PERGAMON

European Journal of Cancer 37 (2001) 2143–2146

European Journal of Cancer

www.ejconline.com

Editorial Comment

Commentary on the paper "A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated". A critical review of an innovative approach

H. Bartelink*

Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands

Received 1 June 2001; accepted 3 August 2001

The first results of intra-operative radiotherapy (IORT) in limited breast cancer published in this issue by Veronesi and colleagues [1] where a single fraction is given to the tumour bed during operation is at first glance an appealing approach. The main advantage of IORT is the avoidance of 5 weeks external irradiation in selected patients with early breast cancer. It is correctly argued that whole breast irradiation is not needed for all patients. Currently, however, selection criteria deciding which patients will or will not require whole breast irradiation are lacking. Before adapting this treatment policy outside of clinical trials, one has to question the safety of this approach. The patient population with early breast cancer is characterised by both an excellent local control and life expectancy. For example, in a recent trial by the European Organization for Research and Treatment of Cancer (EORTC) involving 5569 patients with early breast cancer, a 5-year breast recurrence rate of 4% and a 5-year survival rate of 92% was achieved with breast conserving therapy (BCT) [2]. One is, therefore, entitled to wonder whether the IORT approach is based upon clinical evidence, or whether this is a novel tool in search of a clinical application. Before applying this approach into routine clinical practice, several questions must be answered. Do local recurrences always occur in the tumour bed after BCT (supporting the concept that whole breast irradiation can be avoided)? To what extent is the breast recurrence rate increased in BCT trials comparing no irradiation versus whole breast irradiation in patients with early breast cancer? Other important questions are: will the short-term results after radiotherapy be a reliable parameter in predicting long-term local control and the occurrence of late side-effects after radiotherapy? Does sufficient evidence exist that local irradiation is as effective in reducing the ipsilateral breast recurrence rate compared with whole breast irradiation.

The first question requiring clarification is: where and when do recurrences in the breast occur. During the initial follow-up, the recurrences are mostly seen at the original tumour site. With increasing follow-up, one sees progressively more recurrences or new tumours outside of the original tumour area [3]. In the above-mentioned EORTC trial, after an average follow-up of 5 years, only 47% of recurrences were located only in the primary tumour bed. This finding is consistent with the suggestions made by Holland and colleagues [4] where they demonstrated that the microscopic spread of invasive tumour occurs throughout the breast large distances away from the original tumour bed. Minimal tumour residuum left after surgery may develop into recurrent tumours long after the initial treatment, because of the generally slow tumour proliferation rate and the small initial tumour burden. Limiting the post-operative radiotherapy to the tumour bed may, therefore, miss a significant percentage of tumours that would have been controlled by whole breast irradiation. The second question concerns the efficacy of radiotherapy after lumpectomy in preventing ipsilateral breast recurrences. Irrefutable evidence exists that post-operative radiotherapy to the whole breast significantly reduces the ipsilateral breast recurrence rate, as shown in numerous phase III trials (Table 1) Although each individual trial did not show improved overall survival, one may predict that long-term follow-up will show that improved local control will also lead to an improved survival rate, as has been shown in a meta-analysis [5] and some recent trials aimed at evaluating the benefit of

* Tel.: +31-20-512-2122; fax: +31-20-669-1101.
E-mail address: hbart@nki.nl (H. Bartelink).

PII: S0959-8049(01)00284-2

Table 1 Crude relapse percentage in the breast (%)

	Years follow-up	IBTR (%)		Hazard ratio
		Without RT[a]	With RT[a]	
NSABP B-06 [17] (lumpectomy)	12	35	9	4.1
Scottish Cancer Trials [16] (lumpectomy)	6	24	6	4.2
Uppsala-Orebro [18] (segment excision)	10	24	8.5	3.1
Ontario [15] (lumpectomy)	8	35	11	4.0
Milan 3 [8] (quadrantectomy)	9	24	6	4.5

NSABP, National Surgical Adjuvant Breast and Bowel Project; IBTR, ipsilateral breast recurrence rate.
[a] RT is whole breast irradiation.

postmastectomy radiotherapy [6,7]. Partial breast radiotherapy without proper patient selection criteria could lead to an unacceptable high local recurrence rate and maybe even to a worse prognosis. The authors argue for partial breast irradiation on updated data of their own trial, where they randomised between quadrantectomy alone versus quadrantectomy and radiotherapy. In this trial they showed that even after an extensive local excision (quadrantectomy) adjuvant radiotherapy still dramatically reduces the recurrence rate [8]. One may suppose that the breast volume irradiated by IORT will be equal to the volume of breast tissue removed by quadrantectomy.

Can we reliably extrapolate the early results of breast conserving therapy for both local control and the late side-effects caused by radiotherapy? Many studies including the long-term follow-up data of the EORTC trial 10801 [9], demonstrated that even after many years ipsilateral recurrences still occur. The data on local control in the Milan trial should, therefore, be considered preliminary. The acute complications after radiotherapy for early breast cancer are usually limited. However, in optimising radiation treatment by dose escalation, one must always weigh the gain in local control against the increase in late side-effects. Late side-effects that may occur after IORT, as used by the authors, are fibrosis, telangiectasia and necrosis. These all cause poor cosmesis. The incidence and severity of side-effects increases with longer follow-up post-radiotherapy as seen in the EORTC trial 10801 [10]. These side-effects are dependent on the total dose, the dose per fraction, and the irradiated volume. In a recent paper, where a similar IORT approach is used with iridium 192 implants [11], it was clearly shown that larger irradiated volumes had significantly more tissue necrosis. The fraction size is another important parameter related to the incidence of late normal tissue complications after irradiation. Biological models have been developed to guide clinicians in developing new treatment schemes. The authors state in their article that 60 Gy in 6 weeks with a daily dose of 2 Gy is equivalent to a single fraction of 20–22 Gy, assuming the radiobiological models described by Tucker and colleagues in 1990 [12]. This model is used by the authors to predict equivalent tumour effect, but it has only been validated for normal tissue toxicity and not for breast tumours. Furthermore, this radiobiological model concept is based upon clinical schedules using a daily dose from 1.5 to 4 Gy per fraction. A single irradiation dose of 21 Gy is outside the tested dose range. Assuming they may be correct with their calculations, the authors should present their statement of equal tumour effect with more caution. Even if one assumes equal local control, the authors tend to overlook an old radiotherapy adage that for a similar cure rate one can significantly reduce late side-effects by increasing the number of fractions. Assuming a α/β value of 3 Gy for late radiation damage (fibrosis) the biological equivalent dose (BED) will be 100 Gy for a daily fractionation schedule of 2 Gy but 168 Gy for fibrosis, for the single intra-operative dose used. If this model is to be believed than a serious increase in fibrosis and tissue necrosis can be expected with long-term follow-up. In a randomised phase III trial from Manchester local irradiation with electrons fractionated to 40 Gy in eight fractions (BED of 107 Gy) with field sizes of 6×8 cm was compared with whole breast irradiation of 40 Gy in 15 fractions (equivalent to BED of 75 Gy). ''A major increase in side-effects was observed with the lower fraction number schedule, despite the relatively small difference in the BED'' [13].

Finally, what is the evidence that whole breast irradiation is necessary after local excision. Local irradiation to the tumour bed by electrons or iridium implant has been attempted previously in several small phase II trials. Guy's Hospital was one of the first to report disappointing breast recurrence rates after local irradiation by performing iridium 192 implants during the tumorectomy [14]. Others claim more favourable results, but have a relatively short follow-up period. The aforementioned Manchester trial randomised 708 patients and demonstrated that whole breast irradiation significantly reduced the recurrence rate in the breast to 13% from 25% for local electron irradiation [15]. Suggestively, the volumes they used for local irradiation were comparable

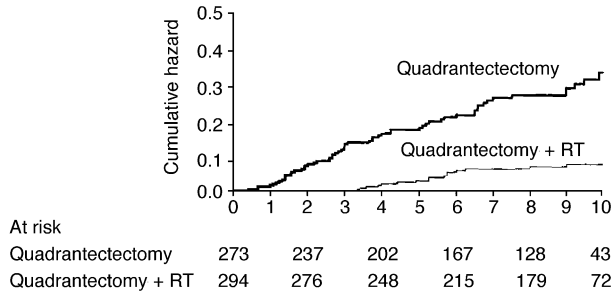

Fig. 1. Cumulative hazard curves for ipsilateral breast tumour reappearance according to treatment assignment [8].

with the Milan IORT approach. The Manchester experience is therefore consistent with the previously mentioned trials demonstrating the benefit of whole breast irradiation after tumorectomy and with the experience of the Milan group that breast irradiation reduced significantly the recurrence rate even after quadrantectomy.

In their recent publication the cumulative hazard was more than 30% ipsilateral breast tumour reappearance with quadirantectomy alone (Fig. 1). With their IORT they probably irradiate to this same quadrant as they exercised in their previous trial (Fig. 1).

Conclusions

Despite the good short-term results for both local control and tolerance for IORT in their patients, one should interpret their results with extreme caution, as they are preliminary data and IORT should not be applied into routine clinical practice. The long-term follow-up data of their planned phase III trial needs to be established first. Since the biological effects of the larger single radiation fraction may result in significantly more late complications such as fibrosis and tissue necrosis. The natural spread of breast tumours may not be controlled with local IORT and result in an increased breast recurrence rate, as shown in several trials comparing lumpectomy versus lumpectomy and whole breast irradiation. The modest reduction in treatment resources may not be justified in a group with such excellent local control and survival as is obtained with the present standard BCT and adjuvant whole breast irradiation.

References

1. Veronesi, U., Orecchia, R., Luini, A, *et al*. A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 2001, **37**, 2177–2182.
2. Bartelink H. Impact of a boost dose of 16 Gy on the local control and cosmesis in patients with early breast cancer: the EORTC 'boost versus no boost' trial. *Int J Rad Oncol Biol Phys* 2000, **48**, 111.
3. Smith T, Lee D, Turner B, Carter D, Haffy B. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical ad pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Rad Oncol Biol Phys* 2000, **48**, 1281–1289.
4. Holland R, Veiling SHJ, Mravunac M, *et al*. Histologic multifocality of Tis, T1-2 carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer Cancer* 1985, **56**, 879–900.
5. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000, **355**, 1757–1770.
6. Overgaard M, Hansen PS, Overgaard J, *et al*. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy: Danish Breast Cancer Group DCG 82b randomised trial. *N Engl J Med* 1997, **337**, 949–955.
7. Ragaz J, Jackson SM, Le N, *et al*. Adjuvant radiotherapy and chemotherapy in node positive premenopausal women with breast cancer. *N Engl J Med* 1997, **337**, 956–962.
8. Veronesi. Radiotherapy after breast conserving surgery in small breast carcinoma. Long-term results of a randomized trial. *Ann Oncol 2001*, **12**, 997–1103.
9. Van Dongen JA, Voogd A, Fentiman IS. Long-term results of a randomized trial comparing breast-conserving therapy with Mastectomy: European Organization for Research and treatment of cancer 10801 Trial. *J Natl Cancer Institute* 2000, **92**, 1143–1150.
10. Curran D, Van Dongen JP, Aaronson NK, *et al*. Quality of life of early-stage breast cancer patients treated with radical mastectomy or breast-conserving procedures: results of EORTC 10801. *Eur J Caner* 1998, **34**, 307–314.
11. Wazer DE, Lowther D, Boyle T, *et al*. Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2001, **50**, 107–111.
12. Tucker SS, Thames HD, Taylor JM. How well is the probability of tumor cure after fractioned irradiation described by Poisson statistics. *Radiat Res* 1990, **124**, 273–282.
13. Magee B, Young EA, Swindell R. C-B Trial. *Br J Cancer* 1998, **78**(Suppl. 2), 24.
14. Fentiman IS, Poole C, Tong D, *et al*. (ICRF Department of Clinical Oncology, UMDS, London, UK). Iridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. *Int J Radiat Oncol Biol Phys* 2000, **48**, 757–765.

15. Clark RM, Whelan T, Levine M, *et al*. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 1996, **88**, 1659–1664.
16. Forrest AP, Stewart HJ, Everington D, *et al*. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. *Lancet* 1996, **348**, 708–713.
17. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995, **333**, 1456–1461.
18. Liljegren G, Holmberg L, Bergh J, *et al*. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999, **17**, 2326–2333.