E17. Update on adjuvant radiotherapy for breast cancer

B. Cutuli

Department of Radiation Oncology, Polyclinique de Courlancy, Reims, France

In this educational session, we will analyse the impact of adjuvant radiotherapy (RT) after breast-conserving surgery [both for ductal carcinoma *in situ* (DCIS) and infiltrating carcinomas], and after radical surgery. We will also discuss the impact of RT on survival and late toxicities, as well as the recent improvements in RT techniques and in delivering the modalities.

For DCIS, mastectomy provides a more than 98% 10-year local control rate [1]. Three randomised trials and several retrospective studies have confirmed that there is a significant reduction in the *in situ* and invasive local recurrence (LR) rates after breast-conserving surgery and irradiation of the whole breast with 50 Gy [2,3]. Indeed, radiation decreases the 10-year LR rate from 25–30% to 10–15%. An incomplete/doubtful excision and an age of less than 40 years were the most important risk factors for LR [1–3].

For infiltrating carcinoma, seven randomised trials have confirmed the significant benefit of post-operative RT [5]. Again, the 10-year LR rate decreases from 25–30% to 6–11%. After mastectomy (+/– chemotherapy and tamoxifen), three randomised trials [one Canadian and two large Danish, including, 1708 premenopausal (trial 82-b) and 1375 postmenopausal (trial 82-c) women (respectively)] and several retrospective studies showed a significant reduction (from 32–35% to 8–9%) following the use of locoregional irradiation in T_3T_4 tumours and/or tumours with histological axillary involvement (both for pN_{1-3} and $pN_{>3}$ cases). These studies also showed a 9% benefit (54% versus 45% and 45% versus 36% in both the Danish 82b and 82c trials) in the 10-year overall survival rates [6,7].

However, the impact of post-mastectomy RT is still a matter for debate [8]. Firstly, the rate of LR is difficult to assess and depends on the possible inclusion of supraclavicular recurrences. Secondly, the quality of axillary surgery could influence the axillary LR rate. Finally, techniques, doses, fractionation protocols and the real volumes (chest wall/supra+/–infraclavicular region/ internal mammary chain/axilla) included in "Locoregional RT" vary widely in the adjuvant treatments.

The indication causing most debate is whether patients at "intermediate risk" with one to three axillary involved nodes should receive RT. Several authors have confirmed an approximately 12–15% LR risk in these patients, and a reduction to 3–5% following RT.

The Oxford meta-analysis [9] showed a significant reduction of locoregional isolated recurrences in patients who had undergone RT, but no difference in the 10-year overall survival (mortality: 40.3% versus 41.4% with and without RT, respectively). However, two other studies, excluding patients treated in "small trials" and those treated before 1970 (with outdated techniques) have demonstrated a significant benefit on the mortality rates for the use of "modern RT" [10,11].

Data with regard to the long-term toxicity associated with RT must be interpreted very carefully. Again, it is extremely important to differentiate the quality of "modern RT" from the older treatments that used cobalt photons, had no provisional dosimetry, and often used high doses, large volumes and fewer fractions. These features can explain the late cardiac toxicity that has been following RT treatment in several older studies. This high mortality rate was reduced to almost zero following improvements in the radiotherapy techniques. Indeed, in both Danish trials (82b and 82c), the death rate from ischaemic heart disease was identical in the women not given locoregional RT to those who were (with the treatment delivered by electrons) (0.8 versus 0.9%, respectively) [12].

On the other hand, the increased risk of developing contralateral breast cancer was considered to be almost non-existent in the most of the studies.

The risk of developing a secondary oesophageal cancer, lung cancer or sarcoma was also very low and was partly due to the RT technique used.

Several 'technical' issues are still being debated: a 16 Gy-boost significantly decreases LR rates after breast-conserving surgery and whole breast irradiation for invasive BC, especially in young women [5]. It is questionable whether an increased dose (20 to 25 Gy) would be beneficial in groups at a very high risk of LR (i.e. women aged under 40 years).

The boost techniques vary and quality control procedures are mandatory (both with electron/photon or brachytherapy techniques) in order to avoid 'geographical misses', as well as complications (fibrosis) or poor cosmetic results. As the incidence of small breast cancers continues to increase, especially in elderly women, and in order to offer optimal treatments, several alternative fractionation schemes have been used: once a week (6.5 Gy per fraction), three or four times a week (3 Gy

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and 2.65 Gy per fraction). The results seem equivalent in terms of the local control rates, without any increases in the side-effects being observed [13]. Since most of LR are observed in the immediate vicinity of the primary tumour bed, several teams have replaced whole breast irradiation with a 'partial breast irradiation' (PBI), using different brachytherapy modalities or various intra-operative techniques. The selection criteria for these techniques are not well established and most studies have only a short follow-up period.

Finally, the optimal sequence of RT and chemotherapy after breast-conserving surgery is not well established [6]. In a study conducted in Boston, the delay in CT increased the rate of metastases, whereas delayed RT increased the incidence of LR. However, in an updated analysis, these increases were not observed in patients with complete excisions of their tumours. In the future, new techniques, such as intensity-modulated radiotherapy (IMRT), could lead to an optimisation of the volumes treated, especially after mastectomy in order to minimise the doses given to the heart and lungs.

In the future, if not now, we can assume that RT will result in the improved overall survival of patients with breast cancer, without the associated long-term toxicities.

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