Overview

When May Adjuvant Radiotherapy be Avoided in Operable Breast Cancer?

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ABSTRACT:
Randomised trials in which the omission of radiotherapy has been tested after breast-conserving surgery, with or without adjuvant systemic therapy, show a significant four- to five-fold reduction in local recurrence. As yet, no subgroup of women managed by breast-conserving surgery has been identified from whom radiotherapy can be withheld. Few randomised data have been published on the effect of omission of radiotherapy on local control, quality of life and costs, particularly in older women for whom the risk of local recurrence is generally lower. Ongoing trials are evaluating the role of radiotherapy in this population of low risk, older women. Adjuvant radiotherapy after breast-conserving surgery or mastectomy significantly reduces the incidence of local recurrence. In women who have had a mastectomy at high risk of recurrence (> 20% risk of recurrence at 10 years), adjuvant radiotherapy improves survival if combined with adjuvant systemic therapy. Among women with T3 tumours, and those with four or more involved axillary nodes treated by mastectomy, postoperative radiotherapy is the standard of care. For women at intermediate risk of recurrence (i.e. < 15% 10-year risk of recurrence after surgery and systemic therapy alone), with one to three involved nodes or node negative with other risk factors, the role of radiotherapy is unclear. Clinical trials to assess the role of postmastectomy radiotherapy (PMRT) in this setting are needed. For pT1—2, pN0 tumours without other risk factors, there is no evidence at present that PMRT is needed. Kunkler, I. H. et al. (2006). Clinical Oncology 18, 191—199 © 2005 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Introduction

The identification of women who can safely avoid postoperative adjuvant radiotherapy for operable (T0—3, N0, N1, M0) breast cancer is an important topic of current debate for women undergoing breast-conserving surgery and mastectomy. It is particularly relevant in the context of a shift in thinking about breast cancer as a systemic disease to a heterogeneous disease [1,2]. In this new model, there is evidence that locoregional radiotherapy, at least after mastectomy, in women at ‘high risk’ may confer long-term survival advantage over systemic therapy alone [3—7].

The Scottish Executive predicts a 40% rise in the number of cases of breast cancer by 2014 [8]. Around 50% of the cases are women over 65 years. It is estimated in the USA that, of 175 000 new cases of breast cancer each year, more than 80 000 will be diagnosed in women aged 65 years or older [9]. Over the past two decades, the proportion of women offered breast-conserving surgery has progressively increased, and therefore the number of women eligible for postoperative radiotherapy has increased. Data from the Geneva cancer registry (Registre genevois des tumors unpublished data, 2000) show that the proportion of women receiving breast-conserving surgery has risen from 3% before 1985, to 51% in 1990 and to 67% since 1998. This places increasing pressure on limited radiotherapy resources internationally. Within limited radiotherapy resources, there is a strong rationale for identifying women in whom the benefits of radiotherapy are too low to justify postoperative radiotherapy. We also know that receipt of breast radiotherapy varies widely in older women [10]. However, at present postoperative breast radiotherapy is advocated as standard treatment, after breast-conserving therapy, irrespective of age [11].

Clinicians are rightly concerned that women with breast cancer should not miss out on the benefits of radiotherapy for locoregional control and survival. High-quality evidence is, therefore, needed to underpin the omission of radiotherapy in particular subsets of patients. In this paper, we discuss whether there are subsets of patients from whom adjuvant radiotherapy can be safely omitted.

One of the most important criteria for determining whether postoperative radiotherapy can be safely omitted is whether the difference in risk of local recurrence is sufficiently small to justify the omission. For breast-conserving surgery and adjuvant endocrine therapy alone, this might be a difference of 5% or less [12]. If we examine the published randomised trials of breast-conserving surgery with or without radiotherapy (Table 1), all of them show a reduction in local recurrence with addition of...
Table 1 – Randomised-controlled trials of the omission of radiotherapy after breast-conserving surgery and endocrine therapy

<table>
<thead>
<tr>
<th>Author/group</th>
<th>Trial period</th>
<th>Number of participants</th>
<th>Tumour size (cm)</th>
<th>% Node positive</th>
<th>Surgery</th>
<th>Margins</th>
<th>Systemic therapy</th>
<th>Follow-up</th>
<th>Local recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al. NSABP B-06 [26]</td>
<td>1976–1984</td>
<td>1137</td>
<td>≤ 4</td>
<td>35.4</td>
<td>Segmental mastectomy</td>
<td>Tumour-free margins</td>
<td>N1 only</td>
<td>5-year life-table results</td>
<td>27.9</td>
</tr>
<tr>
<td>Liljegren et al. Uppsala-Orebro [57]</td>
<td>1981–1988</td>
<td>381</td>
<td>≤ 2</td>
<td>None</td>
<td>Sector resection</td>
<td>Complete excision</td>
<td>None given</td>
<td>5-year life-table results</td>
<td>23.5 (N0)</td>
</tr>
<tr>
<td>Veronesi et al. Milan III [27]</td>
<td>1987–1989</td>
<td>567</td>
<td>≤ 2.5</td>
<td>30.3</td>
<td>Quadrantectomy</td>
<td>Complete excision</td>
<td>N1 postmenopausal received tamoxifen</td>
<td>None given</td>
<td>39 months median follow-up</td>
</tr>
<tr>
<td>Forrest et al. Scottish CTBG [18]</td>
<td>1985–1991</td>
<td>585</td>
<td>≤ 4</td>
<td>22.9</td>
<td>Wide local excision</td>
<td>1 cm margin</td>
<td>All, appropriate to oestrogen-receptor status</td>
<td>5.7 years median follow-up</td>
<td>24.5</td>
</tr>
<tr>
<td>Hughes et al. CALGB [30]</td>
<td>1994–1999</td>
<td>636</td>
<td>≤ 4*</td>
<td>None</td>
<td>Lumpectomy</td>
<td>Complete excision</td>
<td>Tamoxifen for 5 years</td>
<td>5 years median follow-up</td>
<td>4.0</td>
</tr>
<tr>
<td>Fyles et al. Canadian [32]</td>
<td>1992–2000</td>
<td>769</td>
<td>≤ 5</td>
<td>None</td>
<td>Breast-conserving surgery</td>
<td>Complete excision</td>
<td>Tamoxifen for 5 years</td>
<td>5.6 years median follow-up</td>
<td>7.7</td>
</tr>
</tbody>
</table>

*Reduced to 2 cm or less (August 1996); †Axillary node dissection allowed but discouraged; N0 status clinical only; ‡Nodal status (17.3%) determined clinically.
radiotherapy, although the absolute benefit falls as the risk of recurrence after surgery and adjuvant systemic therapy alone also falls. Three of the trials (Table 2) show a reduction in risk of local recurrence with age; one trial has a P value of 0.06, and two show a trend, although they are not statistically significant. Recent attention has focused on obtaining clear excision margins. This may further reduce the risks of local recurrence in contemporary practice.

In individual women, consideration needs to be given to the risks of radiation-induced injury to critical organs, particularly the heart, lung, ribs [13] and brachial plexus. Caution is particularly needed in women with left-sided tumours and established cardiac disease, and in patients with compromised lung function. Similar difficulties are presented to the clinician in women with comorbidities, which might make radiotherapy demanding or burdensome for the patient. At present, some indices of comorbidity exist, which have been reviewed by Extermann [14]. These correlate to increased non-breast cancer mortality. However, Extermann [14] concluded that further work needs to be carried out before a comprehensive index can be produced. Currently, the process of assessment remains subjective and prone to inconsistency between clinicians.

The most firmly based source of data on the effect of adjuvant radiotherapy is the Early Breast Cancer Trialists’ Collaborative Group [15]. Its overview of randomised trials of radiotherapy shows that adjuvant radiotherapy reduces the annual odds of local recurrence three-fold. It shows a clear correlation between a reduction in locoregional failure and reduced breast cancer mortality. A 20% reduction in locoregional recurrence was associated with a 5% absolute increase in survival. However, the reduction in breast cancer mortality was balanced by an equivalent increase in mortality due to causes other than breast cancer, mainly cardiovascular. These observations set a context for identifying women who will not miss out on a benefit in locoregional control or survival, and might be spared the morbidity of radiotherapy.

Differing Natural History of Recurrence after Breast-conserving Surgery and Mastectomy

The natural history of local recurrence after breast-conserving surgery differs from local recurrence after mastectomy. In general, local recurrence can be successfully managed by mastectomy in women initially treated by breast-conserving surgery.

In some studies, in which breast radiotherapy has been omitted, distant metastases were significantly or nearly significantly more common [16–18]. As Sauer et al. [19] have argued, this could, to some extent, be explained by detection bias due to earlier restaging for women who experience a local recurrence. Kurtz [10], in the same paper, makes the point that even if ipsilateral breast-tumour recurrence is a bad prognostic factor and can in some circumstances give rise to dissemination [20], the overview of radiotherapy trials does not show a significant advantage from preventing ipsilateral breast-tumour recurrence by mastectomy or by radiotherapy.

Breast-conserving Surgery with or without Postoperative Radiotherapy: Interpreting the Randomised Trials

Postoperative breast radiotherapy is advocated as standard treatment after breast-conserving surgery, irrespective of age [11]. This is based on a number of randomised and non-randomised trials. Randomised trials that have shown higher rates of local recurrence after breast-conserving surgery, with or without systemic therapy, are shown in Table 1. These trials have compared breast-conserving surgery with or without breast irradiation. The trials are heterogeneous in terms of extent of local surgery, nodal status, use of adjuvant systemic therapy and margin status.

To date, none of the randomised trials (Table 1), in which breast radiotherapy has been omitted, show a decrease in overall survival in the group not receiving radiotherapy. However, the recent pooled analysis [21] of risks of ipsilateral breast-tumour recurrence, comparing 9422 women in published randomised trials of breast irradiation with no breast irradiation, did show a small increase in the risk of mortality from the omission of radiotherapy. The reasons for the discordance between the pooled analysis and the results of individual trials are not clear. It could reflect the effect on survival of a larger number of higher risk women with node-positive tumours, which individual trials were not powered to detect. Some of these trials contained a mixture of women with node-positive and node-negative tumours.

The NSABP B-06 [16] trial included women with tumours 4 cm or over, with or without involved axillary nodes. Women were randomised either to mastectomy or segmental mastectomy, without or without adjuvant postmastectomy radiotherapy (PMRT). It showed a 27.9% recurrence rate in the group receiving conservative surgery alone (segmental mastectomy) compared with 7.7% at 5 years in the group undergoing surgery plus radiotherapy. Negative margins were defined as the absence of tumour cells touching the edge of the surgical specimen. No difference in recurrence above or below the age of 50 years was observed, although the upper age limit of eligibility for the trial is not stated.

By contemporary standards, the definition of negative margins used in the NSABP B-06 trial might be considered suboptimal. In part, this might have accounted for the substantial local recurrence rate in the group undergoing surgery alone. Indeed, although the protocol required tumour-free margins, 10.6% of the segmental mastectomy group and 9.4% of the segmental mastectomy plus radiotherapy group had positive margins [22] when examined at a later date. Women with node-negative tumours did not receive tamoxifen. If given, it may have reduced the local recurrence rate in both arms of the trial.

In the Swedish Uppsala-Orebro Breast Cancer Study Group trial [23], women were included with axillary node-negative
Table 2 – Variation in local recurrence rates by age

<table>
<thead>
<tr>
<th>Author/group</th>
<th>Age range</th>
<th>Number of participants</th>
<th>Age division*</th>
<th>Locoregional recurrence below age division (%)</th>
<th>Locoregional recurrence above age division (%)</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al.</td>
<td>Not given</td>
<td>1137</td>
<td>50</td>
<td>9.1</td>
<td>29.4</td>
<td>6.5</td>
</tr>
<tr>
<td>NSABP B-06 [26]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Liljegren et al.</td>
<td>≤ 80</td>
<td>381</td>
<td></td>
<td>3% decreasing risk per year of age</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Uppsala-Orebro [57]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veronesi et al.</td>
<td>Not given</td>
<td>567</td>
<td>55</td>
<td>12 (separate data not given)</td>
<td>3.8 (separate data not given)</td>
<td>Yes</td>
</tr>
<tr>
<td>Milan III [27]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clark et al.</td>
<td>Not given</td>
<td>837</td>
<td>50</td>
<td>35</td>
<td>13.5</td>
<td>25.7</td>
</tr>
<tr>
<td>Ontario [25]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Forrest et al.</td>
<td>28–70</td>
<td>585</td>
<td>60</td>
<td>8.0, 8.7</td>
<td>31.6, 29.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Scottish STBG [18]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hughes et al.</td>
<td>≥ 70</td>
<td>636</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CALGB [30]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fyles et al.</td>
<td>≥ 50</td>
<td>769</td>
<td>60, 70</td>
<td>6.0, 3.8</td>
<td>3.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Canadian [32]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*The age at which patients are split into 'young' (below the age division) compared with 'old' (above the age division); | At 5 years; | This is a low-risk group, defined as 50 years of age or older with tumours 2 cm or less. It is compared with all other cancers (i.e. the group 50 years or older with tumours 2 cm or less has a locoregional recurrence of 13.5%), whereas 'all other groups' (<50, tumours >2 cm) have a locoregional recurrence of 35%; | Age groups less than 50 years and 50–59 years; | Age groups 50–59 and 60–69 years.
tumours 2 cm or less. The local recurrence rate was 18.4% in the surgery alone arm (sector resection) and 2.3% in the surgery plus radiotherapy arm at a median follow-up of 64 months [24]. The trial recruited women up to the age of 80 years with node-negative, small tumours (<2 cm). Adjuvant systemic therapy was not given. At 10 years’ follow-up, the local recurrence rate in the group not receiving radiotherapy was 24% and 8.5% in the group receiving radiotherapy. Subgroup analysis showed that women older than 55 years, without comedo or lobular carcinoma, had a low risk of local recurrence (11%) in the group not receiving radiotherapy compared with 6.1% for women receiving radiotherapy. It is possible that the addition of tamoxifen might have improved local control.

In the Ontario trial [25], women with node-negative tumours 4 cm or less were treated by lumpectomy without systemic therapy. The local recurrence rate was 25.7% in the group not receiving radiotherapy compared with 5.5% in the group receiving radiotherapy. Median follow-up was 43 months. A subsequent publication [17], with a median follow-up of 7.6 years, reported an 11% relapse in the group receiving radiotherapy compared with 35% in the group not receiving radiotherapy. Age was an independent risk factor for local recurrence, and was higher in women under 50 years compared with women over 50 years. The investigators were unable to define a low-risk group with less than 10% risk of local recurrence. Again, as in the Swedish [23] and NSABP B-06 [26] trials, local control rates are likely to have been improved by systemic therapy.

Women in the Milan III trial [27] had tumours less than 2.5 cm, with or without involved axillary nodes. These women underwent more extensive surgery (quadrantectomy) than the NSABP or Swedish trials. This may explain the lower local recurrence rates in both the groups not receiving radiotherapy (8.8%) and the groups receiving radiotherapy (0.3%). A significantly lower rate of local recurrence was found in women aged 55 years and older; 3.8% compared with 8.8% for the trial population as a whole. However, the median follow-up was relatively short (39 months). Local recurrence is likely to be cumulative.

In the Scottish conservation trial [18], eligible women up to the age of 70 years had axillary node-positive or node-negative tumours up to 4 cm. Systemic therapy was given appropriate to oestrogen-receptor status. The ipsilateral breast recurrence rate (median follow-up of 5.7 years) was 5.8% in the group receiving radiotherapy compared with 24.5% in the group not receiving radiotherapy. No differences in recurrence rates by age cohort were observed. Recurrence rates in the group not receiving radiotherapy were substantial (31.6%, 29.5%, and 25.7% for women aged less than 50 years, 50–59 years and 60–70 years, respectively) compared with the groups receiving radiotherapy (8.0%, 8.7% and 2.7%, respectively). A slight trend was observed towards a lower recurrence rate with age, particularly between women aged 60–70 years compared with women under 60 years in the group receiving radiotherapy. However, no statistical analysis of recurrence rates by age in women at low risk was presented. Recurrence rates were still high in women with node-negative tumours not receiving radiotherapy (21.2%) compared with women receiving radiotherapy (4.3%). Although the Scottish trial does not show a substantially reduced risk of local recurrence below the age of 70 years, it does not provide any data on women over the age of 70 years.

All the trials mentioned above have identified an increased risk of recurrence in younger women, but without a clear age threshold. For young women, therefore, breast irradiation should not be omitted. As age increases, the risks of local recurrence fall. This probably reflects a more benign biology than an effect of age per se. Of the published trials, in only two [27,28] and the Swedish trial [24] was the local recurrence rate so low that radiotherapy might have been omitted. In the Milan III trial, the local recurrence rate for women over the age of 55 years was 3.8% and, in the Swedish trial [24], women over the age of 60 years without comedo or lobular cancer had a relatively low risk of 5.9% after 5 years [24].

Breast-conserving Surgery: Defining Low-risk Subgroups

Low-risk groups in whom radiotherapy might be omitted have yet to be identified. Proposed criteria include age 60 years or older, negative margins, hormone-receptor positivity, small size, low grade, negative axillary node status, absence of multifocality, lobular features or lymphovascular invasion or extensive intraductal component [29]. A dearth of trials provide data on the effect of the omission of radiotherapy in older women treated by breast-conserving surgery and adjuvant endocrine therapy. Only 600 of the 19582 women included in the Oxford Overview [15] were over the age of 70 years.

The CALGB trial [30] is highly relevant to this discussion, as it was confined to women over 70 years with T1, N0, oestrogen-receptor positive, clinically node-negative breast cancer treated by lumpectomy and adjuvant tamoxifen (median follow-up 5 years). The principal question posed was whether radiotherapy significantly adds to the benefits of tamoxifen in older women with small oestrogen-positive breast tumours. The results showed a 1% ipsilateral breast recurrence rate in the group receiving postoperative breast irradiation and 4% in the group not receiving radiotherapy. More than 55% of women were over the age of 75 years. However, the mastectomy rates after local recurrence were similar in both groups [31]. Breast conservation was maintained in 99% of women treated with radiotherapy and tamoxifen and 98% who received tamoxifen alone. It could be argued that it would be more cost effective to carry out a second lumpectomy in the 14 women in the group not receiving radiotherapy who developed local recurrence rather than treat the whole cohort of 317 with radiotherapy. A limitation to this study is the absence of pathological confirmation of axillary node status. The trial may, therefore, have inadvertently included some women who were with clinically N0 but had pathologically axillary node-positive tumours. The possible inclusion of these higher risk women could have contributed to more local
recurrences than would be expected in women with pathologically axillary node-negative tumours. Their findings are limited to T1, N0 tumours (2 cm or less).

In a Canadian trial [32] of women 50 years or older treated by lumpectomy and adjuvant tamoxifen with or without radiotherapy for T1 or T2 node-negative breast cancer (median follow-up 5.6 years), the ipsilateral breast recurrence rate was 7.7% in the tamoxifen group and 0.6% in the tamoxifen plus radiotherapy group. In women 60 years and older, no significant difference was found in local recurrence (1.2% in the tamoxifen group compared with 0% in the tamoxifen plus radiotherapy group; \( P = 0.16 \)). However, the number of events in this subgroup was small, and the lack of benefit of irradiation may be due to the low power of the study to detect a treatment effect.

The BASO trial [33] of women under the age of 70 years with grade I cancers or those of special type shows an annual recurrence rate of 0.44% in the group undergoing breast-conserving surgery and receiving tamoxifen at a median follow-up of 54 months.

Ongoing Trials Assessing the Omission of Postoperative Radiotherapy after Breast-conserving Surgery

A number of ongoing trials are attempting to identify subgroups of women managed by breast-conserving surgery in whom breast-conserving surgery might be omitted. The international PRIME trial [34] is recruiting women with pT1–2 (\( \leq 3 \) cm) tumours with negative axillary nodes and positive hormone-receptor status after breast-conserving surgery with clear margins and adjuvant or neoadjuvant endocrine therapy. The primary end point is ipsilateral breast-tumour recurrence. Target accrual is 1000 patients.

The radiotherapy 55–75, an Italian multicentre trial [35], is currently addressing the role of breast-conserving surgery with or without breast radiotherapy in women aged 55–75 years with early breast cancer.

In summary, clinical trials to date have not identified a subset of women for whom postoperative radiotherapy is not needed after breast-conserving surgery.

Mastectomy with or without Postoperative Radiotherapy: Interpreting the Randomised Trials

For women treated by mastectomy, the effect of PMRT on survival as well as locoregional control must be considered. The St Gallen consensus statement on PMRT [36] suggests a threshold of a 20% risk of locoregional recurrence at 10 years. Women with four or more involved nodes or T3 tumours meet this criterion. However, it may be that women with fewer (<4 nodes) and smaller tumours may have greater gains in survival [37]. This hypothesis is supported by a recent retrospective analysis of three EORTC adjuvant breast cancer trials [38]. It shows that women with one to three positive nodes survived longer (RR 0.48, 99% CI 0.31–0.75; \( P \leq 0.001 \)). These results should be interpreted with caution, as the analysis is retrospective.

In addition, with the evidence of a long-term survival benefit from the addition of locoregional radiotherapy to systemic therapy after mastectomy [3–7], PMRT has been established as the standard of care for women with T3 tumours and four or more involved axillary nodes [36–39].

After mastectomy, local recurrence has a much graver prognosis, and is often the harbinger of distant metastatic disease. The recent 20-year update of a Canadian trial [5] assessing the role of postmastectomy radiotherapy after systemic therapy in premenopausal women with node-positive breast tumours, showed that, of the 39 women with isolated locoregional recurrence, 37 developed a systemic recurrence and died of breast cancer, despite salvage therapy at the time of locoregional relapse [5].

Although postmastectomy radiotherapy has become the standard of care for women with T3 tumours or with four or more involved axillary nodes [40,41], there is no strong evidence base underpinning its use in women with smaller tumours or fewer nodes involved (i.e. <20% risk of locoregional recurrence). The large Danish trial [3] showed an 8% survival benefit at 10 years (62% vs 54%) in women with one to three involved nodes. However, the generalisability of these findings is questionable, as the surgical management of the axilla was considered suboptimal for two reasons. First, an average of only seven nodes were removed from the axilla. A contemporary standard would be at least 10 nodes in an axillary clearance. The locoregional recurrence rate in the group not receiving radiotherapy was in excess of 30%, and was much higher than in other series. The relative survival advantage of the group receiving radiotherapy compared with the group that did not may, therefore, have been overestimated. In the British Columbia trial too, the locoregional failure rate (10-year actuarial rate 16% and 15-year actuarial 33%) was higher than in other series, with at least 5 years’ follow-up with one to three positive nodes (6–13%) reported by other investigators [41–43].

The recent update of the 20-year follow-up of the Canadian trial [5] of high-risk premenopausal women with node-positive tumours shows a 7% gain in overall survival in the group of women with one to three involved nodes (57% vs 50%) treated by radiotherapy in addition to systemic therapy. This compares with a 14% gain in overall survival in the group with four or more involved nodes (31% vs 17%). However, as Whelan and Levine [44] point out in their accompanying editorial, that the highest level of evidence from randomised trials should underpin practice and, at present, for the one to three node-positive group, this is restricted to subgroup analysis.

Mastectomy: International Variations on Clinical Practice

A survey of attitudes of US and European oncologists to different risk factors for local recurrence after mastectomy showed a high degree of consensus for the women at high risk with four or more involved nodes [45]. It showed much
less certainty for women at intermediate risk with one to three involved nodes. Only 36.1% of European radiation oncologists and 40.7% of US radiation oncologists would give radiotherapy to women with one to three involved nodes. These findings reflect the weaker evidence base for irradiation in this subgroup of women, and the need for more definitive data from randomised trials specifically looking at this subgroup.

Mastectomy: Defining Low-risk Subgroups

Data on the risk of locoregional recurrence in different patient subgroups are often limited and conflicting. Recht et al. [42] showed that, from the ECOG trial data on 2016 assessable patients with a median follow-up of 12.1 years for disease-free survivors, the cumulative 10-year incidence of locoregional recurrence (including simultaneous distant recurrence) was 13% for women with one to three positive nodes and 29% for those with four or more positive nodes. These figures are lower than the Danish and British Columbia premenopausal trials, which showed locoregional recurrences of 30% and 33% for one to three nodes and locoregional recurrences of 42% and 46% for four or more positive nodes, respectively.

In women with node-negative breast cancer, the results of postmastectomy radiotherapy are conflicting. No survival advantage was found in this subgroup in the Danish randomised trials [7] or in the combined analysis of the EORTC trials [38]. However, a recent retrospective comparison of women treated by postoperative radiotherapy after mastectomy showed a 2.5–6.9% overall survival benefit compared with a similar population of women from the US SEER database treated without postmastectomy radiotherapy [46]. The authors acknowledge the limitations of a retrospective comparison, and recommend a randomised trial of adjuvant radiotherapy in women with node-negative breast cancer who have undergone a mastectomy. At present, too little information is available to determine whether there are subgroups of women with node-negative breast tumours with, for example, grade 3 histology, large tumours (but smaller than T3) with or without lymphovascular invasion who would benefit from PMRT in terms of locoregional control or overall survival. The UK Medical Research Council phase III SUPREMO trial will investigate this [47].

Using Pathological Factors to Identify Women Requiring or not Requiring Postmastectomy Radiotherapy

Some investigators have attempted to use combinations of prognostic factors to define subgroups with more specific risks of locoregional recurrence than single factors alone. Risk of recurrence is known to be cumulative with increasing number of risk factors [11]. As Recht et al. [42] point out, information on such combinations is limited [48–50]. Prognostic factors, such as vascular or lymphatic invasion [42,51,52], tumour grade [53] and extracapsular nodal extension [51] increase the risk of recurrence. In the absence of randomised trials stratified for these pathological factors, clinicians in practice often define a given number of risk factors as the threshold for advising PMRT. For example, this might be the presence of two or more of the following pathological factors: large tumour size (<5 cm), grade 3 histology, lymphovascular invasion, women with node-positive tumours with one to three involved nodes or large tumour size (<5 cm), grade 3 histology and lymphovascular invasion for women with node-negative tumours. In the absence of level 1 evidence to underpin this process of selection of women with intermediate risk of breast cancer for PMRT, this seems a reasonable approach for the interim. In future, a molecular signature for radiation sensitivity may be detectable, which may provide a better basis for selecting treatments for patients.

Influence of Endocrine Therapy on Local Control

More recent trials (ATAC [arimidex, tamoxifen alone or in combination]) have shown that adjuvant anastrazole after mastectomy reduces the risk of recurrence compared with tamoxifen, although there is no difference in survival [54]. A new generation of more potent aromatase inhibitors, such as anastrazole, exemestane and letrozole have shown improvements in disease-free survival and, in some cases, overall survival when given instead of or sequentially after 2–3 years of tamoxifen. It may be that local recurrence rates may be reduced further by aromatase inhibitors. However, this will have to be confirmed in randomised trials.

Cost Effectiveness: A Criterion for Omitting Postoperative Radiotherapy

Good data are available that show that postoperative radiotherapy after breast-conserving therapy is cost effective [55]. Hayman et al. [55] showed that the incremental cost-effectiveness ratio in this setting was $28 000/QALY. This was well below the $50 000/QALY, a commonly quoted threshold for cost-effective care. However, no specific information on the cost effectiveness of adjuvant radiotherapy is available in women at low risk of relapse. In these women, the incremental cost-effectiveness ratio is likely to be less favourable. Caution needs to be exercised in the translation of findings from a predominantly insurance-based system in the USA to the UK tax-funded NHS. In practice, clinicians are primarily likely to be influenced in their decision making on adjuvant radiotherapy by the effect on local control and survival of the omission of radiotherapy, although they may take resource considerations into account.

Conclusions

Great care needs to be exercised in the omission of radiotherapy after mastectomy and breast-conserving surgery, as there is some evidence to suggest that local
recurrence may increase the risk of distant metastases and death [56]. Whether these events are cause and effect or whether some tumours have a propensity to local recurrence and distant metastases remains controversial. It may be that there are distinct molecular signatures for these different patterns of recurrence, but they have yet to be identified.

At present, data are insufficient to identify any subset of women from whom postoperative radiotherapy after breast-conserving surgery can be omitted. More data from randomised trials are needed in older women with good prognostic factors. For women with fewer than four involved axillary nodes, smaller tumours (<5 cm), or women with node-negative breast cancer, reliable data are insufficient to underpin routine postmastectomy radiotherapy. Clinical trials to evaluate the risks and benefits of PMRT in these subgroups of women using contemporary systemic therapy and three-dimensional radiotherapy treatment planning are needed.

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