

## History revisited: Did NSABP TRIAL B04 get it right?

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Fisher B, Jeong JH, Anderson S *et al.* Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *New England Journal of Medicine* 2002;347(8):567–575.

### Objective

To determine whether the radicality of local treatment of breast cancer influences long-term outcome, in particular survival.

### Study design

A randomised controlled trial of 1665 women with primary operable breast cancer, 1079 with clinically negative axillary nodes and 586 with clinically positive nodes.

Women with clinically negative nodes were randomised to:

- 1 treatment by radical mastectomy (n=362)
- 2 total mastectomy without axillary dissection but with radiotherapy to chest wall and regional lymph nodes (n=352)
- 3 total mastectomy 'alone' (n=365) (see commentary); these women had subsequent delayed axillary node dissection if axillary recurrence occurred.

Women with clinically positive nodes were randomised to:

- 1 radical mastectomy (n=292)
- 2 total mastectomy without axillary dissection but with chest wall and regional radiotherapy (n=294).

Radiation was administered with super-voltage equipment at a dose of:

- 4500 rads (45 Gy) in 25 fractions to both the internal mammary and supraclavicular nodes at a depth of 3cm
- 5000 rads (50 Gy) in 25 fractions to the mid-axilla
- patients with clinically positive axillary nodes received an additional boost of 1000–2000 rads (10–20 Gy).
- tangential fields were employed to treat the chest wall with a tumour dose of 5000 rads (50 Gy) in 25 treatments.

Women with clinically negative nodes who were treated by total mastectomy and subsequently had positive nodes requiring an axillary dissection were not deemed to have had a treatment failure at that time unless the nodes could not be removed completely.

### Results

No significant differences were observed among the groups with respect to disease-free survival, relapse-free survival, distant disease-free survival, or overall survival. Among women with negative nodes, the hazard ratio for death among those treated with total mastectomy and radiation compared with those undergoing radical mastectomy was 1.08 (95% CI, 0.91–1.28, p=0.38), and the hazard ratio for death among those who had total mastectomy alone compared with radical mastectomy was 1.03 (95% CI, 0.87–1.23, p=0.72). Among women with positive nodes, the hazard ratio for death among those treated with total mastectomy and radiation compared with those undergoing radical mastectomy was 1.06 (95% CI, 0.89–1.27, p=0.49).

### Conclusions

The findings validate earlier results showing no advantage from radical mastectomy. Although differences of a few percentage points cannot be excluded, the findings fail to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy.

### COMMENTARY

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 has been one of the most important and influential trials of breast cancer treatment in recent decades. The trial signalled and led to the demise of radical mastectomy as a breast cancer treatment. It also contributed to the development of a new paradigm that breast cancer is a systemic disease at the time of diagnosis and therefore local treatment has little or any impact on survival. This new paradigm has increasingly been questioned in light of other trial results published in the last decade.

NSABP B04 has also been hailed widely as a randomised trial demonstrating 'no survival benefit' for axillary dissection versus none. Accordingly, it has been a landmark in the history of surgical treatment of breast cancer.

This study commenced in 1971 and it is interesting to revisit the trial methods used at that time in light of current knowledge. In fact, the reason for the number of women in each arm of the study and the power of the study to reach the stated conclusions are not published in the current paper or in previous reports.<sup>1,2</sup>

In fact, the study had only a power of approximately 25% to show a real 5% difference in survival between each of the arms of the node-negative group (Number Crunching Statistical System software) and a lower power to show a real 5% difference in outcome for the node-positive group, with fewer than 300 women in each arm of this study. In other words, if a real 5% difference in outcome existed (which is conceivable, looking at the reported survival curves for this study), there was at least a 75% chance that with these participant numbers a statistically significant difference would not have been shown by this study. The study was also underpowered to claim equivalence of the three different treatments.

In addition, for the group allocated to 'total mastectomy alone', the procedure was somewhat more radical than current practice.<sup>1</sup> The area of tissue removed was bounded by the midline of the sternum extending superiorly to the supraclavicular space, inferiorly to the costal margin and, of particular importance, laterally along the edge of the latissimus dorsi muscle. No intervention in the axilla beyond the border of the pectoral muscle was permissible.

As a result, at least 35% of women had lower axillary nodes removed as part of the procedure of total mastectomy alone. On pathological examination, 35% of specimens contained lymph nodes. In 10% of specimens, six or more nodes were found and in 3% of specimens, 11 or more nodes were found in the operative specimen. In the 'radical mastectomy' group, a median of 15.5 nodes were removed. The difference in surgical treatment between the 'radical mastectomy' and 'total mastectomy' alone groups is therefore not as great as might be expected from the operative title.

It is well known from this study and others that radicality of local treatment (both surgery and addition of radiotherapy) does influence local recurrence rates. Despite the fact that axillary recurrence was only considered to be a locoregional event if it was unresectable (1 patient), NSABP B04 showed a significant reduction in locoregional recurrence with more radical treatment – either radical mastectomy or addition of radiotherapy. The locoregional recurrence rate was more than halved with addition of radiotherapy. In addition, 18.6% (n=68) of the women undergoing total mastectomy alone developed positive nodes requiring surgery as a first event. The total number of women developing an axillary recurrence, including those who developed this subsequent to recurrence elsewhere, is not reported. The first group of 68 women, and probably others, therefore had to undergo a second operation a median of 14.8 months after their initial surgery. The psychological, physical and financial impact of dealing with this recurrence and additional surgery must have been significant, although these are issues not normally addressed in studies from this era.

Other studies suggest that radicality of local treatment also influences survival. A meta-analysis by Jack Cuzick *et al.* of randomised trials comparing radical mastectomy against simple mastectomy and radiotherapy,<sup>3</sup> which included over 950 women in each

of the groups, found an approximate 5% difference in 10-year survival, which just reached statistical significance at the p=0.05 level.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of the influence on long-term survival of adding radiotherapy to surgery shows that addition of radiotherapy<sup>4</sup> resulted in a 68.4% reduction in isolated local recurrence and an 8.9% reduction in breast cancer deaths. This meta-analysis, which includes older studies where high doses of radiotherapy were given to the carotid and intra-thoracic areas, shows a significant increase in the risk of non-breast cancer death after 10 years for the irradiated group. A meta-analysis of trials of post-mastectomy radiotherapy in the presence of systemic treatment has shown more dramatic benefits, with a 17% reduction in mortality in favour of more radical local treatment (in this case, radiotherapy).<sup>5</sup>

Further evidence showing that local treatment can affect survival rates is available from controlled and uncontrolled studies.<sup>6,7,8,9</sup> A study by Shukla *et al.*<sup>9</sup> makes interesting reading. It is as close to a randomised trial of more radical versus less radical surgery as possible without actual randomisation. The trial demonstrated a 15% difference in survival at 11-years follow-up favouring more radical surgery. The authors make the point that studies showing little difference in locoregional recurrence rates between treatment arms show little difference in long-term survival (eg NSABP B04), whereas those showing more dramatic differences in locoregional recurrence rates show an impact on survival.

In conclusion, it is encouraging to see that NSABP B04 has demonstrated no significant difference in 25-year overall survival rates for women at relatively low risk of local recurrence receiving different local treatments for breast cancer. However, other studies indicate that local treatment can influence survival, especially for women at higher risk of local failure. NSABP B04 and other studies are consistent in demonstrating that more radical local treatment (both surgery and the addition of radiotherapy) does reduce the risk of locoregional recurrence and this is an important treatment goal in its own right. This is also an important consideration regarding sentinel node-based treatment of the axilla. NSABP B04 is commonly quoted as proof that sentinel node-based management of the axilla is likely to be safe.

Properly powered studies of sentinel node-based management compared with conventional axillary surgery are necessary to prove that locoregional recurrence rates, and indeed survival, are not affected. Publication of the next EBCTCG Overview, which will provide a further meta-analysis of randomised trials of more versus less radical surgical treatment of breast cancer, is eagerly awaited. In the meantime, while not encouraging a return to radical mastectomy, every effort should be made to minimise locoregional recurrence rates for women at higher risk of this problem, whether this is through appropriate choice of operation and meticulous surgical technique or appropriate addition of modern radiotherapy.

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# Adjuvant radiation and/or tamoxifen after surgery for DCIS

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UK Coordinating Committee on Cancer Research (UKCCCR) Ductal Carcinoma in Situ (DCIS) working party on behalf of DCIS trialists in the UK, Australia & New Zealand. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, New Zealand: randomised controlled trial. *Lancet* 2003;362:95–102.

## Objective

To test the efficacy of the addition of radiotherapy (RT) and/or tamoxifen (TAM) to breast conserving surgery in the management of localised ductal carcinoma in situ (DCIS) of the breast.

## Study design

From 1990 to 1998, 1701 women with completely excised DCIS were randomised using a 2 x 2 factorial design to receive one of the following post-operatively:

- no adjuvant treatment
- RT (50 Gy in 25 fractions, no boost)
- TAM (20mg daily for 5 years)
- RT and TAM (doses above).

Surgeons, in discussion with each woman, decided whether to enter her into the 4-way randomisation or one of the 2-way randomisations (ie RT v no adjuvant treatment or TAM v no adjuvant treatment). In the 2-way randomisation, surgeons/ women could request or refuse one of the two adjuvant treatments, before random assignment of the woman to an intervention or control group for the other adjuvant treatment.

Inclusion criteria included unilateral or bilateral localised DCIS and suitability for breast conserving surgery. In 1993, the inclusion criteria were expanded to include patients with micro-invasion (<1mm of invasion). The trial commenced in the UK; the Australian and New Zealand Breast Cancer Trials Group joined in 1991.

The trial was powered to detect a 50% reduction in ipsilateral breast recurrence with 80% power. To assess effects in the two main treatment comparisons (TAM v no adjuvant treatment and RT v no adjuvant treatment), analyses were confined to women who were randomly allocated to each main treatment. Thus treatment comparisons were not confounded by the

non-random treatments. Analyses were based upon intention-to-treat.

## Results

Data for 1694 women, 912 in the 4-way randomisation and 782 in the 2-way randomisation, were included in the analysis. The 4-way randomisation was allocated as follows: no adjuvant therapy (n=226); RT alone (n=220); TAM alone (n=224); RT plus TAM (n=242). In the 2-way randomisation, 664 women made a choice about RT (603 to not have radiation; 61 to have radiation) prior to TAM randomisation, and 118 women made a choice about TAM (29 to not have TAM; 89 to have TAM) prior to RT randomisation. Data for 1030 patients were used for the RT analysis and 1576 for the TAM analysis.

Median follow-up was 52.6 months (range 2.4–118.3 months). Micro-invasive disease (3%, n=59) was equally distributed between the groups. The rate of recurrence for women with micro-invasive disease did not differ from that in the overall group. New breast disease developed in 16% of women (n=263).

For women randomised to TAM, 11% (n=86) stopped taking the drug prior to the completion of 5 years. Post-operative TAM did not significantly reduce the overall event rate or the rate of invasive events. However, it did significantly reduce the overall rate of DCIS recurrence (7% v 11%; p=0.03), predominantly in the ipsilateral breast. Fewer contralateral breast events occurred for women randomised to TAM but numbers were small and the differences non-significant.

Post-operative RT significantly reduced the ipsilateral recurrence of DCIS (3% v 7%; p=0.0004), ipsilateral recurrence of invasive breast cancer (3% v 6%; p=0.01) or any

ipsilateral breast event (6% v 14%; p<0.0001), but had no significant effect on the contralateral recurrence rate. No differences in overall or disease-specific survival were found.

## Conclusion

RT significantly reduces the risk of recurrent DCIS or invasive breast cancer following breast conserving surgery for DCIS. There was little evidence to support the use of adjuvant TAM in these women.

## COMMENTARY

The UKCCCR trial provides further evidence to support the addition of RT to breast conserving surgery in the management of DCIS. It does not provide evidence to support the role of TAM in the reduction of ipsilateral invasive recurrence. These outcomes should be considered in conjunction with those from three prior randomised trials that assessed the role of adjuvant RT or TAM in the conservative management of DCIS. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-17<sup>1,2</sup> and the European Organization for the Research and Treatment of Cancer (EORTC) trial (10853)<sup>3</sup> examined the addition of RT to conservative surgery for DCIS. NSABP trial B-24<sup>4</sup> routinely gave post-operative RT, followed by randomisation to 5 years of adjuvant TAM therapy or no TAM. Table 1 summarises the ipsilateral recurrence rates (invasive and non-invasive) for each trial.

### Role of radiotherapy

The UKCCCR trial findings regarding RT are similar to those from other randomised trials of similar design.<sup>1-4</sup> Each trial showed an approximate halving of the DCIS and invasive cancer recurrence rate with the addition of RT, which is also consistent with two pooled analyses of all randomised and non-randomised data.<sup>5,6</sup>

**Table 1: Summary outcome data for DCIS randomised trials**

	UKCCCR	NSABP B-17 <sup>1,2</sup>	EORTC 10853 <sup>3</sup>	NSABP B-24 <sup>4</sup>
No. of patients	1694	818	1002	1804
Median follow up (mo.)	52.6	144	52	84
Ipsilateral recurrence (invasive breast cancer & DCIS):				
CLE alone (%)	22	31	17	NA
CLE + RT (%)	8	15	11	13
CLE + TAM (%)	18	NA	NA	NA
CLE + TAM + RT (%)	6	NA	NA	8
p values	♣	p<0.0001	p=0.05	p=0.009

NA = not applicable; CLE=complete local excision surgery

♣ p values in UKCCCR are for patients *randomised* to receive or not receive the relevant adjuvant treatment, and hence do not relate to the overall recurrence figures (see study design): p<0.0001 for RT v no RT; p=0.42 for TAM v no TAM.

As DCIS can be relatively slow-growing and can return as either DCIS or invasive disease many years after initial treatment, it is important that long-term follow-up data are collected. The highest recurrence rates were found in NSABP B-17, which may be due to this trial having the longest follow-up period. As the UKCCCR trial follow-up duration is less than half that of NSABP B-17, further follow-up reports will be important.

Based on trials to date, are there women with DCIS whose RT could be omitted without increasing recurrence risk? Variations in recurrence risk according to pathological parameters such as margin clearance, grade or lesion size were not assessed in the UKCCCR publication. Both the NSABP B-17 and EORTC trials reported significant reductions in ipsilateral invasive and in situ recurrence with the addition of radiation for all pathologic sub-groups including small, low-grade lesions. As with most other adjuvant therapies, benefits were greater in women with a higher risk of recurrence. It would be beneficial to define a group of women who are at such a low risk of recurrence of either invasive disease or DCIS that any gain from RT would be considered negligible and not worth the associated cost, toxicity, and inconvenience. The National Breast Cancer Centre recommendations for the management of small, low-grade DCIS<sup>7</sup> state that "Although RT offers a statistically significant benefit over conservation alone, for these women, the absolute benefit may only be small. In such cases, the small gain in local control should be weighed against the inconvenience and morbidity of RT in discussion with the woman". Boyages *et al.*<sup>5</sup> and Bijker *et al.*<sup>8</sup> have attempted to quantify the benefits of RT in women with different pathological criteria. Further statistical analysis of the UKCCCR data to assess recurrence risk by pathological sub-type will be useful and is planned.

The UKCCCR trial found no difference in overall survival with the addition of RT. This is hardly surprising as the salvage rates for patients who develop an invasive or in situ recurrence are relatively good, and large randomised trials in invasive cancer have not identified a survival benefit. A very large trial would be needed to have sufficient power to address the survival issue adequately. However, survival should not be the only endpoint. Further surgery may compromise the final cosmetic

outcome by requiring the removal of further breast tissue, and increasing the likelihood of mastectomy.

#### *Role of tamoxifen*

The UKCCCR trial failed to show any statistical advantage of post-operative TAM for lowering the risk of ipsilateral invasive recurrence (6% v 4%;  $p=0.23$ ), which contrasts with NSABP B-24 findings of a small, but statistically significant, reduction in the risk of ipsilateral invasive cancer (4.2% v 2.1%;  $p=0.004$ ).<sup>4</sup> The UKCCCR trial did show a reduction of DCIS recurrence for women randomised to receive TAM (7% vs 11%;  $p=0.03$ ).

There are several possible explanations for the difference in findings for ipsilateral invasive recurrence. It may be that the benefit of adjuvant TAM is small and that large patient numbers are required to show statistical significance (although the trials had similar patient numbers). Alternatively, it is possible that adjuvant TAM has no therapeutic benefit and the statistical significance in the first trial is a chance result. A third explanation could be the different trial designs. For example, all participants in NSABP B-24 received RT compared with 50% in the UKCCCR trial; and participants in the UKCCCR trial were older than those in NSABP B-24. A fourth possibility, which is the subject of current trials, is that TAM is effective for receptor-positive disease only, but this was not assessed in the UKCCCR trial. Based on current conflicting evidence, the routine use of TAM to lower local recurrence cannot be recommended. Future studies focusing on other endocrine agents, such as aromatase inhibitors, may find an agent with clear clinical benefit.

#### *Treatment decisions*

An interesting finding of the UKCCCR trial was the choices made by the surgeons and/or women when deciding between the 2-way and 4-way randomisation processes. Of all women recruited, 36% ( $n=603$ ) elected to not have RT, while only 2% ( $n=29$ ) elected not to receive TAM. These data suggest a bias against the use of RT at the time of the trial. Perhaps the surgeons or women felt that the potential advantages of RT were not sufficiently compelling to warrant having RT or at least agreeing to randomisation. However, data from the NSABP and EORTC trials, which included a review of pathological status, were not available at the time the UKCCCR trial commenced. Future analyses of pathologic

parameters may indicate that the women who chose not to receive RT were more likely to have low-grade lesions. The fact that so many patients elected not to have RT may also be related to difficulties in accessing RT services or direct access to RT consultation, particularly for women in rural areas. An analysis of these choices would prove very interesting.

#### *Conclusion*

The UKCCCR trial findings were very similar to those of three preceding trials, indicating that RT should be considered for all women with complete excision of localised DCIS. Whether patients with smaller lower grade lesions can avoid RT has not been adequately addressed in this trial. The role of TAM remains uncertain because of the conflicting results of this trial compared with earlier trials; at the present time TAM is not recommended.

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