Whole breast irradiation (WBI) is considered standard of care among both patients having undergone breast-conserving therapy for invasive breast carcinoma and selected cases post mastectomy. Since the introduction of WBI, clinical trials have been conducted to define the optimal dose, schedule and length of WBI aiming to increase efficacy while reducing toxicity. In the paper discussed in this issue’s journal club, Whelan et al. present the latest in a series of randomized clinical trials on hypofractionated radiotherapy.

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Commentary – Rainer Souchon, Tanja Fehm, Tübingen

Randomized clinical trials (RCT) in patients with early breast cancer provided high-level evidence that percutaneous whole breast irradiation (WBI) following breast-conserving surgery (BCS) reduces the relative risks of locoregional relapse and results in an absolute improvement in 15-year overall survival [1].

An optimal dose and fractionation schedule for radiation therapy (RT) after BCS has not yet been defined. WBI is normally administered over about 5 weeks using standard fraction of 1.8–2.0 Gy per day (i.e. conventional fractionated RT; cf-RT) resulting in total doses in the range from 45 to approximately 50 Gy in 25–28 fractions. The rationale for fractionated RT is that reducing the radiation dose per fraction while increasing the number of fractions and the total dose, the damage to normal tissue can be limited, as increased dose per fraction is known to be associated with increased normal tissue damage. This effect, significantly associated with progressive radiation-related microvascular damage, may limit the therapeutic gain. Keeping in mind that the optimal fractionation schedule of WBI following BCS for early breast cancer is still unknown, schedules for WBI with higher daily doses of radiation for a shorter period (i.e. accelerated hypofractionated radiotherapy; hf-RT) appears to be more convenient for affected women.

During the past several years, 4 RCT investigated effectiveness and safety of hf-RT schedules compared to cf-RT regimen for WBI [2–6]. Hitherto published data of RCT suggest that different fractionation schedules will – if ever – lead to minimum outcome differences in terms of locoregional tumor control, cosmesis as well as overall survival. Nevertheless, with the exception of the Canadian trial [2], reported
results of long-term outcomes in these RCT are limited due to relatively short follow-up periods not exceeding 6 years. Thus, up to now, the key question of how much of possible differences in local recurrence or overall survival might be due to different RT schedules of WBI, is unlikely to be answered sufficiently. The main reason for this might be the fact that beneficial effects of RT on mortality will be observed at the earliest after a follow-up period of 10 years [1].

Whelan et al. [2] now presented the first results of a large RCT which covers a 10-year period for hf-WBI. Enrolment was limited to breast cancer patients who had undergone lumpectomy for invasive breast cancer with clear surgical margins and negative axillary lymph nodes. The hf-RT was administered with daily doses per fraction of 2.65 Gy over a period of 22 days.

At 10 years, the probability of survival was similar in both groups (84.4 vs. 84.6%). The cumulative incidence of local recurrence of invasive or non-invasive breast cancer at 10 years showed no difference between the experimental and control arms either. There were also no differences in disease-free survival or in the percentage of women with an excellent or good cosmetic outcome (ca. 70% in each arm). Therefore, the authors conclude that accelerated hf-WBI was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes.

Despite the convincing results, some limitations should be considered:

1. In the subgroup analysis, patients with high-grade tumors (18.8% of the trial cohort) had a higher risk for local recurrence in the hf-RT group (hazard ratio 3.08, 95% CI 1.22–7.76). The analysis of tumor grade in this trial was post hoc. Thus, this result may be unreliable limiting the authors’ suggestion that hypofractionation might be relatively less effective in patients with high-grade tumors. Furthermore, these findings are different from the data of a recent, not yet published meta-analysis of the UK Standardisation of Breast Radiotherapy (START) A and B trials suggesting that the response to radiotherapy fraction size is not affected by tumor grade [7]. Further limitations arise considering the secondary endpoints: distant (including regional) recurrence; second cancers, including contralateral breast cancer; breast cosmesis; late toxic effects of radiation. The cause of death (cancer, a cardiac-related cause, or another cause) was also evaluated as a possible indicator of radiation-associated morbidity.

2. Type of systemic treatments might influence local tumor control as well as overall survival and side effects due to normal tissue toxicity – 41.8% of the patients received adjuvant tamoxifen, 10.9% chemotherapy, most commonly cyclophosphamide, methotrexate, and fluorouracil. Both worsening of cosmesis and toxicity after RT increase over time if systemic treatment, especially modern chemotherapy regimens, is added. The Canadian trial has reported similar cosmetic appearance after 10 years, which was good or excellent for 69.8% women treated with the shorter schedule and 71.3% of controls. However, a substantial subset of the patients was treated primarily with adjuvant tamoxifen, and only a minority received chemotherapy. Therefore, the results from this trial may not adequately represent the potential long-term complications of WBI in the presence of chemotherapy. Clinically even more important is the cardiac toxicity after RT. In this trial, in the cf-RT group (n = 612 patients) 9 deaths were related to cardiac disease (1.5%), as compared to 12 deaths (1.9%) in the hf-RT group (n = 622 patients). Increase of long-term risks of cardiac disease (including pericardial, myocardial, cardiovascular disease) related to RT in patients with early-stage breast cancer is detectable at a follow-up of at least 10 years [8]. Unpublished data from the EBCTCG revealed an increase of fatal cardiac disease 20 years after RT of about 4%. Therefore much longer follow-up of the RCT investigating hf-RT schedules is needed.

Considering the impact of WBI following BCS, the data from the meta-analysis provided by the EBCTCG [1] suggest that pN0, ER-positive patients, especially if older, are likely to gain less from RT as compared with pN+, high-grade patients. Therefore, the use of unconventional hypofractionation RT regimens (more than 2 Gy per fraction) should be limited to patients who fulfill all the following criteria:
- age 50 years or older
- pT1–2, pN0 treated with BCS
- does not receive systemic chemotherapy
- no radiation boost to the tumor bed after BCS
- acceptable dose homogeneity (i.e. dose distribution in the radiated breast) is feasible
- long-term risk of cardiac disease is clinically irrelevant.

Thus, detection of clinically sufficient selection criteria for patients indicating which patients will benefit from an individualized fractionated WBI remains a challenge.

References
Commentary – Normann Willich, Münster

This trial from Canada [1] is the latest in a line of further 3 randomized trials addressing the topic of hypofractionation in radiation treatment for breast cancer [2–4]. Basing on well substantiated radiobiological considerations the sensitivity to fraction size of adenocarcinomas of the breast was expected to be similar to that of the normal tissues in breast irradiation, with an alpha/beta value of about 3–5 Gy. This finding is in a notable contrast to squamous cell carcinomas of the bronchus, the cervix uteri or the head and neck region, where the alpha/beta ratios of about 10 Gy show that these tumors are less sensitive than late responding healthy tissues to the size of individual fractions. That means that adenocarcinomas of the breast could be more effectively treated with larger fraction sizes than previously thought, possibly without the risk to impair the ratio of local cure to late normal tissue complications.

The Canadian trial demonstrates 10 year results with low local recurrence rates and good to excellent cosmetic outcome in a high proportion of patients, which are not inferior to the standard fractionation arm. These findings are consistent with findings from the earlier reported British trials, particularly the START B trial. Although results only after 5 years are available from this trial, which is obviously too early for any final assessment, there is in general an increasing knowledge that hypofractionation for breast cancer treatment is becoming more and more feasible.

Nevertheless some limitations from the available studies have to be kept in mind:

- The Canadian trial was restricted to women who had node-negative, invasive breast cancer with clear margins after lumpectomy. At present it is not clear whether the results can be extrapolated to women with carcinoma in situ only.
- Women with node-positive breast cancer were excluded from the study, therefore the results are not applicable to patients for whom nodal irradiation is planned.

- Women with large breasts were not included and it is not known whether they may have increased risks for normal tissue late effects by larger fraction sizes.
- Only few women (10.9%) received adjuvant chemotherapy (mainly CMF). Such patients can be at increased risk for an adverse cosmetic outcome with standard radiotherapy, so it is unclear whether hypofractionation would lead to an outcome that would be any worse than that with standard treatment.
- Boost irradiation was not used in the study, so confounding effects of boost irradiation on local recurrences or breast cosmesis have not been examined.

In the subgroup of patients of the Canadian trial with a high-grade histology hypofractionation appeared to be less effective than for patients with low or moderate grading. This effect was statistically significant but could be a chance finding. However, any biological reasons assuming a different inherent radiation sensitivity of high grade tumors or biologic subtypes of breast cancer that are associated with high grade tumors are speculative.

From these reasons the authors conclude, that the results of the trial provide support for the use of accelerated, hypofractionated, whole-breast irradiation only for selected women. It is to be expected that some of the open questions addressed above will be clarified with longer follow-up from the Canadian study and the British START trials as well. The real limits of hypofractionation in breast cancer treatment will probably be better determined from an ongoing British study using higher fraction doses (5.7 and 6.0 Gy) in 5 fractions over 5 weeks [5].

References


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