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EDITORIAL

Early breast cancer: Adjuvant chemotherapy or radiotherapy, or both?

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Patients with early breast cancer may currently benefit from various adjuvant treatments evaluated in large randomised trials and in individual data-based meta-analyses [1,2]. Systemic treatments improve results by decreasing the rate of distant relapses, and loco-regional radiotherapy by decreasing the local recurrence rate. More recently, it has been recognised that an improved local control has an impact on overall survival [2,3]. However, it is also of importance to evaluate the late iatrogenic effects of such treatments to improve our knowledge and refine therapeutic indications.

In this issue, Rutqvist et al. [4] report long-term results of a large randomised trial performed in the Stockholm region. The trial had a pragmatic approach [5] as it compared postoperative loco-regional radiotherapy with the administration, for most patients, of 12 cycles of conventional CMF as initially described by Bonadonna et al. [6]. At the time of the trial planning, the former treatment was standard in Stockholm and the latter in Milan. The direct comparison of these treatment attitudes does not allow evaluating the addition of one treatment to another. Also, postmenopausal patients were randomised to receive or not adjuvant tamoxifen. The trial was open until the worldwide meta-analysis showed that adjuvant chemotherapy and tamoxifen were effective treatments in these patients [7].

Loco-regional radiotherapy showed a clear benefit in terms of local control, both in 547 pre- and 679 postmenopausal patients. In contrast, distant metastases were decreased in the chemotherapy arm, even if only significant for premenopausal patients. This effect translated in a significant therapeutic gain in relapse-free survival for the latter group of patients.

As the median follow-up was longer than 18 years, the authors were able to analyse late effects. The most striking finding was a significant increase of second malignancies in the radiotherapy group, but this effect was only limited to postmenopausal patients, mainly related to an excess of lung cancers. Why has such an effect only been detected in postmenopausal patients? It could be related to a play of chance, or because postmenopausal patients are at a higher risk of malignancies because of ageing.

In a previous publication, in the same material but with a shorter follow-up (seven years), a decrease of second malignancies in the chemotherapy arm was reported [8]. This interpretation was reinforced by a similar rate (6% at 10 years) of second cancers in the radiotherapy arm and in a concurrent non-randomised untreated series versus a rate of 1% at 10 years for the chemotherapy arm. The 15-year rates in the current study for postmenopausal patients were 11% for radiotherapy and 5% for chemotherapy. These patients developed more second cancers than premenopausal patients (3% and 2%, respectively). The alternative hypothesis is that CMF does not decrease the risk of second malignancies, but that radiotherapy increases this risk after long-term follow-up.

At the present time, we have more data reporting long-term effects on large cohort series [9,10] or in randomised materials, directly comparing radiotherapy versus no radiotherapy [2]. The Thames report [9] showed an excess of myeloid leukaemia, contralateral breast cancer, lung and oesophageal cancer for 33 763 patients treated with radiotherapy as compared with 31 019 untreated women. Similarly, Darby et al. [10] showed, in a SEER cohort of more than 300 000 patients, an excess of lung cancer and heart disease for the irradiated patients. Finally, the last EBCTCG radiotherapy overview [2] showed an excess of mainly lung cancer, but also of oesophageal cancer, leukaemia, soft tissue sarcoma and contralateral breast cancer for patients allocated

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to radiotherapy versus those who did not receive this treatment in a total population of 32 800 randomised patients.

The technique of radiotherapy is certainly important, but so are the volumes to be treated. There is evidence that the second malignancy risk is related to the radiation dose between ranges of low to moderate doses [11]. In the reported Stockholm trial, the chest wall was irradiated with electrons but the lymph nodes were treated by direct photon beams probably giving a wide variation of moderate and low doses to the mediastinum, lung, oesophagus and vertebral bodies. Thus, theoretically the lymph node irradiation may have an impact on the incidence of second malignancies. The irradiation of lymph nodes remains controversial. The decision to irradiate lymph nodes is mainly based on the fact that most of the results of radiotherapy were obtained in trials in which this treatment was performed. A large randomised trial has specifically explored the question of the addition of lymph node areas [12], but closed its recruitment only in 2004. Novel techniques of irradiation, including intensity-modulated radiotherapy (IMRT) and proton beam therapy [13] have been proposed. In general the IMRT techniques increase the number of beams to protect critical organs, but at the same time increase the volume irradiated to low or moderate doses. This could be a factor of increased late carcinogenesis and should be evaluated carefully with a long-term follow-up [14]. Proton beam therapy can manage the dose better without this radiation bath of low and intermediate doses to large tissue volumes [13]. For the time being, if the irradiation of lymph nodes is decided, it is recommendable to keep to small volumes: only the first three intercostals spaces for the internal mammary chain, the inner part of the supraclavicular area and not to irradiate the axilla if a satisfactory axillary surgery has been done [15]. Larger irradiated volumes may increase the risk of sarcomas developed within the fields, even if this type of event remains rare [16].

Another important issue discussed in the current paper [4] is the role of smoking on breast cancer survivors. The described increased risk of lung cancer has been confirmed in a recent case-only study [17].

All of the discussed information stresses the importance to analyse late iatrogenic effects on large databases with long-term follow-up and to ensure a good quality follow-up for patients included in randomised trials. Figure 1 shows the time scale to evaluate the impact of radiotherapy on loco-regional recurrences, mortality (breast cancer specific and overall) and late iatrogenic effects. The latter would have been completely ignored in the absence of long-term information. The same recommendation should be certainly applied to the evaluation of systemic treatments.

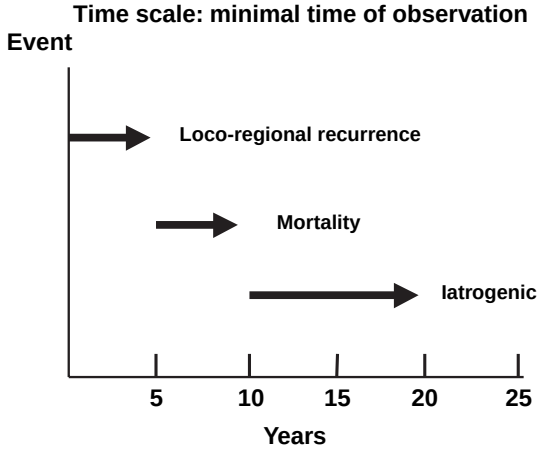

Figure 1. Time scale to evaluate different effects of loco-regional radiotherapy in breast cancer.

Basically, the discussed paper [4] shows the different effects of radiotherapy and chemotherapy on local and distant disease control, respectively. Other data [1,2] show the interest to use both treatments, most often in a sequential combination. A recently published trial showed that the delay of locoregional radiotherapy after six courses of anthracycline-based chemotherapy did not affect local control [18]. The optimal definition of volumes to be irradiated, according to the level of local recurrence risk, and radiation techniques sparing normal structures at risk should allow for an overall benefit of treatment, by improving local control and secondary dissemination while decreasing long-term hazards.

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