant chemotherapy. Tumor characteristics, local recurrence, and first detection of distant metastases had been prospectively registered for each patient and mean values were calculated in the various subsets of patients.

The proportion of metastasis-free patients was lower by about 80% in all subsets of patients with LR *(Fig. 1).*

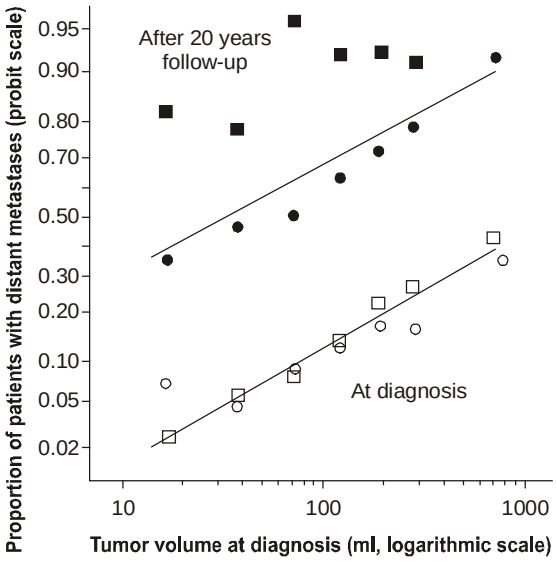


Fig. 1. Relationship between clinical tumor volume (log-scale) and proportions of metastases at long-term (probit scale). Each symbol corresponds to a group of patients: circles to groups of LR- patients, and squares to LR+. Groups are defined at 1 cm step in diameter. Patients with metastases are not excluded. The lower curve displays the relationship between tumor volume and proportion of patients with synchronous metastases. The slopes of the curve corresponding to metastases detected during the follow-up of LR- patients and of the lower curve are equal. In LR+ patients, there is no significant correlation between tumor size and proportion of patients with metastases, and the curve is not parallel to the curve corresponding to propoptions of patient with synchronous metastases. The regression lines were calculated after pooling data concerning LR+ and LR- patients.
(from ref. 8).

In patients without LR, 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 than 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 [8]. The assumption that even in patients with local recurrence the metastases in excess were initiated from the primary tumor is not plausible because if this were the case the growth of the metastases would have to be much slower than that of the metastases initiated from the tumors of patients without local recurrence. On the other hand it is known that the most malignant tumors have

a more rapid growth rate [17,21,22,23]. Moreover, if the metastases had a slower growth rate, the time interval between emergence of the metastases and death would be longer [23], which is not what was observed [8]. Hence our results are at variance with the hypothesis that a greater tumor aggressiveness in patients with LR explains the excess of metastases. Therefore, it can be concluded that most of the metastases in excess observed in patients with local recurrence originated after initial surgery from the residual tumor [8].

Metastatic growth duration was estimated in each subset of patients *(Table 1).* Patients with local recurrence have shorter growth duration. This is in keeping with the well known clinical observation: local recurrence occurs preferentially in patients with the most malignant tumors.

Furthermore, the lack of any relationship between tumor size and cumulative proportion of metastases in patients with local recurrence is consistent with the hypothesis that residual tumor is the nidus for distant spread [8]. As shown in *Table 2*, among patients with LR the long-term proportion of patients with metastases is often equal to 80% - 90%. Even in the most favourable subset of patients it is superior to 75%. This is in contrast with grade 1 patients without local recurrence in whom the cumulated proportion plateaus around 25% after a follow-up of 20 years. These data emphasize that the prognosis of tumors becomes dramatically worse when a locoregional recurrence occurs. However, the delays between initial treatment and clinical detection of metastases can be very long in patients with local recurrence. Among patients with favourable prognostic factors: the superior limit of the 95% confidence interval can be as long as 30 years in grade 1 tumors. These data underline the need for a very long follow-up in patients with local recurrences and show also the fallacy of conclusions based on a follow-up of less than 10 years, in particular for patients with breast cancers of good prognosis.

RT can prevent distant metastasis only by controlling the residual tumor which could be a nidus for distant spread. RT, therefore, can be beneficial only in patients without occult distant metastases at the time of initial treatment, and with a residual tumor after surgery [26]. Thus, accurate estimation of the likelihood of distant spread in each subset of patients is a prerequisite for identifying the subset of patients for whom more effective local treatment could improve the outcome. In patients with poor prognostic factors, the proportion of patients without occult metastases is small. Conversely, in patients with good prognostic factors, the proportion of patients with a residual tumor after surgery is small. Thus the beneficial effect of RT is likely to be small and, therefore, difficult to evidence [26].

Post-op RT can control residual tumors, but it has no impact on the growth rate of metastases. On the other hand, adjuvant chemotherapy reduces the number of viable cells in metastasis at each administration, and therefore, slows down their growth rate during the treatment period. It can be expected that it increases the time interval between initial treatment and clinical detection of the metastasis and reduces the rate of emergence of distant metastases during the first few years after treatment.

DISCUSSION OF THE CLINICAL DATA

This knowledge of breast tumor natural history and of the impact of treatment on the growth rate of occult metastases facilitates the interpretation of clinical data. In the first controlled trial comparing conservative treatment and mastectomy by Atkins [1], the incidence of distant metastases was higher in stage II patients treated by conservative surgery + radiotherapy than in those treated by mastectomy. This appears to be the consequence of a too low radiation dose which was unable to control residual tumor. Later it was shown in several controlled trials that when a dose of 50 Gy was delivered after conservative surgery with a proper fractionation and protraction there was no difference in overall survival between conservative treatment and radical mastectomy [37,38,39,40].

Several controlled trials have compared patients with or without post-op RT after

surgery [29,41]. Meta-analyses of these trials have been carried out [7,42,43]. In the 1995 overview of 35 randomized trials of surgery and RT (including 28,465 women for whom data on mortality was available) there was no survival advantage of the irradiated over the non-irradiated group after mastectomy or breast conserving surgery [42]. RT reduced death from breast cancer but was associated with an increased risk of death from other causes. However, as discussed in the introduction, no analysis was made in this study of the radiation dose and the technique of RT, whereas both these factors are likely to have a strong impact on the therapeutic results. In the subsequent meta-analysis published in 2000 by the Oxford Group [43], there is a small benefit: the mortality caused by the cancer is reduced; however this advantage is partly offset by an increase in cardiovascular mortality. The better results of post-op RT in the recent meta-analysis are probably due to the inclusion of more recent trials, in which the radiation technique was better. It is also due to a longer follow-up since, as discussed above, the favourable consequences of the control of residual tumor are observed after relatively long follow-ups (over 7 or 8 years). This is why the excess of distant metastases attributable to the residual tumor is easily overlooked at a follow-up of only five years. Indeed our data show that only about half of the distant dissemination in excess in patients with local recurrence are detected during the first five years of follow-up [8]. This proportion is smaller in patients with good prognostic factors (histologic grade I or absence of nodal involvement).

However, it should be recognized that there is a wide discrepancy between the spectacular reduction in the incidence of local-regional recurrence and the small decrease in cancer mortality. In 1986, we already discussed this point and showed that, as discussed above, post-op RT can avoid distant dissemination only in patients without occult metastases at initial treatment and with residual tumor, which will cause local recurrence when post-op RT is not performed [26]. In 1986, we estimated that only 15% to 20% of the patients belonged to this category. This proportion is probably not much greater today, which is why the potential gain is limited. However, even if not very large, this gain compares favourably with that associated with adjuvant chemotherapy and does not compete with it.

RESULTS OF A RECENT CLINICAL TRIAL COMPARING CHEMOTHERAPY AND POST-OP RT

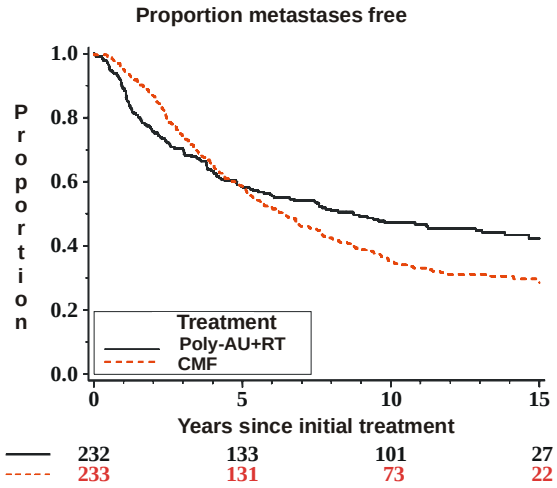
It is relevant, in this context, to discuss the results of a French Federation of Cancer Centers (FFCC) controlled trial recently updated at the Institut Gustave Roussy [44] and which, in 500 patients with stage II and III breast cancer with involved axillary nodes treated by mastectomy, compared two adjuvant treatments: chemotherapy with CMF versus post-op RT associated with immunotherapy by poly A-poly U. The incidence of local recurrence was identical in the two arms during the first two years. Thereafter there were only few recurrences in the RT-AU arm. At 15 years follow-up, the cumulative incidence of local recurrence was 18% (CI95 13-24) in the post-op AU arm and 45% (CI 38-53) in the CMF arm. This 40% reduction is highly significant ($p<10^{-6}$). Thus despite the reduction in local recurrence induced by chemotherapy [45], the reduction in post-op RT appears much greater despite the fact that in this multicenter trial the RT technique was probably not optimal, as shown by the relatively high incidence of local recurrence in the RT arm. Among operable patients with tumors of the inner quadrants and with involved internal mammary chain, the model predicts that over one third of them have no distant metastases. This result as we have emphasized [26,28,41] is consistent with the effecttiveness of the treatment of the internal mammary chain.

The annual incidence of distant metastases was lower in the CMF arm during the first two years, and the difference was statistically significant (log rank). However, from the third year till the fifteenth, *(Fig. 2)* it became lower in the RTAU arm, and the difference is highly significant. At 15 years follow-up, the cumu-

lative incidence is 43% (CI95 50-37) in the RTAU arm and 29% (CI 36-23) in the CMF arm (p=0.04) *(Fig. 5).* The overall survival (OS) was nearly identical in the two arms till the seventh year of the follow-up. From the ninth year, it became slightly higher in the RTAU arm, but the difference is not statistically significant. At the ten - year follow-up the OS is 55% (CI 48-61) in the RTAU arm and 48% (CI 40-54) in the CMF arm and at 15 years follow-up they are respectively 43% (CI 36-50) and 36% (CI 30-42). The relative risk of death in the RT poly AU arm, as compared with the CMF arm, is RR=0.87. There was no difference in the time interval between the clinical emergence of distant metastases and death between the two arms of the trial, which shows that among patients with distant metastases the growth rate and aggressiveness of the disease were comparable in the two arms [8,23]. A comparison of the metastases-free survival arm as a function of its histological grade [46], is of interest. In patients with grade 1 tumors, there is no difference in the proportion of metastases at 5 years whereas at 15 years follow-up there is a clear difference *(Fig. 3).* In patients with grade 3 tumors, the two curves diverge after the second year, and are parallel from the fifth till the fifteenth year of the follow-up *(Fig. 4).* The data concerning grade 2 tumors are intermediary. These curves are consistent with what is known regarding the slow growth rate of grade 1 tumors, and the rapid growth of grade 3 tumors [8,9].

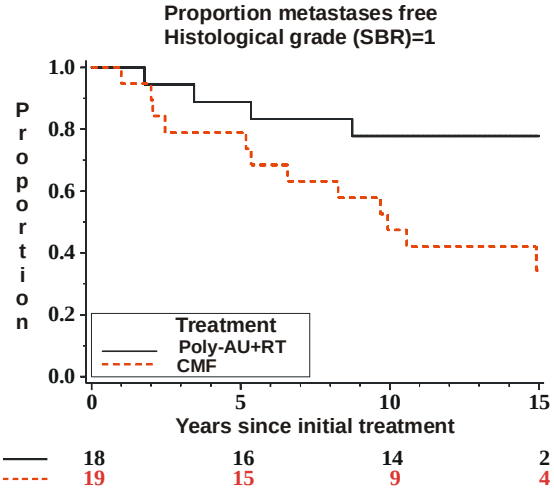
The FFCC trial was stopped prematurely because the incidence of local recurrence was identical in the two arms during the first two years; moreover the preliminary data suggested that CMF might give a lower incidence of distant metastases. In fact, after a longer follow-up there is a reduction in the incidence of distant metastases by nearly one third, which is greater than the gain observed in the trials where post-op (RT) is added to systemic therapy. Unfortunately, the number of patients included in the trial comparing CMF versus post-op RT + poly AU was not sufficient to make detailed comparisons. Nevertheless, it allows several remarks: [1] The long-term incidence of distant metastases is significantly lower in pa-tients treated by RT+AU than in patients treated by CMF. In this pragmatic trial it is difficult to distinguish the role of post-op RT and that of immunotherapy. Nevertheless, we have attempted to estimate the respective impact of the two treatment modalities. The first method that we used was to censor patients with local recurrence at the time of the detection of the first distant metastases *(Fig. 5).* With this method, the metastases that could have been initiated in the residual tumor are ignored, and the metastases which are taken into account are mostly those which originated from the primary tumor. In this case the metastases-free survival rates are similar, which suggests that the effectiveness of CMF and poly AU is analogous [2] Another method is to introduce a correction factor *(Fig. 6).* Our previous study enabled us to evaluate the excess incidence of distant metastases which are associated with local recurrence. If we introduce these data in a simulation model the benefit arising from a lower incidence of local recurrence can be excluded and it becomes possible to assess the independent role of immunotherapy. Indeed the curves of metastases-free survival, when corrected for the metastases associated with local recurrences, also suggest that the efficacy of CMF is not greater than that of poly A – poly U. This conclusion is consistent with the results of the previous controlled trial comparing patients with breast cancer receiving poly A – poly U as an adjuvant immunotherapy to with those not receiving it [47,48]. If this conclusion is correct the difference between the two groups in the incidence of distant metastases can be attributed to post-op RT. This result is in accordance with the results of recent trials assessing the impact of post-op RT in patients receiving adjuvant chemotherapy to be discussed below.

Another study, the second Stockholm trial [29,49], compared, CMF versus post-op RT in 1020 patients with breast cancer. The incidence of local recurrence was markedly reduced in patients receiving post-op RT, and the analysis of cumulated recurrence demonstrated a strong correlation between the loco-



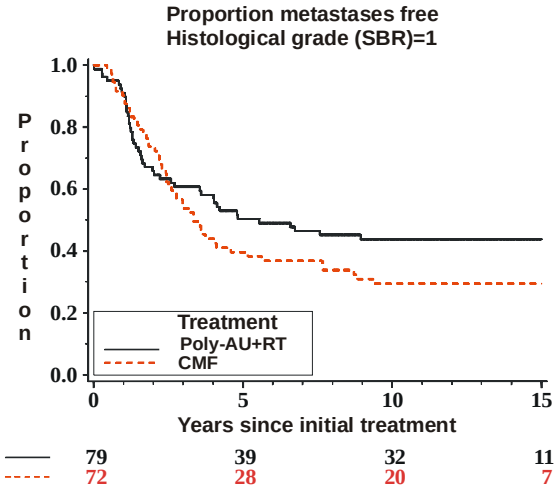
Log Rank test value: 3.47 p=0.06

Fig. 2. Proportion of metastasis-free patients studied by Kaplan Meier. During the first two years, the incidence of metastatic dissemination is lower in the chemotherapy arm. However, from the third to the fifteenth, the incidence becomes lower in the radiotherapy + poly AU arm. At 15y, the cumulative incidence is 43% (CI 50-37) in RTAU arm and 29% (CI 36-23) in the CMF arm.



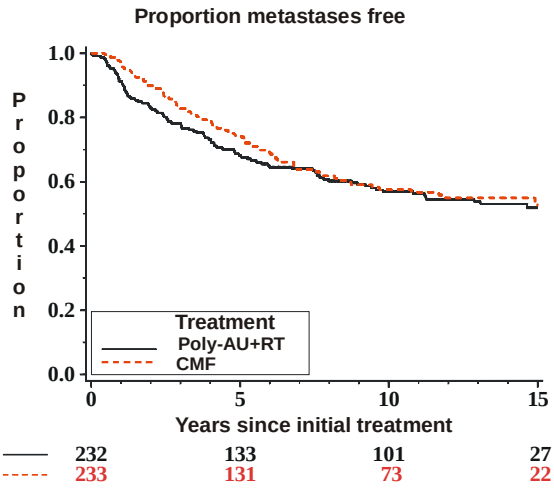
Log Rank test value: 4.73 p=0.03

Fig. 3. Proportion of metastasis-free patients in the group with histological grade 1.



Log Rank test value: 1.76 p=0.18

Fig. 4. Proportion of metastasis-free patients. Although after the third year the incidence of distant metastasis is lower in the RT + poly AU arm, the difference is smaller and statistically not significant.



Log Rank test value: 0.6 p=0.44

Fig. 5. In order to eliminate the impact of local recurrence on the incidence of distant dissemination, patients are censored at the time of local recurrence. The difference between the two arms after the third year disappears.

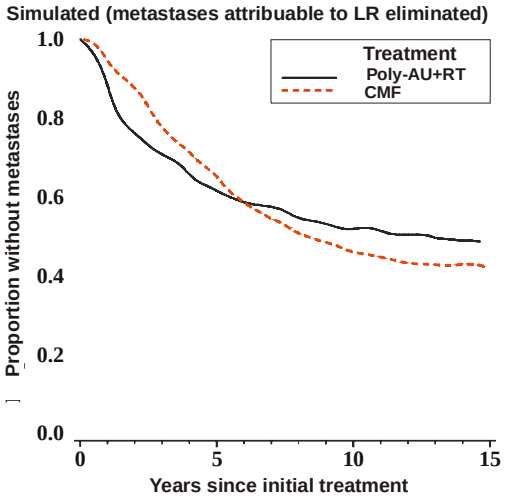


Fig. 6. In this simulated curve, a corrective factor is introduced. This factor is based on a previous study (ref. 8) which enabled the evaluation of the excess incidence of distant metastases associated with local recurrence. With this corrective factor, the difference between the two metastasis-free survival curves also becomes very small.

regional control and subsequent distant metastases. Thus the data are consistent with the above results of the FFCC trial. Unfortunately, in the Stockholm trial, only the first site of recurrence was monitored, therefore a detailed comparison with the FFCC trial is difficult.

RT acts by controlling the residual tissue, and thereby suppressing the nidus for further dissemination. The aim of adjuvant chemotherapy is to destroy distant micro metastases. An analysis with a simulation mathematical model of the metastasis appearance curve in treated and in control patients has shown that the maximum number of cells in the occult metastases controlled by the chemotherapy is approximately 10^6 [50]. Assuming that the proportion of clonogenic cells is 10^{-3}, it follows that the proportion of surviving tumor cells after completion of 6 cycles of CMF is 10^{-3} [50]. This corresponds to a radiation dose equal to $10D_{50}$ (approximately 25 Gy) delivered to the whole body in six sessions. Thus adjuvant chemotherapy and postoperative RT do not compete but are complementary. Indeed, the most recent trials have compared in patients treated by surgery and adjuvant systemic therapy (chemotherapy or tamoxifen) those with or without post-op RT [51,52]. The meta-analysis which has been carried out in the eighteen trials identified (involving 6367 patients), has shown a strong reduction in local recurrence, improved relapse-free survival and overall survival, confirming the results of these three trials [53]. Some authors have hypothesized that this favourable effect is observed because adjuvant systemic therapy allowed locoregional radiation to manifest its effect [53]. Rather the above discussion suggests that the beneficial effect has become significant because 1) the trials are more recent and, therefore, the irradiation technique of adequate quality and, 2) the follow-up is longer.

In these studies, adding post-op RT to classical systemic therapy did not raise any ethical problems and is readily accepted, whereas it was clear in the FFCC trial that many oncologists were reluctant to withhold systemic adjuvant therapy in patients who could benefit from it.

Moreover, the statistical study of Fortin et al. [54] concurs with ours [8] in demonstrating the causal responsibility of local failure in the death of a significant proportion of patients.

The role of immunological factors in breast cancer is another topic which remains controversial. In the 1970s, some authors [55] described the depression of immunological defenses caused by radiotherapy and the alleged increase of distant spread in some patients treated by radiotherapy. Later, doubts have arisen regarding the efficacy of immunotherapy despite it's positive effect observed in our previous trial [47,48]. The FFCC study brings new data to this debate [44], and justifies the opportunity to carry out new controlled clinical trials to assess the respective benefit of post-op RT and immunotherapy.

Most trials assessing the benefits of post-operative radiotherapy have included node positive patients; it would be of interest to undertake studies on node negative patients. In this context, the problem discussed in the current literature is whether post-op RT is merited in patients with good prognostic factors and high probability of cure without post-op RT [45,56,57,58]. Our data show that although local recurrences are more frequent in patients with poor prognostic factors, the in-

cidence remains relatively high even in the best subset of patients. A. Wallgren [57] has recently argued that in patients with small tumors only 6% of them will experience local relapse after a 5 - year follow-up. Our data lead us to expect that this proportion will increase up to 10 to 12% at a 10 - year follow-up, and that 70% of patients with local recurrence will experience distant metastases. The delay between initial treatment, emergence of distant metastases and death, might be long (ten to twenty-five years) but nevertheless this sequence of events is likely to be observed [8]. Thus the benefit of post-op RT should be of about 7% to 8%, a gain which should not be overlooked since it corresponds to about a quarter of the overall mortality in this type of breast cancer. However, this potential gain might be offset by the long-term toxicity of radiation if the irradiation technique is not optimal.

The rationale behind post-operative RT after mastectomy or tumorectomy is currently well documented [26,29,31,33,43, 54,58,59,60]. Here again the main question is, therefore, the cost of the potential gain in terms of radiation toxicity on lung, heart and the great vessels, and to what extent this toxicity can be reduced or avoided by advances in radiation techniques. The analysis of cardiac toxicity has shown that the toxicity is much greater in patients with large volumes of the heart irradiated with relatively high doses (in particular in patients with tumors located in the left breast) [6,61]. As recently discussed in several papers [6,62,63], we can reasonably expect that with electrons, multileaf collimators and conformal RT or intensity modulated RT, the dose to the heart and the great vessels can be dramatically diminished, thereby minimizing vascular and cardiac morbidity. This would eliminate the main reason for denying the benefit of post-op RT to low risk patients.

The last question is whether RT or systemic treatment should come first. In principle, it would be logical to start with RT, and this was the conclusion of a retrospective study [64]. This conclusion was challenged by a controlled trial carried out on 244 patients [65]. However, our data show that the follow-up was much too short to draw any conclusions. Another possibility could be interdigitated treatment, which may decrease the toxic risk, but this is a complex technique.

In conclusion, the analysis of the available data shows that there is a causal relationship between the lack of local control of the primary tumor and the increase in the incidence of distant metastases in patients with local failure. Post-operative radiation therapy is therefore justified, but the dose should be sufficient and the radiotherapy technique should aim at minimizing the dose to the heart and the great vessels, which is now possible thanks to the modern methods of radiotherapy.

REFERENCES

1. Atkins H, Hayward JL, Klugman DJ, Wayte AB. Treatment of early breast cancer: a report after ten years of a clinical trial. BMJ 1972;2:423-9.

2. Fletcher GH, Montague ED. Does adequate irradiation of the internal mammary chain and supraclavicular nodes improve survival rates. Int J Rad Oncol Biol Phys 1978; 4:481-92.

3. Arriagada R, Mouriesse H, Sarrazin D. Radiotherapy alone in breast cancer. I. Analysis of tumor parameters, tumor dose and local control: the experience of the Gustave-Roussy Institute and the Margaret Hospital. Int J Radiat Oncol Biol Phys 1986;11:1751-7.

4. Tubiana M, Sarrazin D. The role of post-operative radiotherapy in breast cancer. In Ariel JM, Cleary JB. Breast Cancer Diagnosis and Treatment. New York, McGraw Hill 1987;280-99.

5. Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fontaine F, Travagli JP, et al. Analysis of locoregional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys 1985;11:137-45.

6. Kunkler I. Adjuvant irradiation for breast cancer: Modern radiotherapy techniques should reduce cardiovascular mortality. Brit Med J 2000;320:1485-6.

7. Cuzick J, Stewart H, Peto R, Baum M, Fisher B, Host H, et al. Overview of randomized trials of post-operative adjuvant radiotherapy. Cancer treat rep 1987;71:15-30.

8. Koscielny S, Tubiana M. The link between local recurrence and distant metastases in human breast cancer. Int J Radiat Oncol Biol Phys 1999;43:11-24 and 1999;45:245-6.

9. Malaise EP, Chavaudra N, Tubiana M. The relationship between growth rate, labelling index and histological type of human solid tumours. Eur J Cancer 1973;9:305-12.

10. Koscielny S, Tubiana M, Le MG, Valleron AJ, Mouriesse H, Contesso G, et al. Breast cancer: relationship between the size of the primary tumour and the probability of metastatic dissemination. Br J Cancer 1984; 49:709-15.

11. Atkinson EN, Brown BW, Montague ED. Tumor volume, nodal status and metastasis in breast cancer women. J Nat Cancer Inst 1986;76:171-8.

12. Koscielny S, Tubiana M, Valleron AJ. A simulation model of the natural history of human breast cancer. Br J Cancer 1985; 52:515-24.

13. Koscielny S, Le MG, Tubiana M. The natural history of breast cancer: the relationship between involvement of axillary lymph nodes and the initiation of distant metastases. Br J Cancer 1989;59:775-82.

14. Carter CL, Allen C, Herson DE. Relation of tumor size, lymph node status and survival in 24740 breast cancer cases. Cancer 1989;63:181-7.

15. Tubiana M, Koscielny S. Natural history of human breast cancer: Recent data and clinical implications. Breast Cancer Res Treat 1991;18:125-40.

16. Kamby C, Andersen J, Ejlertsen B, Birkler NE, Rytter L, Zedeler K, et al. Pattern of spread and progression in relation to the characteristics of the primary tumour in human breast cancer. Acta Oncol 1991;30:301-8.

17. Tubiana M, Chauvel P, Renaud A, Malaise EP. Vitesse de croissance et histoire naturelle du cancer du sein. Bull Cancer (Paris) 1975;62:341-58.

18. Tabar L, Fagerberg G, Day NE, Duffy SW, Kitchin RM. Breast cancer treatment and natural history: new insights from results of screening. Lancet 1992;339:412-4.

19. Tubiana M. The growth and progression of human tumors: implications for management strategy. Radiotherapy and Oncology 1986;6:167-84.

20. Slack NH, Blumenson LE, Bross IDJ. Therapeutic implications of a mathematic model characterizing the course of breast cancer. Cancer 1969;24:960-71.

21. Tubiana M, Pejovic MH, Koscielny S, Chavaudra N, Malaise E. Growth rate, kinetics of tumor cell proliferation, and long-term outcome in human breast cancer. Int J Cancer 1989;44:17-22.

22. Tubiana M. Tumor cell proliferation kinetics and tumor growth rate. Acta Oncol 1989; 28:111-21.

23. Malaise EP, Chavaudra N, Charbit A, Tubiana M. Relationship between the growth rate of human metastases, survival and pathological type. Eur J Cancer 1974;10:451-9.

24. Charbit A, Malaise EP, Tubiana M. Relation between the pathological nature and the growth rate of human tumours. Eur J Cancer 1971;7:307-15.

25. Clarke R, Brunner N, Thompson EW, Katzende Uenbogen BS, Norman MJ, Koppic C, et al. Progression of human breast cancer cells from hormonal dependent to independent growth both in vitro and in vivo. Proc Nat Acad Sci USA 1989;86:3649-53.

26. Tubiana M, Arriagada R, Sarrazin D. Human cancer natural history, radiation induced immunodepression and post-operative radiation therapy. Int J Radiat Oncol Biol Phys 1986;12:477-85.

27. Anderson P, Dische S. Local tumor control and subsequent incidence of distant metastatic disease. Int J Radiat Oncol Biol Phys 1981;7:1645-8.

28. Arriagada R, Le MG, Mouriesse H, Tubiana M. Long-term effect of internal mammary chain treatment: results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. Radiother Oncol 1988;11:213-22.

29. Arriagada R, Rutqvist LE, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment of early breast cancer may prevent secondary dissemination. J Clin Oncol 1995;13:2869-78.

30. Hayward J, Caleffi M. The significance of local control in the primary treatment of breast cancer. Arch Surg 1987;122:1244-7.

31. Hellman S. Stopping metastases at their source. N Engl J Med 1997;337:966.

32. Kemperman H, Borger J, Hart A, Peterse H, Bartelink H, van Dongen J. Prognostic factors for survival after breast conserving therapy for local I and II breast cancer. The role of local recurrence. Eur J Cancer 1995;31A:690-8.

33. Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. How important is adequate radiotherapy for the long term results of breast-conserving treatment. Radiother Oncol 1991;20:84-90.

34. Levitt SH, Aeppli DM, Nierengarten ME. The impact of radiation on early breast carcinoma survival. A Bayesian analysis. Cancer 1996;78:1035-42.

35. Stotter A, Atkinson EN, Fairston BA, McNeese M, Oswald MJ, Balch CM. Survival following locoregional recurrence after breast conservation therapy for cancer. Ann Surg 1990;212:166-72.

36. Elkhuizen PH, van de Vijver MJ, Hermans J, Zanderland HM, van de Velde CJ, Leer JW. Local recurrence after breast conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys 1998;40:859-67.

37. Clark RM, Whelan T, Levine M, Roberts R, Willian A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node -negative breast cancer: an update. J Natl Cancer Inst 1996;88:1659-64.

38. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-ear results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985;312:665-73.

39. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985;312:674-81.

40. Sarrazin D, Dewar JA, Arriagada R, Benhamou S, Benhamou E, Lasser P, et al. Conservative management of breast cancer. Brit J Surg 1986;73:604-6.

41. Auquier A, Rutqvist LE, Host H, Rotstein S, Arriagada R. Post-mastectomy megavoltage radiotherapy: the Oslo and Stockholm trials. Eur J Cancer 1992;28:433-7.

42. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med 1995; 333:1444-55.

43. Early Breast Cancer Trialists' Collaborative Group: favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. Lancet 2000;355:1757-70.

44. Laplanche A, Alzieu L, Delozier T, Berlie J, Veyret C, Fargeot P, et al. Polyadenylic-Polyuridylic acid plus regional radiotherapy versus chemotherapy with CMF in operable breast cancer: a 14 year follow-up analysis of a randomized trial of the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC). Breast Cancer Research and Treat 2000;64:189-91.

45. Sauer R. Adjuvant radiotherapy after breast conserving surgery for breast cancer. Eur J Cancer 2000;36:1073-8.

46. Lacour J, Lacour F, Spira A, Michelson M, Petit JY, Delage G, et al. Adjuvant treatment with polyadenylic-polyuridylic acid (poly A – poly U) in operable breast cancer. Lancet 1980;2:161-4.

47. Lacour J, Lacour F, Ducot B, Spira A, Michelson M, Petit JY, et al. Polyadenylic-polyuridylic acid as an adjuvant in the treatment of operable breast cancer: recent results. Eur J Surg Oncol 1988;14:311-6.

48. Dalberg K, Johansson U, Johansson H, Rutqvist LE. for the Stockholm Breast Cancer Study Group. A randomized trial of long term adjuvant tamoxifen plus postoperative radiation therapy versus radiation therapy alone for patients with early stage breast carcinoma treated with breast-conserving surgery. Cancer 1998;82:2204-11.

49 Rutqvist LE, Cenark B, Glas U, Johansson H, Rotskin S, Skoog L, et al. Radiotherapy, chemotherapy, Tamoxifen as adjuncts to surgery in early breast cancer: a summary of three controlled trials. Int J Rad Oncol Biol Phys 1989;16:629-39.

50. Guiguet M, Valleron AJ, Tubiana M. Distribution de la taille des metastases à la détection et traitement adjuvant: approche biomathématique. Compte Rendus Acad Sc (Paris) 1982;294:15-8.

51. Overgaard M, Hansen PS, Overgaard J, Rose C, Anersson M, Bach F, et al. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group S26 Trial. New Engl J Med 1997;337:949-55.

52. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641-8.

53. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A metaanalysis. J Clin Oncol 2000;18: 1220-9.

54. Fortin A, Larochelle M, Laverdière J, Lavertu S, Tremblay D. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. J Clin Oncol 1999;17:101-9.

55. Stjernsward J. Decreased survival related to irradiation post-operatively in early operable breast cancer. Lancet 1974;2:1285-6.

56. Liljegren G, Lindgren A, Bergh J, Nordgren H, Tabar L, Holmberg L. Risk factors for local recurrence after conservative treatment in stage I breast cancer. Definition of a subgroup not requiring radiotherapy. Ann Oncol 1997;8:235-41.

57. Wallgren A. Adjuvant radiotherapy after breast conserving surgery for breast cancer. Contra. Eur J Cancer 2000;36:1078-82.

58. Kurtz JM. Adjuvant radiotherapy after breast conserving surgery for breast cancer – Arbiter. Eur J Cancer 2000;36:1082-4.

59. Recht A, Bartelink H, Fourqvet A, Fowble B, Haffty BG, Harris JR, et al. Postmastectomy radiotherapy: questions for the twenty-first century. J Clin Oncol 1998;16:2886-9.

60. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995;333: 1456-61.

61. Gyenes G, Fornander T, Carlens P, Glas U, Rutqvist L. Myocardial damage in breast cancer patients treated with adjuvant radiotherapy: a prospective study. Int J Radiat Oncol Biol Phys 1996;36:899-905.

62. Hojris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischemic heart disease in 3083 high-risk breast patients given adjuvant systemic therapy treatment with or withour postmastectomy irradiation: analysis of DBCG 82b and 82c randomised trials. Lancet 1999;354:1425-30.

63. Tubiana M, Eschwège F. Conformal radiotherapy and intensity-modulated radiotherapy – Clinical Data. Acta Oncologica 2000;39:555-567.

64. Buchholz TA, Austin Seymore MM, Moe RE, Ellis GK, Livingston RB, Pelton JG, et al. Effect of delay in radiation in the combined modality treatment of breast cancer. Int J Radiat Oncol Biol Phys 1993;26:23-35.

65. Recht A, Come SE, Henderson IC, Gelman RS, Silver B, Hayes DF, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996;334: 1356-61.