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Radiotherapy in the Management of Early Breast Cancer: a Review

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INTRODUCTION

THE ROLE of radiotherapy in the treatment of breast cancer has changed significantly during the last decade. Originally radiotherapy was widely applied as an adjuvant treatment after mastectomy. It has been shown that such a therapy could significantly reduce the loco-regional recurrence rate; for example, in a CRC trial the loco-regional recurrence rate dropped from 29% to 11% when radiotherapy was given after mastectomy [1]. The mutilating aspects of mastectomy, however, had stimulated radiotherapists to develop alternative approaches. This became a reality when higher radiation doses could be given to the tumor volume with sparing of the normal tissues by using megavoltage equipment and implantation of radioactive sources in the breast. With these improvements and the efforts of a few pioneers like Baclesse, Mutaskallio and Peters, breast conserving therapy became possible. The first two trials carried out at Guy's Hospital, however, failed to demonstrate that breast conserving therapy was as good as radical mastectomy in forms of local control and survival. This was caused by the unfortunate use of rather low radiation doses [2]. The data of both trials suggested that good loco-regional treatment should be performed in order to obtain a high control rate, otherwise a detrimental effect on the survival may occur due to the high percentage of the loco-regional failures.

Since the early seventies many, especially French, radiotherapists have applied higher radiation doses using booster techniques with iridium implantation of iridium-192 sources or external irradiation. With these higher doses a much higher loco-regional control rate has been obtained [3–5].

BREAST CONSERVING THERAPY TRIALS

In two randomized trials performed in Milan [6] and Paris [7], high radiation doses were used in patients treated with breast conserving therapy. The excellent results obtained in the above-mentioned centers were confirmed in these trials. The entry criteria for both trials were, however, limited to patients with tumors up to 2 cm diameter, which were excised completely. This means that breast conserving therapy was still limited to a small proportion of the breast cancer population.

The NSABP-06 trial extended the entry criteria to patients with tumors up to 4 cm diameter [8]. Again, similar results have been obtained when segmentectomy and irradiation was compared with total mastectomy. The role of radiotherapy as an integrated part of breast conserving therapy became clear with the results of this trial. The recurrence rate in the breast was significantly reduced when patients were irradiated after segmentectomy compared with a group of patients who did not receive radiotherapy (Fig. 1).

A disappointingly high local recurrence rate occurred in the group of patients with histologically proven lymph node metastases treated with segmentectomy alone. This high local failure rate appeared despite the adjuvant chemotherapy and the fact that only patients with a tumor excision with histologically free margins were accepted for breast conserving therapy. In this group of patients the local recurrence rate at 5 years dropped from 38% to 4% when radiotherapy was added (Fig. 1, panel c).

In the EORTC trial 10801, the entry criteria were even further extended. Patients with tumors up to 5 cm or incompletely excised tumors, were entered into this trial where breast conserving therapy was compared with radical mastectomy. Preliminary results indicate equal local control and survival in both arms. The excellent local control rates with adequate breast conserving therapy observed in the trials in Milan, Paris and from the NSABP, together with the preliminary data from the EORTC, demonstrate that breast conserving

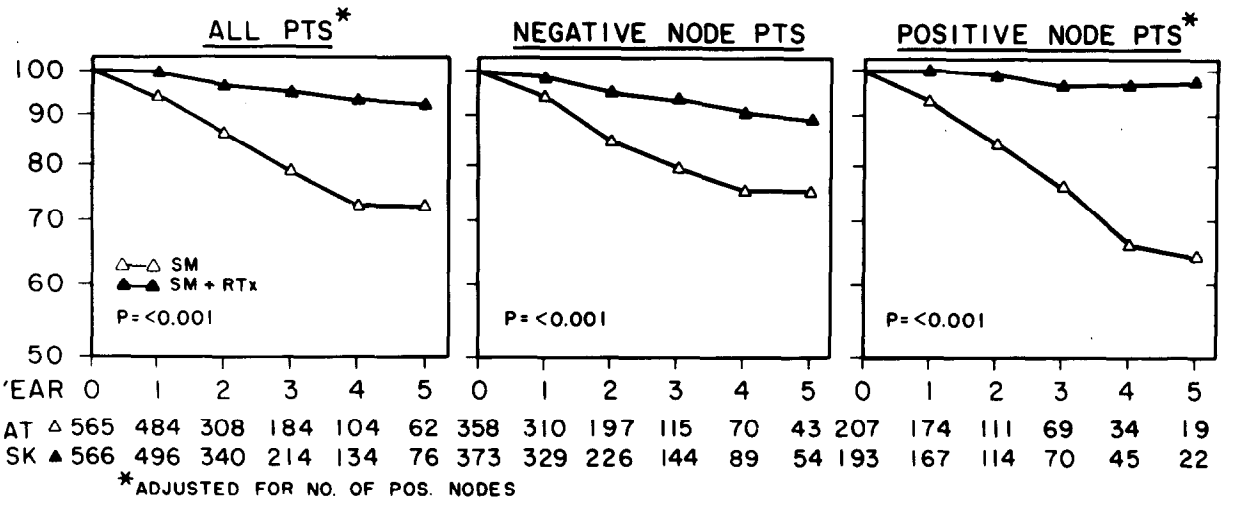

Fig. 1. Breast recurrence following segmental mastectomy (lumpectomy) with and without breast irradiation (RT) in the NSABP B-06 trial (reprinted with permission [8] Fisher, Wolmark 1986).

therapy results in loco-regional control and survival equal to the results of radical mastectomy.

Following the entry criteria used in the EORTC trial, it can be concluded that breast conserving therapy is now applicable to the majority of breast cancer patients.

LIMITATIONS OF BREAST CONSERVING THERAPY

After the establishment of breast conserving therapy as an alternative to radical mastectomy, further investigation is required to identify subgroups of patients with a high risk of local recurrence, and to quantify side-effects of radiotherapy. Such information should lead to further improvement of patient selection and treatment strategy.

A. *Factors related to a higher change of local recurrence*

Histology may provide information to identify risk groups, as suggested by Connolly *et al.* [9]. This group showed that patients with extensive ductal carcinoma *in situ* (DCIS) have a much higher chance of a local recurrence in the breast (Fig. 2). The criteria used to define this category were: more than 25% of the invasive tumor should consist of DCIS and that DCIS should extend to surrounding breast tissue. Other groups, however, did not confirm this finding: for example, no correlation has been observed up till now in the NSABP-06 study [8]. This may be explained by the fact that in this study all patients with incomplete excision of the primary tumor underwent mastectomy, and that the follow-up is still too short to detect a difference. Calle and co-workers [3] could also not confirm the relevance of this prognostic factor, although recently

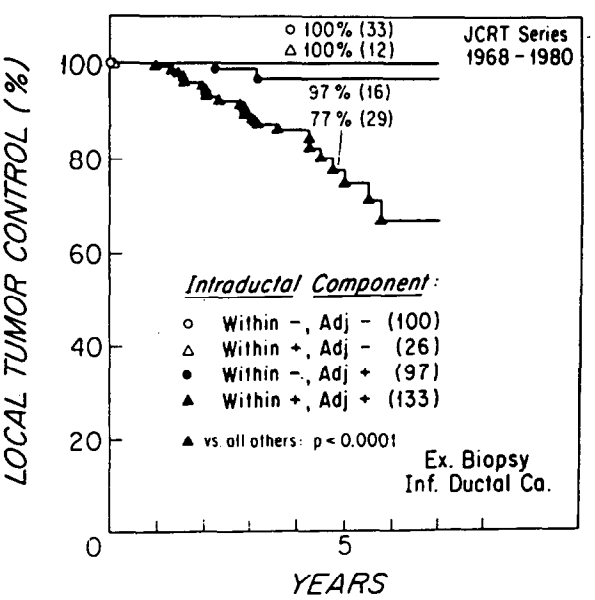

Fig. 2. Effect of the intraductal component on local tumor control, JCRT: excisional biopsy: infiltrating ductal histology only, 1968 to 1980 (reprinted with permission [10] Recht 1986).

they also observed an increased recurrence rate in this predicted high risk group (Zafrani, personal communication). At the Netherlands Cancer Institute extensive DCIS was associated with a significantly higher recurrence rate, although the recurrence rate in the breast was much lower (8%) than in the Boston series (38% at 5 years) [10]. The patients treated in our institute received 50 Gy to the whole breast and a booster of 25 Gy with iridium 192 with approx. 2–3 cm margins around the original tumor using a two-layer implant. The percentage of local recurrences in the Amsterdam group is so low that breast conserving therapy up to now is

not considered to be contra-indicated for patients with extensive DCIS. The difference between the NSABP experience and the experience of Boston suggests that, if possible, complete excision of the primary tumor, including the DCIS component, should be performed when breast conserving therapy is applied.

The finding of histologically proven invasive tumor positive margins may be another factor which is correlated with local recurrences. In some series [10, 11], it was shown that an incomplete excision of the primary tumor was correlated with a higher local recurrence rate. To sterilize such an increased amount of tumor cells left after lumpectomy, higher radiation doses are required [12]. Van Limbergen *et al.* showed in their study that with higher radiation doses better local control could indeed be accomplished. The disadvantage of using higher radiation doses, however, is that with increased doses more fibrosis will occur. The long term results of the EORTC trial will therefore be of great interest, especially because the large majority of the patients had large tumors (2–5 cm) and about 25% of the patients had a microscopically incomplete excision of the primary tumor.

Age has also been mentioned in the literature as a possible prognostic factor [3, 4, 13]. Patients younger than 35 years have a higher chance of local recurrence. It is unclear whether this higher incidence of recurrences in the breast is the result of different biological behavior in the younger group of patients or is caused by a longer treatment delay or less extensive surgery.

B. *Side-effects of treatment*

The side-effects of irradiation, e.g. fibrosis, induction of cardio-vascular disease or second malignant tumors, need to be studied more in detail. Recently, two interesting papers of Cuzick and co-workers [14, 15] suggest that post-operative radiotherapy after radical mastectomy or mastectomy could lead to a detrimental effect on long term survival (Fig. 3). The suggestion that this could have an impact on breast conserving therapy was based upon an enormous effort of this group to analyze the data of

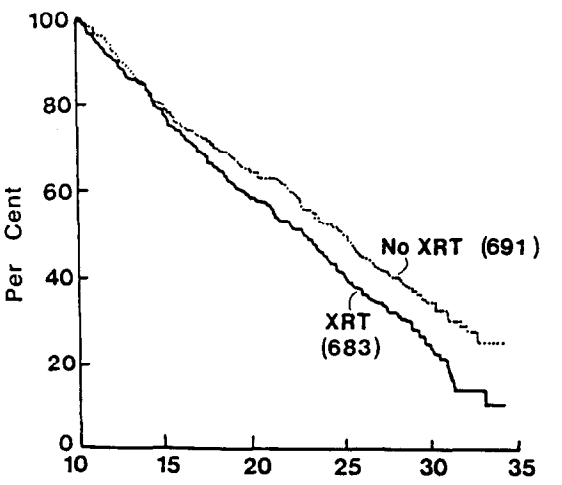

Fig. 3. Subsequent survival in patients surviving 10 years who were in a trial employing radical mastectomy whether or not combined with irradiation (XRT). For this analysis 691 and 683 patients were at risk in the no XRT and the XRT arm respectively (reprinted with permission Cuzick 1987 [15]).

8000 patients entered in eight trials. The clinical relevance of the suggestions of the above mentioned group, seems, however, limited due to the fact that the excess of deaths after 15 years concerned only 24 patients (see Table 1). The limitation of this study is formed by the fact that follow up information after 15 years is limited to a small subset of patients and mortality rate is not specified for cause of death. Conclusions are therefore premature and this situation can be compared with that of interim analysis of clinical trials with all the possible misleading conclusions inherent to such an analysis. Nevertheless it remains important to focus attention on side-effects of irradiation in relation to doses, volume of irradiated organs of breast, heart and lung and the irradiation techniques used. This information will lead to improved guidelines for this treatment.

A point of concern is also the induction of second malignant tumors by irradiation. From retrospective studies [16, 17] it appeared that there was a linear relationship between the absorbed dose in

Table 1. Patients at risk in each treatment arm and number of deaths for different follow up periods (Cuzick [14])

	All patients	Alive at 10 years	Number of deaths 10–15 years	> 15 years
RM + SM	4006	2077	170	134
RM + SM + XRT	3935	2071	191	158
Excess of deaths	—	—	21	24

RM + SM = radical and simple mastectomy.
XRT = radiotherapy.

the breast and the chance of inducing breast cancer. Induction of breast cancer by irradiation has mainly been observed in the younger age group. The available data in the literature [18–20] suggest that there is a decreased risk with an increasing age at exposure. Basco and co-workers [21] accordingly could not establish an increased risk of second breast cancer in the contralateral breast in a group of 14,000 patients with breast cancer. These patients were irradiated post-operatively for breast cancer, and as a result of the technique applied, the contralateral breast received a dose varying from 1.8 to 7.1 Gy. In this patient material no increased risk of breast cancer in the higher radiation dose areas has been observed.

In retrospective studies [7, 11] no increase in second malignancies has been observed so far. If the aforementioned linear dose–effect relationship applies after doses exceeding 8 Gy, a large amount of induced malignancies would in fact have been predicted. There is evidence, however, that above 10 Gy a reduction of second malignancies occurs, for example with the induction of leukemia (Fig. 4). This may be explained by the fact that DNA damage at doses higher than 10 Gy is so severe that cells containing potentially carcinogenic mutations are doomed to die. On the other hand, with minor DNA damage after low radiation doses unimpeded proliferation of the damaged cells may occur [22].

The above-mentioned possible limitations of breast conserving therapy should stimulate a careful follow up of the randomized trials, identification of patients with a high risk of local recurrence and measurement of the side effects of treatment.

AREAS FOR FUTURE RESEARCH

Further improvement of the results of breast conserving therapy will be obtained by reducing the percentages of loco-regional recurrences and by reducing the side-effects of therapy. It is important to assess how extensive radiotherapy should be. A dose of 50 Gy in 5 weeks may be sufficient for patients who receive a complete excision of the primary tumor while this is insufficient if the tumor is not completely excised. Dose–effect studies should, therefore, be performed to reach an optimal local control rate with a minimum of side-effects. It can also be argued that irradiation of the whole breast is not required due to the fact that most recurrences are observed in the tumor bed area. This is supported by the suggestion that new tumors in other areas of the treated breast are observed with the same frequency as in the contralateral breast [3]. Information should also be obtained on the possibility of using radiation therapy to sterilize premalignant disease: for example, is radiotherapy effective in patients who have only ductal carcinoma *in situ*?

The techniques of radiotherapy also need further improvement. The irradiation of the breast and the regional nodes is however one of the most complicated techniques in radiotherapy, due to the irregular shape of the breast and chest wall, and the location of the adjacent lymph nodes. It is necessary to spare sensitive normal tissues like heart and lung, and to deliver homogeneous doses to the breast.

CONCLUSIONS

A dramatic change in the role of radiotherapy in early breast cancer has been observed during the last decade. From an adjuvant treatment, irradiation has now become an integral part of the treatment of early breast cancer. The criteria for treating patients with breast conserving therapy in the past was limited to patients with tumors up to 2 cm. The NSABP and EORTC trials, however,

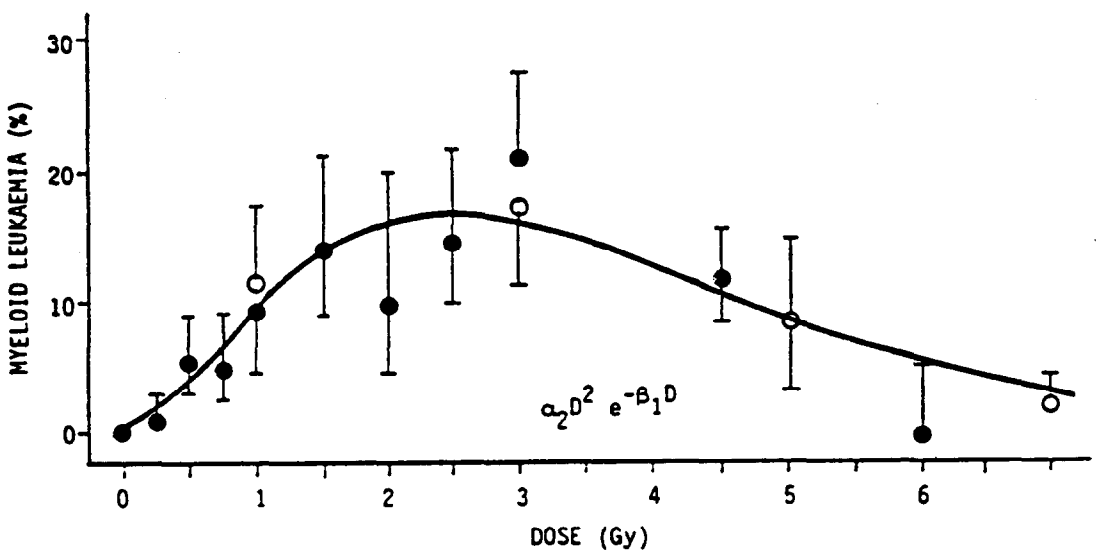

Fig. 4. Dose–response relationship for incidence of myeloid leukemia after brief exposures of male CBA mice to 250-kVp *X-rays* [22] (*Mole, Di Majo*).

suggest that in future patients with tumors up to 5 cm, and even within complete excision of the primary tumor, can be treated with breast sparing procedures. This means that breast conserving therapy will become the treatment of choice for the large majority of breast cancer patients.

SUMMARY

Breast conserving therapy with adequate radiotherapy results in similar local control and survival in patients with early breast cancer. Radiotherapy has proven to be an integral part of this treatment as in the NSABP trial a significant reduction of breast recurrences occurred after irradiation, compared with tumorectomy alone. The entry criteria of the performed randomized trials were initially limited to patients with tumours up to 2 cm diameter, but even patients with incompletely excised tumours up to 5 cm have been accepted in the recently closed EORTC trial 10801. This means that this conservative approach is now accessible for a much larger group of patients with breast cancer.

A few factors related to a somewhat higher recurrence rate in the breast are: extensive ductal carcinoma *in situ*, younger age and incomplete excision. These factors are, however, not absolute contraindications for breast conserving therapy because wide reexcision of the primary tumour or a high booster dose are likely to correct for these unfavourable factors.

Future clinical research is required to optimize the irradiation with reduction of side-effects and maintaining a high local control rate.

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