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# Post-mastectomy Radiotherapy: Is It Cure After All?

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IT IS extraordinary that 45 years after the first randomised trial, we still do not know what proportion of patients with early breast cancer are cured by postmastectomy radiotherapy. Does this tell us something about the effects of radiotherapy or does it say more about how we conduct clinical trials? Is the question worth bothering about? The benefits of radiotherapy in reducing the incidence and morbidity of recurrent local–regional disease are well recognised, so poor risk patients are getting treated anyway. However, the group with the most to gain in terms of palliation may be quite distinct from a potentially curable group. The question is also worth considering because it concerns hypotheses that have dominated the management of early breast cancer over the last 20 years, namely that all breast cancer is disseminated at the time of presentation, and that lymph nodes are markers of tumour behaviour rather than determinants of spread [1].

In 1987, most people thought we had the answer concerning radiotherapy. A meta-analysis presented by Cuzick and associates looked at randomised trials started before 1975 evaluating postmastectomy radiotherapy [2]. There was no difference in survival up to 10 years, but in 4309 patient living beyond 10 years, the 25-year survival rate was 42% after postmastectomy radiotherapy compared with 51% after surgery alone. An update of this analysis in 1994 confirms that the excess mortality associated with radiotherapy was due to cardiac damage, and that this is probably balanced by a reduction in breast cancer deaths [3]. As a result of these findings, it is right to review the information available from these trials, and reassess the impact of radiotherapy on overall survival in breast cancer.

The first point to note is that the metaanalysis of almost 8000 patients is not a systematic overview of all postmastectomy radiotherapy trials. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) is currently analysing 17 000 women randomised worldwide since 1949, and is expected to report next year. However, the additional 9000 patients may contribute relatively little information beyond 10 years because many trials are not yet mature. The second point is that more than 1400 patients in Cuzick's metaanalysis are from the early Manchester trials (1949–1955) which were randomised according to patients' dates of birth. Date of birth is not regarded as a reliable approach to randomisation because the clinician knows in advance what treatment the patient will receive. The same system of randomisation was used for the concurrent ovarian ablation trial at Manchester. It turns out that substantially more women randomised to mastectomy alone were randomised to ovarian ablation. This is a potentially important imbalance considering the impact of ovarian ablation on long-term survival. Another source of bias is that 18% of patients in the NSAPB B-04 trial randomised to simple mastectomy alone had some form of lower axillary dissection.

Surgical approaches changed considerably between 1949 and 1975. The Manchester Q & P; Oslo I and II, Heidelberg and Stockholm trials used radical mastectomy, whereas the Manchester R, CRC and NSABP-B-04 trials used simple mastectomy. Important aspects of radiotherapy also changed, the most crucial being the shift from orthovoltage to megavoltage techniques. Orthovoltage radiotherapy was used in the Manchester Q P and R trials, Oslo I and approximately 30% of patients in the CRC trial. Other differences relate to the areas treated. The Manchester P, Oslo II and Heidelberg trials omitted the chest wall, but all trials attempted to include the internal mammary chain (IMC) and axilla. Techniques used to treat the chest wall varied between groups, the Oslo II trial using direct anterior photon fields, the NSABP-B04 utilising tangential photon fields, and the Stockholm trial using electrons. Field arrangements used in the Oslo I and the CRC trials meant that the IMC was often underdosed. A wide variety of radiotherapy dose-time schedules was used. It is tempting to invoke these points of difference to explain variations in trial outcome, but there are strict statistical limits to how far this is a legitimate exercise.

When all is said and done, what do Cuzick's updated results show? The all-cause mortality figures show an 18% (95% CI, 3–33%, $P = 0.02$) deficit in survival beyond 10 years for patients given radiotherapy after radical mastectomy, and a non-significant difference favouring radiotherapy after simple mastectomy. The analysis shows a strong and significant trend for the radiotherapy arms of recent trials to do relatively better than the corresponding arms of earlier trials ($P = 0.003$). The cause-specific mortality data confirm an excess number of cardiac deaths following radiotherapy. This was already known from the reports of the individual trials [4–7]. The highest risks were seen in the Oslo II, Heidelberg and Stockholm trials which had the highest estimated IMC doses. Additional analysis of the Stockholm trial revealed the excess cardiac mortality in left-sided tumours treated with tangential CO60 fields [6]. Fuller and colleagues documented the dose and volume of the heart treated by different radiotherapy techniques in the CRC trial, and showed how inadequate orthovoltage techniques could be [8]. Although there was a trend for excess cardiac mortality to be less marked in more recent trials in the meta-analysis, this did not reach statistical significance. The meta-analysis does not so far confirm an increased risk of death from non-breast cancer malignancies which the CRC trial reported [7].

Where breast cancer deaths are concerned, the relative risk after radical mastectomy and radiotherapy was 1.08 (95% CI, 0.83–1.84, ns). The corresponding risk after simple mastectomy and radiotherapy was 0.77 (95% CI, 0.67–0.97, $P = 0.03$). The 95% confidence limits of these two estimates overlap, and so are

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not significantly different from each other. Taken together, the relative risk of dying of breast cancer after postmastectomy radiotherapy was 0.9 (95% CI, 0.76–1.1, ns). To rationalise the null result for radiotherapy after radical mastectomy in terms of old-fashioned treatment, and to focus on the encouraging results after simple mastectomy risks highlighting a false positive result by subgroup analysis. Nevertheless, it is tempting to assume that, although postmastectomy radiotherapy contributes to a large increase in cardiac death risk, it also contributes to a reduction in breast cancer death risk.

It is helpful to look at the absolute number of events to put the observations in perspective. Among the 2149 women surviving 10 years after postmastectomy radiotherapy, 43 more cardiac deaths were recorded and 51 fewer breast cancer deaths than after surgery alone. When these figures are broken down by type of surgery (and hence, era), in 902 women surviving 10 years after radical mastectomy and radiotherapy, there were 32 more cardiac deaths and 5 more breast cancer deaths than in the surgery-alone group. In 1247 women surviving at least 10 years after simple mastectomy and radiotherapy, there were 11 more cardiac deaths and 46 fewer breast cancer deaths than in the surgery-alone arm. The reduced cardiac mortality in the simple mastectomy trials reflects shorter follow up as well as improved radiotherapy techniques. If the reduction in breast cancer mortality is real in trials testing radiotherapy after simple mastectomy, it could be a reflection of better radiotherapy techniques, or reflect the important difference between radical and simple mastectomy relating to axillary dissection.

The meta-analysis does not address the role of radiotherapy in combination with adjuvant systemic therapy, even though ovarian ablation was employed in the early Manchester and Oslo trials. In women <50 years, adjuvant ovarian ablation, chemotherapy and tamoxifen address the issue of micrometastatic spread, and each has been shown to improve overall survival [9]. However, adjuvant therapies have not been shown to provide loco-regional control in many studies, including ABMT and high dose chemotherapy setting [10–15]. Selected trials have reported overall survival benefit for postmastectomy radiotherapy in the presence of chemotherapy. The Danish Breast Cancer Group report a study of women at a high risk of relapse randomised to CMF chemotherapy alone or in combination with radiotherapy [16]. A significant benefit in overall survival was reported within 5 years of follow-up. The British Columbia Trial reported a 10-year follow-up of stage 2 patients randomised to chemotherapy alone or in combination with radiotherapy [17]. Overall survival in the radiotherapy arm was 68% compared with 58% in the control arm ($P<0.05$). Although both trials suggest radiotherapy contributes to survival, it will be essential to review all randomised data available before reliable conclusions can be drawn.

In conclusion, postoperative radiotherapy almost certainly makes a contribution to overall survival in women with breast cancer. The effects of treatment were originally dominated by radiation-induced cardiac damage, but four of the five most recent trials, initiated between 1970 and 1975, show an overall survival advantage in favour of radiotherapy. Depending on which estimate is chosen, postmastectomy radiotherapy reduces mortality risk from breast cancer in women surviving beyond 10 years by approximately 10–23%. A reduction of this magnitude might result in an extra 4–8 women alive between 10 and 20 years for every 100 women irradiated provided they do not succumb to heart disease or a second primary. One of the interesting features is that the benefit appears to arise in the group of women with at least 10 years' survival after mastectomy alone. This is probably a reflection of limited statistical power to detect small differences rather than a real effect. Other issues are less clear, for example, the contribution of each component of the radiotherapy to improved survival. It is conceivable that it would be necessary and sufficient to completely dissect the axilla or to irradiate it, but the data do not tell us this because the chest wall, IMC and supraclavicular fossa were usually included. If next year's EBCTCG systematic overview leaves many of these questions unanswered due to the statistical and technical limitations of earlier trials, we may be faced with repeating them all over again.


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