

## E6. Radiotherapy in breast cancer

A. Fourquet, F. Campana, R. Dendale, A. Renard, J.R. Vilcoq

Department of Radiation Oncology, Institut Curie, Paris, France

One of the main achievements of radiotherapy was to allow breast preservation in women with early breast cancer, by combining a wide tumour excision and breast radiotherapy, instead of mastectomy. Following the pioneer works of European and Canadian investigators, several randomised trials have confirmed the equivalence of treatments, thus establishing breast conservation with tumorectomy and radiotherapy as a standard for women with early, unifocal breast cancer. The results of recent trials and meta-analyses demonstrated that:

In ductal carcinoma *in situ* (DCIS) the rate of breast recurrences following breast-conserving surgery was decreased by at least 50% when breast radiotherapy is delivered [1,2].

In early invasive breast cancer, breast radiotherapy decreased local recurrences by a factor 3 (66%) compared with no radiotherapy [3]. The same magnitude of effect was observed following mastectomy.

The improved locoregional control obtained with radiotherapy translated into a significant improvement of long-term survival [3], whether adjuvant medical treatment was given or not [4].

Numerous issues are unresolved and represent future challenges for clinical research.

### Toxicity of radiotherapy

Studies have shown that, in trials conducted before 1982 [5], postmastectomy radiotherapy (PMRT) was associated with an increased long-term risk of mortality from intercurrent, cardiovascular diseases which counterbalanced the reduction in mortality from breast cancer [3]. However, this was not observed in more recent trials [6] using modern radiation techniques. Modern techniques for treating patients with breast cancer should include: adequate imaging systems, elaborate treatment planning, simulation, adequate range of high energy radiation, beam modifiers and adequate set-up devices.

### Radiation dosage

The standard dosage of radiation is 50 Gy in 25 fractions over 5 weeks. The results of a large European Orga-

nization for Research and Treatment of Cancer (EORTC) trial [7] including 5318 patients treated with wide excision with free margins and whole-breast radiotherapy to 50 Gy showed that an additional dose (boost) of 16 Gy significantly reduced the rate of breast recurrences during the first five years. This benefit was significant in women below 50 years of age. Another smaller trial gave the same results [8].

### Regional nodal irradiation

The need for radiotherapy directed at the regional nodes is a debated issue. Retrospective studies failed to demonstrate a benefit from this irradiation. Although many were biased due to patient selection, and because of the potential toxicity of lung and heart irradiation, there exists considerable variations in the management of patients with involved axillary nodes, or of patients at risk for internal mammary node involvement. Whether the improved survival rates observed in the PMRT trials were related to local control on the chest wall, or regional nodes, or both, was not determined. Trials are to answer these questions.

### Omission of radiotherapy

Large trials have demonstrated that breast irradiation following breast-conserving surgery reduces the risk of breast recurrence by a factor 3 in the long-term. However, a proportion of patients who did not received radiotherapy will not recur. Thus, identifying common tumour features in these patients would help to determine which patients would not need radiotherapy. In DCIS, no such subgroups could be identified in two multicentric trials. Selected retrospective studies [9] suggest that very wide margins of excision (>10 mm) could avoid the need for radiotherapy. However, this has to be confirmed by prospective trials.

In early invasive cancer, some retrospective studies [10] suggest that, because older patients have a very low rate of recurrence, the benefit of radiotherapy is very limited, but others [11] showed that the rate of recurrence was high when radiotherapy was omitted, even in highly selected patients.

## Sequencing radiotherapy and chemotherapy

Adjuvant chemotherapy is delivered to an increasing number of patients with breast cancer, which raised the issue of the most efficient sequence of treatment after surgery. Apart from one trial [12] which showed no significant differences whether radiotherapy was given before or after a 3-months course of four cycles of chemotherapy, other retrospective studies are inconclusive. The current practice in most countries is to deliver the chemotherapy first. Although the optimal length and number of chemotherapy cycles were not determined, a tendency is to extend the length of chemotherapy to six cycles or more. Consequently, radiotherapy is initiated six months or more after surgery, which might impair local control and possibly survival [4].

## Improving the radiosensitivity of breast cancer

The adverse impact of risk factors of recurrence (young age, high grade) is not modified by radiotherapy. Hence, young age is associated with a high risk of failure which raises the issue of whether breast-conservation is appropriate in these patients. The EORTC trial [7] showed that increasing the radiation dose can significantly reduce the risk of recurrence in these young patients, however, without bringing it down to the level of risk of older patients.

Future research should therefore focus on the identification of the genotypic and phenotypic tumours profiles in patients who recur after radiotherapy, in order to determine the mechanisms by which resistance to treatment occurs. Various preclinical and clinical studies are underway to test the potentiation of radiotherapy by chemotherapy drugs, or biological modifiers, such as inhibitors of growth factor receptors.

## References

- [1] Fisher B, Land S, Mamounas E, Dignam J, Fisher E. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. *Semin Oncol* 2001; 28: 400–418.
- [2] Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, Avril A, Sylvester R, Mignolet F, Bartelink H. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet* 2000; 355: 528–533.
- [3] EBCTCG. 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.
- [4] Whelan TJ, Julian J, Wright J, Jadad AR. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000; 18: 1220–1229.
- [5] Paszat LF, Mackillop WJ, Groome PA, Boyd C, Schulze K. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. *J Clin Oncol* 1998; 16: 2625–2631.
- [6] Hojris I, Overgaard M, Christensen JJ. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. *Lancet* 1999; 354: 1425–1430.
- [7] Bartelink H, Horiot JC, Poortmans P, Struikmans H, van den Bogaert W, Barillot I, Fourquet A, Borger J, Jager J, Hoogenraad W, Collette L. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional irradiation. *N Engl J Med* 2001; 345: 1378–1387.
- [8] Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997; 15(3): 963–968.
- [9] Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, Gamagami P. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med* 1999 May 13; 340(19): 1455–1461.
- [10] Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, Salvadori B. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 2001; 12: 997–1003.
- [11] Schnitt SJ, Hayman J, Gelman R, Eberlein TJ, Love SM, Mayzel K, Osteen RT, Nixon AJ, Pierce S, Connolly JL, Cohen P, Schneider L, Silver B, Recht A. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. *Cancer* 1996; 77: 1094–1100.
- [12] Bellon JR, Come SE, Gelman RS, Henderson IC, Shulman LN, Silver B, Harris JR. Sequencing of chemotherapy and radiation therapy for patients with early stage breast cancer: updated results of a prospective randomized trial [Abst.]. *Int J Radiation Oncology Biol Phys* 2001; 51: 2.