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Preoperative X-ray therapy in cancer of the breast

By Sigvard Kaae, Aarhus

Blood-borne metastasization may take place in two ways. Tumour cells may pass direct from the primary tumour into the blood stream or else the mechanism is an indirect, lymphogenous one, tumour cells entering the blood stream by way of the thoracic duct or the right lymphatic duct. Recent investigations indicate yet another possibility, i.e. transmission from lymph nodes direct to the blood stream through lymphatico-venous connections which are normally closed, but which may open up after occlusion of efferent lymphatic channels from the nodes [1].

Blood-borne metastasization from cancer of the breast is common [3], but it is difficult to decide to what extent it is due to the entrance of tumour cells direct from the primary tumour and to what extent it is by way of the lymphatic channels. Microscopic studies of tumours showing tumour cells in the blood vessels [6] as well as the demonstration of tumour cells circulating in the blood of patients with operable breast cancer [2, 7] indicate that direct blood-borne metastasization is an important factor. However, it is difficult to evaluate how frequently this presence of tumour cells in the blood stream leads to manifest metastasization.

Distant metastases, which must be blood-borne—direct or by the lymphatic channels—are common in breast cancer, also in the operable stages. Does this metastasization take place, in an appreciable degree, in connection with the surgical treatment, or did it happen, in the main, before that time? The finding of an increased number of tumour cells in the blood at operation might indicate that the surgical procedure increases the risk of haematogenous metastasization.

Investigation into the growth rate of the metastases, especially pulmonary metastases, with the assumption that 1 cell divides into 2, 2 into 4, 4 into 8 at a fairly constant interval, indicate that metastases may have been present for a long time, presumably for years, before they are recognized. From a single cell about 20 cell division periods are

required until the tumour is 1 mm, 30 before it is 1 cm in diameter, and the interval between the cell divisions appears to be in some cases several months [8]. It is possible, therefore, that e.g. a pulmonary metastasis detected one year after the operation has been present, but undetectable, several years before the operation.

One of the objects of preoperative irradiation may be to damage the tumour cells so much that if they enter the blood stream at the time of the operation they are unable to give rise to metastases. The only reliable way of assessing this effect of preoperative irradiation in breast cancer is to run clinical experiments including 2 random series treated by the same operation, radical mastectomy, one after preoperative irradiation and the other without any supplementary irradiation. To my knowledge such random series do not exist.

Although it is not quite satisfactory, I shall therefore try to compare two, not randomized series of breast cancer from the Radium Centre, Copenhagen. During the period June 1st 1938 to 1944 the treatment of breast cancer was intensive X-ray therapy followed by radical mastectomy. During the period November 1st 1951 to 1957 the patients with breast cancer were divided into two groups (random series). One was treated with extended radical mastectomy without supplementary X-ray therapy and the other with simple mastectomy and postoperative X-ray therapy according to the McWhirter principle. In an effort to assess the possibility that preoperative irradiation has of reducing the frequency of blood-borne distant metastases I shall compare the material from 1938-1944 having preoperative X-ray therapy and radical mastectomy with the group having extended radical mastectomy during the period 1951-1957.

The two groups are not randomized, and this gives rise to a factor of uncertainty. However, all patients of both groups were examined primarily at the Radium Centre, Copenhagen, are accurately described in its records, and were followed up there. I have previously published both series (1952, 1962), but have now again gone through the records to ensure a uniform evaluation of both groups. As operable I have included cases which fulfil the criteria of Haagensen from 1942.

The patients of the preoperative group received X-ray irradiation, 180 kV, H.V.L. 2 mm Cu, to two tangential fields to the breast, 2750 r to each, one axillary field from below, 2250 r, and one field in the supra-infra-clavicular region directed against the axilla, 3000 r. The depth dose in the breast, axilla and supraclavicular region was about 3500 to 3800 r in 4 weeks. The operation was classical radical mastectomy carried out in the Surgical Department of the Finsen Institute. The planned

Table 1
Total material

	Number of cases	Axillary node metastases
Preop. X-ray-radical mastect.	308	43%
Extended radical mastectomy	180	32%

time of operation was 4–6 weeks after the irradiation had been completed, but for various reasons a longer period elapsed in a number of cases. Cases were excluded from the analysis if the interval between X-ray therapy and operation exceeded 90 days. In 67% the interval was a maximum of 45 days, and it exceeded 60 days in only 10%.

The patients of the other group had extended radical mastectomy by the method of Dahl-Iversen, carried out in the Surgical Department C of the University Hospital, Copenhagen. This procedure is radical mastectomy supplemented with dissection of the lymph nodes in the supraclavicular region and in the internal mammary chain. No supplementary irradiation was administered in this series.

In the group treated by preoperative X-ray therapy there were among 330 patients 22 postoperative deaths, while no postoperative deaths occurred in the group of extended radical mastectomy. In assessing the distant metastasization the postoperative deaths were excluded.

This leaves 308 cases in the group having preoperative X-ray therapy and 180 in the group of extended radical mastectomy. All have been followed up for at least 5 years. There was microscopic evidence of axillary lymph-node metastases in 43% of the patients having preoperative X-ray therapy and in 32% of those having extended radical mastectomy (Table 1).

Fig. 1 presents the recurrence-free survival for all the patients. There is a 5-year recurrence-free survival of 57% in the group having preoperative X-ray therapy as compared with 61% in the other group, a slight difference which may be due to the somewhat higher frequency of axillary metastases in the irradiated group. Fig. 2 presents the recurrence-free survival in cases with axillary lymph-node metastases (5 years: 38% and 39% respectively) and Fig. 3 that in cases without axillary lymph-node metastases (5 years: 70% and 71% respectively). In other words, there is no difference in respect to the 5-year recurrence-free survival between the two groups, but the recurrences appear to

ALL CASES

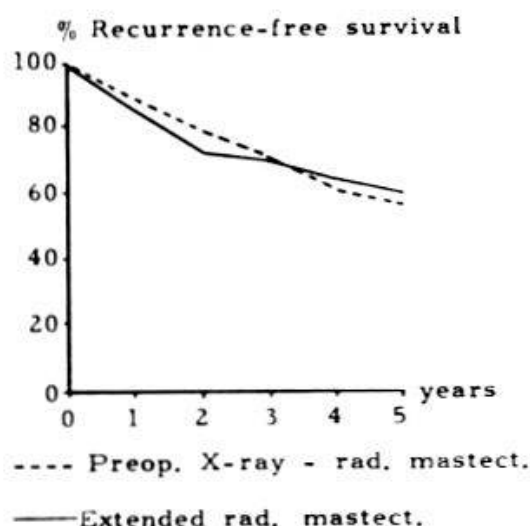


Fig. 1.

+ AXILLARY NODE METASTASES

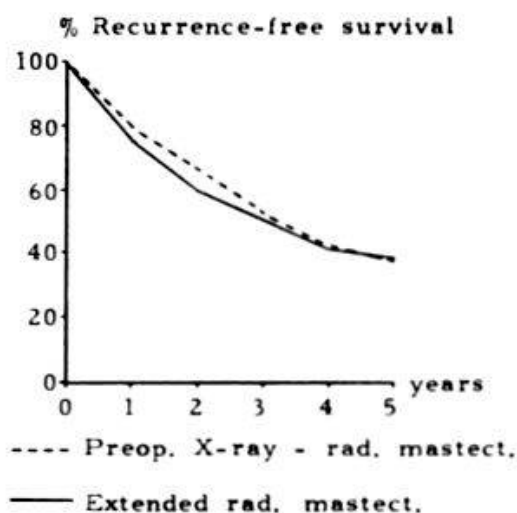


Fig. 2.

NO AXILLARY NODE METASTASES

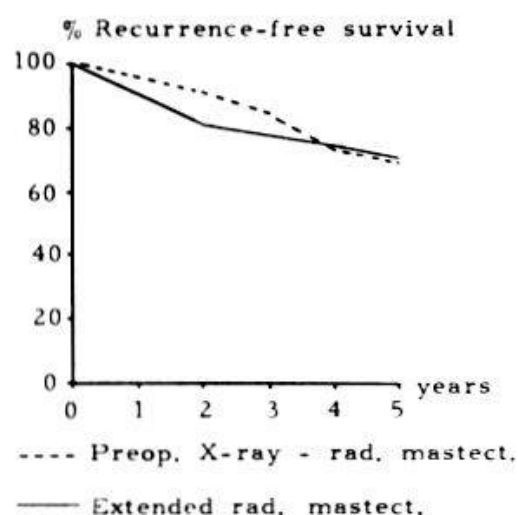


Fig. 3.

ALL CASES

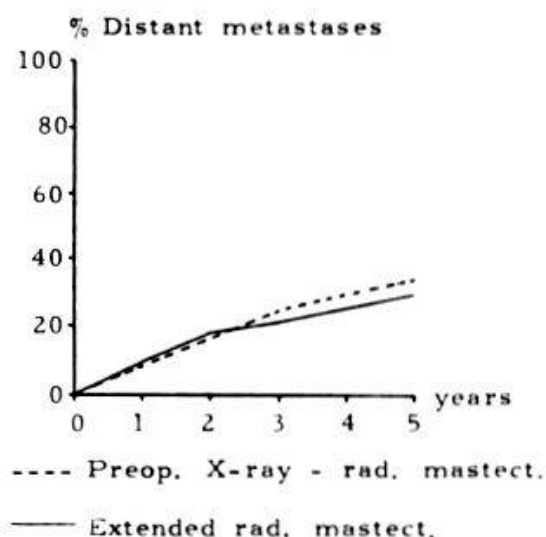


Fig. 4.

develop a little earlier in the group having extended radical mastectomy without any supplementary irradiation.

In what is to follow, a distinction will be made between distant metastases and local regional recurrences. In assessing blood-borne metastasization the term regional recurrence will be used in a more extended sense than usual. Local and regional recurrences will be taken to include recurrences in the operative field, in both axillae, both supraclavicular regions, as well as the recurrences which appear at the lateral border of the sternum, presumably derived from metastases to the internal mammary chain. These recurrences must be ascribed to tumour

+ AXILLARY NODE METASTASES

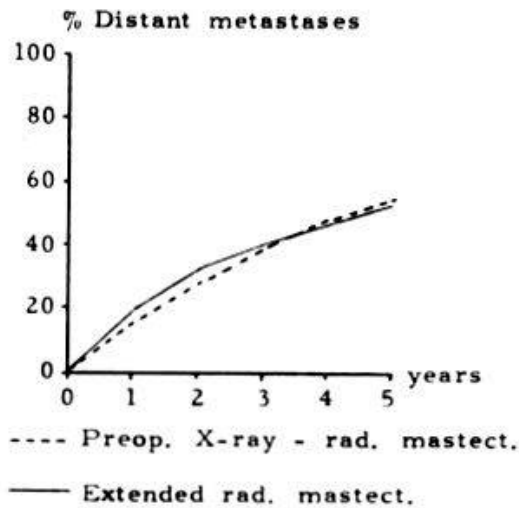


Fig. 5.

NO AXILLARY NODE METASTASES

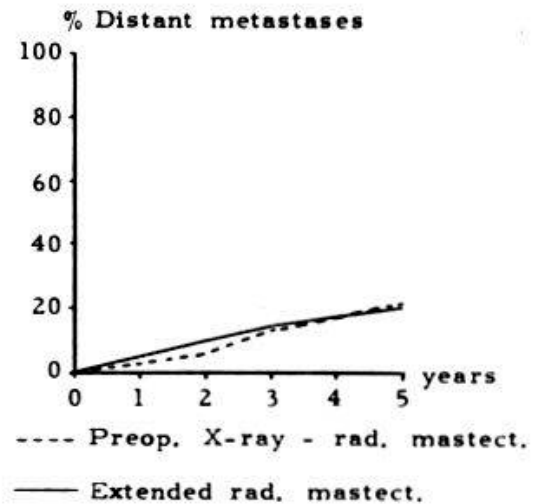


Fig. 6.

+ AXILLARY NODE METASTASES

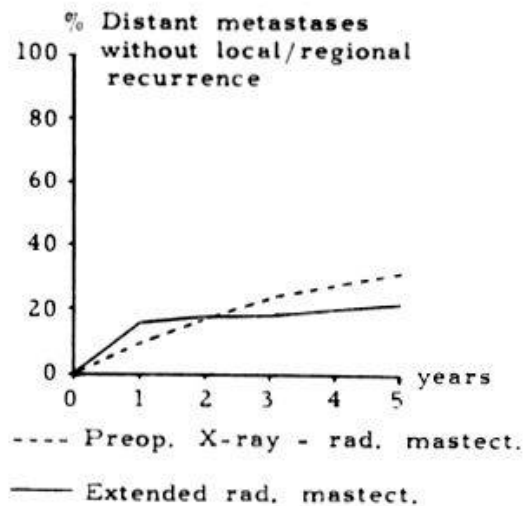


Fig. 7.

+ AXILLARY NODE METASTASES

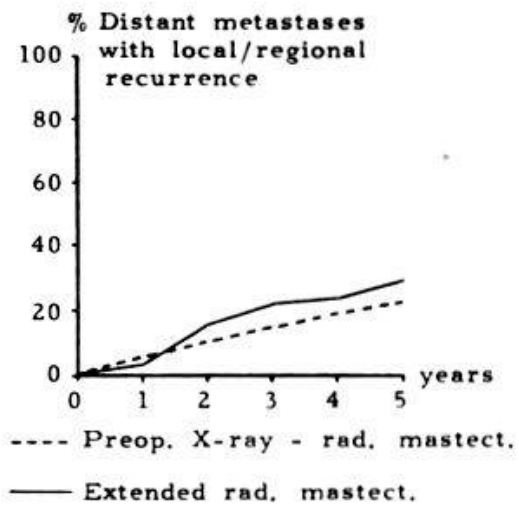


Fig. 8.

tissue left behind in the operative area or to lymphogenous metastasization.

The frequency of distant metastases with and without local/regional recurrences is shown in Fig. 4. Distant metastases developed within 5 years in 35% of the group having preoperative X-ray therapy as compared with 30% in the group having extended radical mastectomy—corresponding to the slightly higher frequency of axillary-node metastases in the former. Fig. 5 gives the frequency of distant metastases in cases with axillary node metastases at the time of operation (5 years: 55% and 53% respectively) and Fig. 6 that in cases without axillary metastases (5 years: 21% and 20% respectively). Thus, there is no difference in the frequency of distant metastases in the two groups.

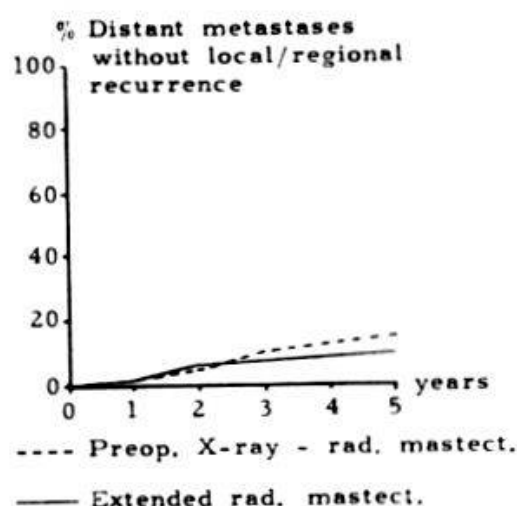


Fig. 9.

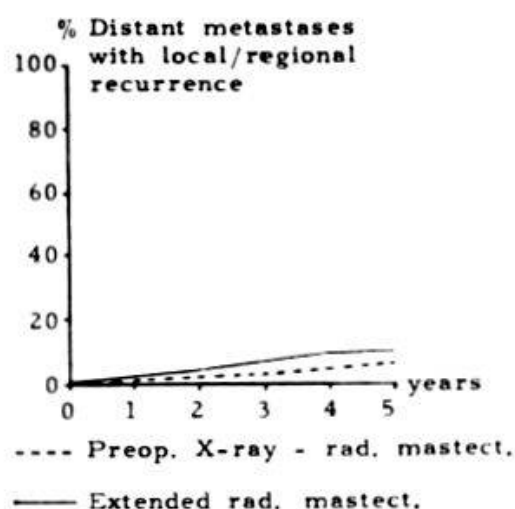


Fig. 10.

Table 2
5-year results + axillary lymph node metastases

	Number of cases	Alive recurrence-free	Local/regional recurrence	Distant metastases
Preop. X-ray-radical mastectomy	131	38%	23%	55%
Extended radical mastectomy	57	39%	33%	53%

On the other hand, there is a difference in the frequency of distant metastases in the presence of and in the absence of local/regional recurrence in the two groups. Fig. 7 presents the frequency of distant metastases without local/regional recurrence in cases having axillary node metastases at operation. Within 5 years metastases appeared in 33% of the group having preoperative X-ray therapy as compared with 23% in the group having extended radical mastectomy. Fig. 8 gives the frequency of distant metastases co-existing with local-regional recurrence which is, within the 5-year period, 22% in the group having preoperative X-ray therapy and 30% in the group having extended radical mastectomy. Exactly the same was found in cases showing no axillary lymph node metastases at operation. The 5-year frequency of distant metastases without local-regional recurrence (Fig. 9) is 14% and 9% respectively and that of distant metastases with local-regional recurrence (Fig. 10) 7% and 11% respectively.

Thus, the preoperative X-ray therapy appears to have caused fewer

Table 3
5-year results no axillary lymph node metastases

	Number of cases	Alive recurrence- free	Local/ regional recurrence	Distant metastases
Preop. X-ray-radical mastectomy	177	70%	10%	21%
Extended radical mastectomy	123	71%	15%	20%

Table 4
5-year results

	+ axillary node metastases		No axillary node metastases	
	Number of cases	Distant metast.	Number of cases	Distant metast.
Preop. X-ray-radical mastectomy	93	59%	114	20%
Interval \leq 45 days				
Extended radical mastectomy	57	53%	123	20%

local and regional recurrences, and thereby a somewhat higher recurrence-free survival during the first years after the operation, but it has not been able to affect the frequency of distant metastases which occur with the same frequency in both series (Tables 2 and 3).

The interval between the completion of preoperative X-ray therapy and radical mastectomy was up to 90 days. In order to exclude the possibility that the sometimes long interval has reduced the effect of preoperative X-ray therapy, the frequency of distant metastases following extended radical mastectomy was compared with that following preoperative X-ray therapy—radical mastectomy at an interval of at most 45 days (Table 4). Neither the patients with nor those without axillary lymph node metastases at operation had fewer 5-year distant metastases following preoperative X-ray therapy-radical mastectomy than following extended radical mastectomy.

Distant metastases of certain sites are usually lymphogenous, while those of other sites must be blood-borne. It might be of interest, therefore, to compare the localization of the first distant metastases following preoperative X-ray therapy-radical mastectomy and following extended

Table 5

5-year results first localization of distant metastases + axillary metastases at operation

	Preop. X-ray- -radical mastectomy	Extended radical mastectomy
Pleura, mediast., abdomen	25%	25%
Bone, lung, brain etc.	27%	26%
Localization unknown	3%	2%
Total	55%	53%

Table 6

5-year results first localization of distant metastases no axillary metastases at operation

	Preop. X-ray -radical mastectomy	Extended radical mastectomy
Pleura, mediast., abdomen	8%	6%
Bone, lung, brain etc.	12%	13%
Localization unknown	1%	1%
Total	21%	20%

radical mastectomy. The distant metastases were divided into two groups. One includes cases in which the first distant metastasis was localized to the pleurae, the mediastinum, or abdomen (peritoneum, liver) and thus must be considered to have been lymphogenous in most cases. The other group comprises all other cases, mainly metastases to the bones, lungs (without primary pleural changes), and brain. These metastases must be considered blood-borne.

Tables 5 and 6 give the frequency of the first distant metastases in the two groups. They show the same per cent frequency of distant metastases to the pleurae-mediastinum-abdomen as to bones-lungs-brain in the two groups, in cases with as well as without axillary node metastases at operation. When considering also the different frequencies of local/regional recurrences in the two groups, the preoperative X-ray therapy seems to have had no influence upon the haematogenous metastasization. This indicates that the distant metastases were present at the time of the operation, although they were not clinically manifest until later.

This analysis gives no decisive information as to whether other forms of preoperative irradiation, e.g. short-lasting, intensive irradiation followed by operation immediately after its completion, can reduce the frequency of blood-borne metastases. This can be decided only by running two random series.

Summary

Preoperative irradiation as a supplement to surgery in operable breast cancer is possibly able to reduce the frequency of blood-borne metastasization caused by the surgical procedure.

In order to assess this possibility, the frequency of distant metastases was compared in two groups of patients treated at the Radium Centre, Copenhagen. One group had preoperative X-ray therapy-radical mastectomy and the other extended radical mastectomy without supplementary irradiation.

No difference was found between the two groups in respect to the frequency of distant metastases within 5 years. On the other hand, fewer local/regional recurrences appeared in the group having preoperative X-ray therapy.

Thus, the preoperative X-ray therapy has possibly reduced the frequency of local-regional recurrences, but it has been unable to reduce the incidence of distant metastases. This indicates that the distant metastases have been present even before the operation, although they have not until later acquired a size which permitted their detection.

Whether preoperative irradiation can reduce the frequency of blood-borne metastasization elicited by the surgical procedure cannot be definitely decided except by running two random series, one with and the other without supplementary irradiation.

Zusammenfassung

Die die chirurgischen Maßnahmen ergänzende Vorbestrahlung des operierbaren Brustkrebses vermag die Häufigkeit der nach einem Eingriff auf dem Blutwege erfolgenden Metastasenbildung möglicherweise zu reduzieren.

Um diese Vermutung zu prüfen, wurden die Frequenzen der Fernmetastasenbildung bei zwei Patientengruppen des Radiumzentrums von Kopenhagen miteinander verglichen. Die eine Gruppe erhielt vor der radikalen Mastektomie eine Vorbestrahlung. Bei der anderen wurde die ausgedehnte radikale Mammaamputation ohne zusätzliche Bestrahlung durchgeführt.

In bezug auf die Häufigkeit von Fernmetastasenbildung konnte innerhalb von 5 Jahren bei beiden Gruppen kein Unterschied gefunden werden. Andererseits zeigten sich bei der vorbestrahlten Gruppe weniger lokal-regionale Rückfälle.

Also hat die Vorbestrahlung möglicherweise die Häufigkeit lokal-regionaler Rückfälle verringert. Auf die Bildung von Fernmetastasen

konnte sie jedoch keinen entscheidenden Einfluß ausüben. Dies zeigt, daß die Fernmetastasen schon vor der Operation vorhanden waren, obgleich sie erst später eine Größe erreichten, die ihre Entdeckung erlaubte.

Ob die präoperative Bestrahlung die Häufigkeit der auf dem Blutwege disseminierten Metastasen, die nach dem operativen Eingriff zutage treten, reduzieren kann, ist nicht definitiv zu entscheiden, ausgenommen durch das vergleichende Untersuchen zweier zufälliger Serien, deren eine mit und deren andere ohne zusätzliche Bestrahlung mastektomiert wurde.

Résumé

Dans les cancers du sein opérables, l'irradiation préalable semble pouvoir diminuer la fréquence des métastases par voie hématogène, mises en liberté par l'intervention chirurgicale. Pour contrôler cette hypothèse, l'on a comparé la fréquence des métastases à distance dans deux groupes de malades du Centre du Radium de Copenhague. Dans un groupe, l'on a fait une irradiation préopératoire avant l'ablation radicale de la glande mammaire, dans l'autre groupe, l'on a fait une ablation large du sein, sans traitement radiothérapique supplémentaire.

On n'a vu aucune différence entre les deux groupes pour ce qui est de la fréquence des métastases à distance dans les 5 premières années. Par contre, l'on a eu beaucoup moins de récurrences locales et régionales dans le groupe qui avait eu un traitement radiologique préopératoire.

Le traitement par rayons-X préopératoire semble par conséquent avoir diminué la fréquence de récurrences locales et régionales, mais n'a pas pu influencer l'apparition de métastases à distance. Ceci semble prouver que les métastases distantes étaient déjà disséminées avant l'intervention chirurgicale, mais qu'elles n'avaient pas encore atteint un développement qui aurait permis de les déceler.

Il n'est pas possible de dire avec certitude si l'irradiation préopératoire est capable de diminuer la fréquence des métastases par voie hématogène et qui ont été libérées par l'intervention chirurgicale, sans observer des séries de cas, dans lesquels, les uns ont, et les autres n'ont point d'irradiation supplémentaire.

Riassunto

Nei cancri al seno operabili, l'irradiazione preventiva sembra poter diminuire la frequenza delle metastasi per via sanguigna, liberate dall'intervento chirurgico. Per controllare questa ipotesi, si è comparato la frequenza delle metastasi a distanza, in due gruppi di malati del centro

Radium di Copenaghen. Ad un gruppo, è stata applicata un'irradiazione pre-operatoria prima dell'ablazione radicale della glandola mammaria, all'altro si è proceduto ad un'asportazione larga del seno senza trattamento radioterapeutico supplementare. Nessuna differenza è stata osservata nei due gruppi, per quanto riguarda le metastasi a distanza nei primi 5 anni. Invece si ebbero molto meno recidivi locali e regionali, nel gruppo sottomesso a trattamento radioterapeutico pre-operatorio. Il trattamento pre-operatorio ai raggi x, pare perciò aver diminuito la frequenza dei recidivi locali e regionali, ma non ha potuto influenzare l'apparizione di metastasi a distanza. Questo sembra provare che le metastasi distanti erano già disseminate prima dell'intervento chirurgico, ma che non avevano ancora raggiunto uno sviluppo che avrebbe permesso di scoprirle. È impossibile dire con certezza se l'irradiazione pre-operatoria sia capace di diminuire la frequenza delle metastasi per via sanguigna, liberate dall'intervento chirurgico, senza osservare la serie di casi nei quali gli uni abbiano e gli altri no, subito un'irradiazione supplementare.

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