

# LOCAL THERAPY IN A SYSTEMIC WORLD: THE EVOLUTION AND INCARNATIONS OF ADJUNCT RADIOTHERAPY FOR BREAST CANCER

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## Abstract

Alan Coates' career has seen the evolution of radiotherapy in the adjuvant treatment of breast cancer move from the only modality available, through a period of little utilisation, to its current resurgence amid technology that can provide treatment to regions at risk with little dose delivery to sensitive normal tissues. The results of the early randomised trials reflected poor trial entry procedures, poor dose delivery of the radiotherapy and little accurate targeting of the regions to be treated. Alan was a leader in the era of evidence; if a treatment modality was to be used there must be evidence as to its efficacy. With the development over the last 15 years of high quality machinery and clinical practice that delivers precise radiation doses to areas at risk, the evidence for the role of radiotherapy both in improved survival as well as local control now exists both in the postmastectomy and breast conservation settings.

In farewelling Professor Alan Coates it is easy to consider matters in evolutionary terms. How far back must we go to reach an era in which he has not dominated the breast cancer literature?

Halsted described his mastectomy in a paper in 1894.<sup>1</sup> There was at that time no adjuvant therapy. The discovery of the properties of radiation a small number of years later led to its rapid inclusion in the treatment of breast cancer.<sup>2</sup> It was an era in which there was no systemic therapy, certainly no chemotherapy. Radiotherapy remained for over 70 years, the sole modality for reducing the risk of recurrence after surgery for breast cancer. It clearly worked. The role for radiation therapy in reducing the risk of local recurrence has not been disputed.<sup>3</sup> During the 1980s as clinical trials confirming the benefits of adjuvant chemotherapy on survival became widespread, the benefits of radiotherapy on survival and even its role in reducing local recurrence once chemotherapy was employed, was seriously questioned.

## Postmastectomy radiation therapy: historical data

The early randomised trials of radiotherapy after mastectomy did little to enhance the value of the modality.<sup>4-8</sup> We can look at them now and all were seriously flawed in some way, be it statistically,<sup>4,5</sup> in terms of the dosing for the radiation,<sup>5,7</sup> or in terms of the volume of the patients treated,<sup>4,5,7,8</sup> usually an unacceptable amount of cardiac inclusion. The best of the trials was the Stockholm I Trial.<sup>9</sup> It was started in 1971 and included 960 patients with operable disease. The study compared adjuvant radiotherapy with modified radical mastectomy alone. There was a clear improvement in the recurrence-free survival with radiotherapy ( $p < 0.001$ ) and in the higher risk group with node-positivity as well as improvement in both loco-regional recurrence ( $p < 0.001$ ) and distant metastases ( $p < 0.01$ ). With follow-up there was a non-significant

trend to improved survival.<sup>9</sup> This was set against an emerging literature of a decreased survival for those patients undergoing adjuvant radiotherapy.<sup>10-14</sup> The publications of Cuzick highlighted this and pointed specifically at an excess of cardiac deaths in those early trials reviewed.<sup>14</sup>

Chemotherapy alone however, did not adequately address local control.<sup>15-17</sup> While there was a small reduction in the rates of local relapse, patients at medium to high risk continued to accrue local recurrences, with the rates increasing over time. Even the introduction of high dose chemotherapy did not reduce the rate of local chest wall recurrence. This era however, where many patients received adjuvant systemic therapy without radiotherapy, has allowed us to identify those groups of patients at highest risk of local recurrence. The largest of these data series is from the International Breast Cancer Study Group,<sup>17</sup> an analysis of 5352 women, which is able to identify that for node negative patients, factors associated with increased risk of loco-regional relapse were vascular invasion and tumour size greater than 2cm for premenopausal women and vascular invasion for postmenopausal women. The 10-year cumulative incidence of locoregional failure was 16% for premenopausal and 19% for postmenopausal women. For the node positive group, the number of nodes and tumour grade were important for pre and postmenopausal groups, the additional predictors of vascular invasion for premenopausal women and tumour size for postmenopausal women. The 10-year risk of local relapse was 35% for the high-risk premenopausal group and 34% for the postmenopausal group. Clearly for such a group of patients the delivery of postmastectomy radiation is important. The challenge is to deliver the treatment without the late principally cardiac morbidity.

## Postmastectomy radiation therapy: the modern era

In the past 15 years, the development of new equipment and techniques, coupled with an expansion

of radiobiological understanding of dose-response relationships for breast cancer, has revolutionised the delivery of radiotherapy for this disease. Modern radiotherapy avoids direct irradiation of the heart and delivers a more effective dose to the regions most at risk of recurrence. Evidence is emerging that this is now converting the reduction in breast cancer deaths to improvements in overall survival.

The publication of two randomised trials in 1997 by Ragaz<sup>18</sup> and Overgaard<sup>19</sup> were the first suggestions of such improvements. Both trials showed significant improvements in overall survival, in addition to the benefits of their chemotherapy. The Overgaard trial (9% at 10 years) and the Ragaz trial (10% at 20 years),<sup>20</sup> showed improvements in overall survival from the addition of radiotherapy. A separate cardiac substudy with the Overgaard study showed no excess cardiac morbidity.<sup>21</sup> Such single institution data needs confirmation however, and that has been achieved with the publication of a meta-analysis.<sup>22</sup> The most compelling evidence that the effect is truly a reflection of improved delivery and targeting of the radiotherapy, as opposed to confounders in surgery and chemotherapy, came earlier this year. Gebski et al<sup>23</sup> published a sophisticated analysis of all postmastectomy radiotherapy studies according to the biologically equivalent dose delivered, the region and volume included in the target volume and whether the radiotherapy was delivered in a truly adjuvant situation or to compensate for inadequate surgery. They demonstrated in a meta-analysis of trials using optimal radiation therapy dose, delivered to appropriate target volumes, that there was an improved overall survival benefit. Furthermore, the relative risk reductions in all-cause death were calculated to be greatest for those at greatest risk of death, with a 16% reduction in the risk of death for this group. A 13% relative risk reduction was seen for the medium risk group and 7.8% for the low risk group. This is consistent with the clinical benefits seen in the Ragaz and Overgaard studies.

## Breast conservation

Meta-analysis of the 15 randomised breast conservation studies has shown a similar survival benefit of 8% relative reduction in all-cause death (hazard ratio = 0.92, 95% CI = 0.85 to 0.98).<sup>24</sup> The decision to advocate for radiotherapy in the breast conservation setting however, has always been more compelling, as the risks of local relapse carry with them increased rates of mastectomy in this group of women who have chosen to keep their breast.

## Multidisciplinary care

Clearly the clinical challenge is to optimally integrate all modalities of treatment. This is the fundamental outcome of multidisciplinary care. The multidisciplinary clinic in which Alan Coates practised his clinical oncology was a great forum for that, producing guidelines for the delivery of systemic therapy for patients not on clinical trials as early as 1996. At the same time we had guidelines for the indications for radiotherapy and both were freely discussed, as were the patients being seen. The radiotherapy and chemotherapy clinics ran side by side in the

environment of great intellectual flair. As national bodies and governments endeavor to establish criteria by which such clinics can be optimised,<sup>25</sup> a clinic in which systemic and local therapy decisions are optimally integrated must remain an ideal. □

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