Eur J Cancer, Vol. 26, No. 6, pp. 653–655, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00
© 1990 Pergamon Press plc

Comments and Critique

Breast Conservation and Management of Early Breast Cancer

THE long-term results (p. 668) of the first Milan breast conservation trial (1973–1980) are welcome and reassuring. No differences in disease-free or overall survival were seen in 701 women with a tumour diameter under 2 cm at frozen section randomised to mastectomy or quadrantectomy plus breast radiotherapy (QUART). Since this trial was first reported in 1981, the National Surgical Adjuvant Breast Protocol (NSABP) has confirmed equivalent overall survival with mastectomy or breast conservation techniques in women with tumours of 4 cm or less in clinical diameter [1, 2].

Professor Veronesi and his colleagues detected no increased risk of contralateral breast cancer 16 years from the start of the trial in women treated by QUART. This finding is consistent with other long-term results of randomised trials reporting no significant excess of contralateral breast cancer in women randomised to postoperative radiotherapy after mastectomy [3, 4]. There is no mention of imbalance in the numbers of women dying from ischaemic heart disease or other second malignancies between the two arms of the Milan trial, whereas an excess of both has been reported in patients randomised to chest wall and lymphatic radiotherapy after mastectomy [5–7]. Part of the explanation probably lies in the fact that most women in the Milan trial (87%) avoided lymphatic radiotherapy. Glancing tangential fields to the breast alone are associated with low radiation doses to the heart and much less scattered dose to other parts of the body, compared with lymphatic fields encompassing the internal mammary chain and supraclavicular fossa.

One other point relating to lymphatic irradiation is illustrated by the outcome of axillary positive patients (26%) randomised to parasternal and supraclavicular radiotherapy or a watch policy. No difference in survival was seen between these treatment policies, in common with large randomised trials testing the survival advantage of postoperative lymphatic radiotherapy after mastectomy [6, 7]. Despite lingering doubts held by some radiotherapists about inner quadrant primaries, there is no identifiable subgroup of patients whose overall survival is improved by lymphatic radiotherapy [8, 9]. Criteria for prophylactic lymphatic radiotherapy are therefore concerned with reducing the morbidity of uncontrolled regional relapse rather than improving overall survival.

The early analysis (p. 671) of the second Milan breast conservation trial (1985–1987) suggests that this study is likely to clarify the surgical contribution to local control after limited surgery. In 705 women with a tumour diameter under 2.5 cm at frozen section, this study compared a 2–3 cm excision margin with overlying skin and underlying fascia plus breast radiotherapy (QUART) with a tumorectomy including a 1 cm margin around the tumour and a thin ellipse of overlying skin plus whole breast radiotherapy (TART). The early data suggest that surgical margins beyond the tumour edge are important determinants of local control. In the QUART group, 4 patients have developed tumour in the treated breast so far compared with 27 in the group treated by TART, a statistically significant difference.

Professor Veronesi and his colleagues distinguished local recurrence (defined as arising within 3 cm of a QUART scar and within 5 cm of a TART scar) and new primary tumours that arise further afield. All but 4 of the 31 ipsilateral relapses were defined as local recurrences by these criteria. This pattern of breast relapse, with the majority occurring in the vicinity of the original breast lump, is well described [10–12]. Professor Veronesi's group concluded that the early imbalance between treatment arms justified the use of QUART to reduce the psychological distress of breast recurrence despite inferior cosmesis with this approach. The inferences drawn by the Milan group can be questioned if the iridium implant boost was difficult to place accurately into the tumour bed at the end of whole breast radiotherapy. In this case, the imbalance in local recurrences might be explained by inadequate boost dose in women treated by TART, and less need for a radiation boost in women treated by QUART.

Both trials from Milan highlight the contrast in predictive factors of local relapse following breast conservation compared with mastectomy. For example, tumour size does not correlate with increased risk of local recurrence after tumour excision and breast radiotherapy, a finding that is confirmed in several large retrospective studies [13–15]. In addition, isolated breast relapse is not a poor prognostic sign, unlike chest wall relapse after mastectomy, even with follow-up extending over 20 years [10, 11]. These observations suggest that the pathogenesis of breast relapse after local excision and radiotherapy is distinct from that of chest wall relapse after mastectomy. The proximity of most breast relapses to the site of original tumour coupled with favourable prognosis suggests that most relapses in the breast arise from remnants of the primary tumour, at least in the first 10 years after treatment. With longer follow-up, the proportion of breast relapses occurring in other quadrants rises, suggesting that these may be independent new primaries. This hypothesis is difficult to test at present.

If local recurrence usually arises from remnants of the primary tumour, how are these missed at operation? The explanation seems to lie in our underestimation of spread by permeation of the breast duct system. Several years ago, Schnitt *et al.* [15] reported that an extensive intraduct component (EIC), defined in terms of the relative area of a histological tumour section

occupied by intraduct disease, correlated strongly with breast relapse after local excision and breast radiotherapy. The same workers have now shown that patients with EIC in their invasive cancers are twice as likely to have bulky residual, predominantly intraduct, disease in the tumour bed at re-excision, compared with scant foci of infiltrating and/or intraduct carcinoma in patients without EIC [16].

The findings of a detailed examination of 264 mastectomies from women presenting with discrete breast primaries up to 4 cm in clinical diameter are entirely consistent with the findings of Schmitt *et al.* This study described foci of intraduct and/or invasive cancer over 2 cm beyond the macroscopic tumour edge in 36% of women, regardless of tumour size or node status [17]. In half of these women (18% of the total) disease extended more than 4 cm beyond the tumour edge, but it is impossible to know if these lesions represent distant foci derived from the primary tumour or new primary tumours. The probability of disease beyond the edge of the primary tumour was correlated with EIC, an important observation that ties in with the data of Holland and his colleagues [18].

Not all studies have confirmed the association between EIC and a high rate of relapse after breast conservation, but the explanations for these differences may lie in wider margins of excision and/or higher total irradiation boost doses [19]. The second Milan trial data are likely to clear up these uncertainties in time. In the meantime, patients with EIC in their primary invasive cancers should at least be considered for re-excision of the tumour bed before proceeding with high dose radiotherapy if the original macroscopic margins are less than 1 cm at any surface. As Schnitt *et al.* point out [16], the extent of intraduct permeation often cannot be grossly appreciated at the time of surgical excision because a palpable scirrhous component is often lacking.

A third report in this issue (p. 674) addresses the significance of another variable in the treatment of early stage breast cancer by conservative techniques, namely total radiation dose. Dr. Van Limbergen and colleagues reviewed the long-term results of radiotherapy without tumour excision in 221 women with $T_{1-3}N_{0-1}M_0$ breast cancer. Radiotherapy is no longer considered a useful alternative to tumour excision and radiotherapy in most women because the high radiation doses required offset the cosmetic advantages of leaving the primary *in situ*. Although the European Curietherapie Group have reported local control data on 4896 women irradiated with T_{1-3} tumours *in situ*, only Arriagada *et al.* have previously analysed in detail the radiation dose–control relations on such a large group of women [14, 20]

The Leuven study confirmed Arriagada's dose–response data in that the slope of the dose–response curve for the eradication of T_{1-3} tumours irradiated *in situ* was such that the relative risk of local recurrence was halved by a fractionated 15 Gy increase in total dose above 60 Gy. In other words, the absolute risk of local recurrence was reduced by 15% by increasing the total dose from 60 to 75 Gy in 2 Gy fractions.

The wide range of radiation dose schedules used at Leuven between 1967 and 1984 reflect changing fashions over the period rather than selection based on prognostic factors. Nevertheless, one can never rule out selection bias from a non-randomised study, and this reservation extends to the discussion of breaks in treatment and their impact on local control. In particular, 18 out of 21 patients had breaks in their treatment of 75 days or longer. This group had a 39% local recurrence rate compared with 15.3% in the main group, a statistically significant difference. The investigators choose to explain these results on the basis of tumour repopulation, a reasonable hypothesis but based on a small number of observations.

Breast conservation techniques are well established as useful alternatives to mastectomy that can be safely offered to most women with early stage breast cancer. Many long-term hazards of comprehensive local-regional radiotherapy are avoided when radiotherapy is confined to glancing tangential fields to the breast. Surgical margins of 2–3 cm around the main tumour are safer than 1 cm margins in terms of local control at the expense of breast cosmesis. It is hoped and expected that current studies will identify reliable features that are good guides to the requirements for surgical margins and radiation in individual patients.

J.R. Yarnold
Academic Radiotherapy Unit
Royal Marsden Hospital
Downs Road
Sutton
Surrey SM2 5PT
U.K.

1. Veronesi U, Saccozzi R, Del Veccio M *et al.* Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981, **305**, 6–11.
2. Fisher B, Redmond C, Poisson R *et al.* Eight-year results of a randomised clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989, **320**, 822–828.
3. Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer—long-term results from the Oslo study. *Int J Rad Oncol Biol Phys* 1986, **12**, 727–732.
4. Haybittle JL, Brinkley D, Houghton J, A'Hern RP, Baum M. Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. *Br Med J* 1989, **298**, 1611–1614.
5. Jones JM, Ribeiro GG. Mortality patterns over 34 years of breast cancer patients in a clinical trial of post-operative radiotherapy. *Clin Radiol* 1989, **40**, 204–8.
6. Cancer Research Campaign Working Party. Cancer Research Campaign (King's/Cambridge) trial for early breast cancer. A detailed update at the tenth year. *Lancet* 1980, 55–60.
7. Fisher B, Redmond C, Fisher ER *et al.* Ten year results of a randomised clinical trial comparing randomised mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985, **312**, 614.
8. Yarnold JR. Selective avoidance of lymphatic irradiation in the conservative management of breast cancer. *Radiother Oncol* 1984, **2**, 79–82.
9. Arriagada R, Le MG, Mouriesse H, Fontaine F *et al.* Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. *Radiother Oncol* 1988, **11**, 213–222.

10. Kurtz JM, Amalric R, Brandone H *et al.* Local recurrence after breast-conserving surgery and radiotherapy. *Cancer* 1989, **63**, 1912–1917.
11. Recht A, Schnitt SJ, Connolly JL *et al.* Prognosis following local recurrence after conservative surgery and radiotherapy for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1989, **16**, 3–9.
12. Price P, Walsh G, McKinna AJ, Ashley S, Yarnold JR. Patterns of breast relapse after local excision + radiotherapy for early stage breast cancer. *Radiother Oncol* 1988,. **13**, 53–60.
13. Bartelink H, Borger JH, van Dongen JA, Peterse JL. The impact of tumour size and histology on local control after breast-conserving therapy. *Radiother Oncol* 1988, **11**, 297–303.
14. Pierquin B, Mazeron J-J, Glaubiger D. Conservative treatment of breast cancer in Europe: report of the Groupe Européen de Curiethérapie. *Radiother Oncol* 1986, **6**, 187–198.
15. Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early local recurrence in stage I and II breast cancer treated by primary radiation therapy. *Cancer* 1984, **53**, 1049–1057.
16. Schnitt SJ, Connolly JL, Khettry U, Hellman S, Cohen RB. Pathologic findings on re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy. *Cancer* 1987, **59**, 675–681.
17. Holland R, Veling SHJ, Mravunac M, Hendriks JHCL. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving treatment. *Cancer* 1985, **56**, 979–990.
18. Holland R, Connolly JL, Gelman R *et al.* The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. *J Clin Oncol* 1990, **8**, 113–118.
19. Calle R, Vilcoq JR, Zafrani B, Vielh P, Fourquet A. Local control and survival of breast cancer treated by limited surgery followed by irradiation. *Int J Radiat Oncol Biol Phys* 1986, **12**, 873–878.
20. Arriagada R, Mouriesse H, Sarrazin D, Clark RM, Deboer G. Radiotherapy alone in breast cancer. I. Analysis of tumour parameters, tumour dose and local control: the experience of the Gustave-Roussy Institute and the Princess Margaret Hospital. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1751–1755.

Eur J Cancer, Vol. 26, No. 6, pp. 655–656, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00
Pergamon Press plc

Breast Cancer Prevention with Tamoxifen

The Role of Tamoxifen in the Prevention of Breast Cancer

THE ENDOCRINE sensitivity of breast cancer sets it aside from the other common malignancies. Early carcinogenic events have not yet been characterised, but subsequent promotional role of ovarian steroids is recognised [1]. Partial protection against breast cancer is acquired naturally in women who have a late menarche and early menopause, or unnaturally by early oophorectomy, albeit at the cost of side-effects of oestrogen withdrawal [2, 3].

It is fortuitous that tamoxifen blocks the effects of oestrogens on the breast, but does not act as a pure anti-oestrogen. Thus tamoxifen stimulates the hepatic synthesis of high-density lipoproteins, reduces levels of cholesterol in the blood and has no demineralising effect on bone [4, 5]. Indeed, it has been suggested that the drug protects against osteoporosis [6]. Furthermore, tamoxifen induces synthesis of TGF-β, a breast cancer inhibitory growth factor [7]. For these and probably other reasons, women with breast cancer given adjuvant tamoxifen are less likely to develop contralateral tumours [8, 9].

Which women should be considered for trials of prevention? Since no blood assays have yet been shown reproducibly to be markers of risk of breast cancer, clinicopathological or mammographic criteria have to be used. The most easily family history (first-degree relative developing the disease before age 50 or two first-degree relatives after age 50). Such individuals have a three-fold to four-fold increase in life-time risk. Such criteria have been used at the Royal Marsden Hospital and a carefully conducted randomised pilot study is underway. This has shown that tamoxifen is well tolerated with a compliance of around 80% for both placebo and treated groups at 2 years [10].

Those with a family history of breast cancer may not be the best group in which to test endocrine prevention. Tumours in younger women are more likely to be oestrogen receptor negative and thus might not be influenced by tamoxifen. Hereditary breast cancer represents only 5% of all cases, so that some other factors will need to be used to have a major impact on the disease [11]. An alternative risk factor is lobular carcinoma *in situ* (one in four risk), but this is a rare pathological finding [12]. An almost equally powerful but also rare histological change is atypical ductal hyperplasia [13]. With the combination of Wolfe grade P2/DY and nulliparity or first baby after age 28, a group with a two-fold increase in risk can be delineated [14]. However, to demonstrate an effect in this group would need a trial of 10,000 patients.

Extrapolation from the adjuvant studies indicates that a one-third or one-half reduction in incidence might be achieved. This might not be prevention but procrastination—if the disease is deferred for 20 years an individual may die of other causes. If, however, the malignant phenotype is inhibited for, say 2–5 years with subsequent emergence of a more aggressive hormone-