BREAST IRRADIATION: A COMMENTARY ON THE STATE OF THE ART*

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INTRODUCTION

Viewed from a historical perspective, the concept that the diagnosis of cancer in a woman's breast does not necessarily require complete ablation of the affected organ certainly owes its legitimacy to the effectiveness of radiotherapy. Radiation has been used in the treatment of breast cancer since shortly after Roentgen's discovery of X-rays more than 100 years ago. Although in those early days it was most often used as an adjunct to radical surgery or in the palliation of advanced disease, during the 1920s and 1930s a few practitioners experimented with the notion of replacing total mastectomy with radical radiation treatment. However, it was not until telecobalt machines and high-energy X-ray beams became available during the 1950s and 1960s that curative doses could be delivered without untoward injury to normal tissues, a prerequisite for breast-conserving therapy. Furthermore, during the same period it became apparent that results could be improved by associating breast irradiation with local excision of the primary tumour, rather than relying exclusively on irradiation for local control. Considerable experience was acquired with these techniques before the equivalency of breast-conserving and radical surgical treatments was demonstrated conclusively during the 1970s and 1980s by appropriately conducted randomised clinical trials.[1]

Breast irradiation has subsequently become one of the most extensively-studied treatments in clinical oncology, and an enormous amount of information has been generated regarding indications, techniques, efficacy, and side effects. This paper will attempt to summarise the most salient information regarding breast irradiation, to mention some areas of current investigation, and to suggest areas of future development. The matters of post-mastectomy radiotherapy and irradiation of regional lymph node areas will not be discussed.

CURRENT PRACTICE

How is radiotherapy currently administered?

As breast conservation was conceived as a 'radical' treatment, irradiation is traditionally administered to the entire breast. This is generally accomplished using simple, reproducible techniques, preferably with the patient lying comfortably in the supine position, and with the arm abducted to allow access to the breast by the radiation beam. Two opposed photon beams are used (telecobalt or 4-8 Mv X-rays), tangentially oriented in relation to the chest wall, with their deep edges often angled slightly to minimise lung irradiation. These beams are set up with the help of medical imagery, using either fluoroscopy and conventional radiographs ('simulator'), or using computerised tomography (CT-simulation).[2]

Once the radiotherapy beam arrangement has been established, it is essential to assure that the radiation machine actually delivers the dose prescribed by the oncologist. This involves optimisation of beam parameters (e.g., beam weighting, wedge filters) to produce a satisfactory dose distribution within the configuration of the patient's breast, and translating this output into parameters that can be set on a daily basis on the command console of the therapy machine. This entire process is greatly facilitated by the use of dedicated computer systems. Moreover, it is highly desirable that a system of quality control be established in order to assure the reliability of day-to-day treatment.[3]

Although dose-response relationships are the clinical expression of radiobiological phenomena, the choice of radiotherapy dose and 'fractionation' (dose per session, rhythm and total number of treatment sessions) for a given clinical situation is highly empirical and varies between therapists. An 'optimal' schedule is thought to provide the most favourable relationship between local tumour control and minimal treatment-related side-effects. Currently it is widely believed that the optimal schedule for breast irradiation involves delivery of small daily doses of 1.8-2 Gray (1 Gy = 1 joule/kg), five days per week, over a period of about five weeks, attaining thereby a total dose of 45-50 Gy.[4] This represents a dose that is generally well tolerated by large soft tissue volumes, such as the entire breast, without inducing a significant degree and frequency of unacceptable normal tissue injury.

As the risk of intramammary recurrence is numerically highest in the vicinity of the tumour bed, it is the practice in many centres to deliver additional localised irradiation (a 'boost' of 10-20 Gy) to this site. The boost potentially reduces local recurrence rates, at the potential price of a localised area of fibrosis. The boost can be administered using either an external electron beam of limited penetrating power, or by the temporary interstitial implantation of radioactive isotopes ('brachytherapy', e.g., with the gamma emitter, Iridium-192). Definition of the volume to be targeted for boost irradiation is problematical. Many centres advocate marking the borders of the tumour bed by the surgeon at time of lumpectomy using radioopaque metallic clips.[4]

What does breast irradiation achieve?

Although tumour excision was formerly considered a local adjunct to radical radiotherapy, surgeons currently strive if possible to carry out a microscopically 'complete' resection. Radiotherapy has thus come to be considered as an 'adjuvant' to surgical treatment, and randomised trials have allowed an assessment of the proportional reduction in recurrence

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risk using radiotherapy compared with surgery alone (Table 1). A dose of 50 Gy reduces the risk of local recurrence by a factor of about 4, an effect that may be even more pronounced if chemotherapy or tamoxifen are prescribed as well. Although this *relative* risk reduction is probably independent of the type of surgery used, the absolute recurrence rate depends on the extent of resection. Using simple 'lumpectomy' with clear resection margins, 50 Gy reduces recurrence rates from 30-40% 'local' to less than 10%. With optimal use of re-excision, boost irradiation, and systemic chemotherapy, five-year recurrence rates may be reduced to less than 5%. It should also be mentioned that after conservative excision of non-invasive intraductal *in situ* carcinomas, 50 Gy breast irradiation results in a reduction in the rate of subsequent invasive carcinoma by a factor of about 3.[5]

Although failure in the eradication of the tumour in the breast is usually controlled locally by further surgery, recent analyses have shown that intramammary recurrence is associated with about a threefold increased risk of development of distant metastases.[11] Surprisingly, however, prevention of local recurrence by breast irradiation or mastectomy has little effect on metastatic risk or survival, at least during the first ten years.[6-8] Longer follow-up may contradict this notion. Thus the main benefits of breast irradiation relate to preventing the consequences of local failure, namely breast loss, uncontrolled local disease, and the anxiety to the patient associated therewith.

Although the benefits of whole-breast treatment are well recognised, the question of 'boost' irradiation is controversial. In the presence of negative excision margins, especially in patients receiving appropriate systemic therapy, local control after 50 Gy breast radiotherapy is very high, leading some to question the utility of boost treatment. Theoretical considerations predict a twofold reduction in local failures (e.g. from 10% to 5%) with 15 Gy boost irradiation. A large randomised trial has recently been completed by the European Organisation for Research and Treatment of Cancer to clarify this question. At present there is no consensus on this subject, nor is there unanimity regarding the optimal technique of 'boost' administration (external beam versus interstitial brachytherapy).

What are the adverse effects of breast irradiation?

In addition to the cost and inconvenience of a treatment course often exceeding five weeks, breast irradiation is associated with a certain number of potentially detrimental effects.[12] Generally, the acute side effects of radiotherapy dissipate rapidly, with the exception of breast oedema, which usually resolves over the first 6-24 months. A small fraction of patients will go on to develop symptomatic changes in tissues within the irradiated volume, leading to breast fibrosis and retraction, or to visible skin changes, potentially affecting the cosmetic outcome. Nonetheless, with modern techniques, cosmetic results should be satisfactory in more than 90% of preserved breasts.

Serious complications should be very uncommon with treatment limited to the breast. Rib fractures, often asymptomatic, are observed in less than 1% of patients. Modest pulmonary function changes have been documented,[13] but associated respiratory symptoms are seldom seen and are always transitory. Although a portion of the heart may be included in left-sided tangential fields, serious cardiac morbidity has not been clearly documented for radiation limited to the breast.[14] The risk of second tumor induction (contralateral breast cancer and other second cancers), certainly small, is currently under investigation in long-term studies. Isolated cases of breast sarcomas have been reported.

FUTURE PERSPECTIVES

Improvement in radiation treatment planning

The objective of treatment planning is to optimise dose delivery to the target volume, whilst reducing to a minimum the irradiation of normal tissues. In breast cancer the most important vital normal tissues are lung and heart. When radiotherapy is limited to the breast, simple treatment planning techniques generally produce satisfactory overall results. Nonetheless, clinically significant heart volumes are found to be irradiated to high dose in a small minority of patients with leftsided tumors.[15] Such patients could benefit from more sophisticated planning techniques. CT-

TABLE 1
Crude intramammary recurrence rates from prospective, randomised clinical trials of invasive carcinomas.
mfu = median follow-up; RT- = conservation surgery alone; RT+ = with radiotherapy.

		Local Recurrence (%)	
	mfu	**RT-**	**RT+**
NSABP B-06 (lumpectomy)[6]	125 mo	200/572 (35%)	51/568 (9%)
Ontario Cancer Institute (lumpectomy)[7]	91 mo	148/421 (35%)	47/416 (11%)
Scottish Cancer Trials (lumpectomy)[8]	68 mo	72/294 (24%)	17/291(6%)
Uppsala-Orebro (segmentectomy)[9]	64 mo	37/197 (19%)	6/184 (3%)
Milan[3] (quadrantectomy)[10]	39 mo	28/273 (10%)	1/294 (0.3%)

based planning also provides the opportunity to recognise and correct possible zones of excessive dose inhomogeneity within the treatment volume, thereby optimising efficacy and normal tissue tolerance, including the end cosmetic result.[16] Moreover, if lymph nodal areas are also to be irradiated, CT-based treatment planning techniques are likely to become the standard of care in the future.

Individualisation of the radiotherapeutic approach

The locoregional results of conservation surgery and standard breast irradiation are excellent in the large majority of patients. Nonetheless, local control remains suboptimal in certain subgoups, and a small fraction of patients receiving standard treatment suffer unacceptable normal tissue injury. More precise knowledge of individual tumour radioresistance and individual normal tissue radiosensitivity will thus be required in order to adapt treatment appropriately, both for those needing more effective therapy, as well as for those who would benefit from a reduction in therapeutic intensity. The mere identification of the subgroup at risk for excessive normal tissue injury might not only allow a beneficial dose reduction to be prescribed in radiosensitive patients, but a significant dose increase to be implemented in the remaining majority of patients, thereby potentially improving the overall treatment results.

The prospect of using differential tumour radiosensitivity to clinical advantage is more problematical. Given the generally disappointing results using hypoxic cell radiosensitizers in other tumour sites,[17] it is unlikely that these will prove useful in breast cancer. Moreover, the improved local control in patients receiving chemotherapy and tamoxifen in addition to breast irradiation may result from an additive effect, rather than a modulation of the cellular response to radiotherapy. Progress in this field will require more precise knowledge of specific molecular biological mechanisms of radioresistance (DNA repair mechanisms, cell cycle regulation, kinetics, etc.) in breast cancer cells,[18] in view of pharmacologically modifying radiation response to allow more reliable tumour eradication. This currently remains an area of basic and applied research.

It is thus theoretically possible that, in the future, radiation dose and fractionation might be individualised as a function of the biological characteristics of the tumour or of the genetic profile of the patient.[19] However, current interest in the question of fractionation is primarily directed at reducing the number of treatment sessions, in order to reduce inconvenience and lighten patient loads in busy oncology departments. A large randomised trial is underway to that effect in the United Kingdom.

On the other end of the spectrum, since early breast cancer is sometimes a truly unifocal disease, it is likely that selected patients could be safely treated with conservative surgery alone. Given the increasingly early stage in which breast cancer is diagnosed by mammography and fine needle aspiration, it will become important to define which patients might be treated with minimal cost and morbidity. This may concern a substantial proportion of patients with intraductal *in situ* carcinomas, as well as those with invasive carcinomas having a low-risk of multifocality or multicentricity. The concept that low-risk subgroups may be reliably defined using clinical and histopathological parameters (e.g. age, tumour morphology) is currently being tested in prospective trials.[20]

As residual carcinoma is frequently confined only to the area immediately surrounding the primary lesion, some have proposed a simplified radiotherapy approach limiting treatment to a localised portion of the breast. A randomised trial in unselected patients has shown unsatisfactory results compared with those achieved by whole breast treatment.[21] This may nonetheless become an attractive option in selected patients thought to have a low risk of multicentric tumour foci, and appropriate clinical trials are underway. Brachytherapy has been proposed as a convenient approach in this setting.[22]

Optimisation of pluridisciplinary treatment programmes

For patients requiring chemotherapy, long delays are often imposed prior to beginning breast irradiation, potentially contributing to a loss of local control. In fact, the sequencing and timing of surgery, radiotherapy, and systemic therapies have not been adequately investigated, either regarding optimisation of effectiveness or of morbidity. Prospective studies are needed in this area.[23] Moreover, multimodality treatment programmes often occupy more than six months, seriously disrupting the patient's life for an extended period. Shortening the intensive phase of adjuvant treatment should be a research objective. Simultaneous administration of chemotherapy and irradiation may be a valid approach in this regard.

'Neo-adjuvant' chemotherapy (i.e. chemotherapy administered prior to locoregional treatment) offers the potential advantage of allowing the effectiveness of systematic therapy to be assessed in the individual patient. Although the full implications of neo-adjuvant chemotherapy in operable breast cancer are still under investigation, it has been demonstrated by randomised trials that a response to chemotherapy extends the possibilities of breast conservation to some patients who would traditionally have been considered candidates for total mastectomy.[24] This development will, in some cases, require modifications of both surgical and radiotherapeutic approaches. For example, in patients obtaining a clinical complete response to systemic therapy, the relative roles of surgery and radiotherapy will need to be defined, regarding treatment of both the breast and the draining lymph nodes.

CONCLUDING REMARKS

In developed western countries, it is likely that breast-conserving treatment will come to be practised with even greater frequency in the coming years in patients with diagnosed breast carcinoma. It is at present unclear whether breast irradiation will continue to be recommended in the large majority of such patients, or to be used in a more selective fashion. Selective use would require establishment of more precise measures of risk, as well as a generally accepted methodology for optimising the cost-benefit ratio associated with breast irradiation in individual cases. However, these considerations may become less relevant in an age where patients are increasingly likely to demand access to all treatment modalities that promise a significant reduction of the relative risk of relapse and spread, regardless of the absolute risk to which they are exposed. [25] Whether or not health care providers will be able to counter this trend remains to be seen. Clearly, the continued active participation of radiation oncologists in clinical breast cancer research will be essential for the development of rational multidisciplinary treatment programmes for the future.

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