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Review

Hypofractionated radiotherapy for early breast cancer: Review of phase III studies

Agata Kacprowska, Jacek Jassem*

Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland

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ABSTRACT

Breast-conserving surgery including whole breast irradiation has long been a recommended procedure for early breast cancer. However, conventionally fractionated radiotherapy requires a lengthy hospitalisation or prolonged commuting to a hospital for radiotherapy. In recent years, hypofractionated radiotherapy has increasingly been used. This method involves higher fraction doses (above 2 Gy) as compared to conventional radiotherapy, so the total dose can be delivered in fewer fractions and in a shorter overall treatment time. This review aims at presenting most important outcomes of four randomised studies comparing conventional and hypofractionated radiotherapy schemes including a total of 7000 patients. These studies have not shown apparent differences in treatment efficacy, incidence of late post-radiotherapy complications or cosmetic effects during a 5–10 year follow-up, but longer observation is warranted to fully evaluate the safety of this method. Currently, major societies consider modestly hypofractionated radiotherapy schemes as a routine management in selected groups of patients undergoing breast-conserving surgery. However, this method should be used cautiously in patients with lymph node metastases, big breasts, receiving chemotherapy or trastuzumab, or those under 50 years of age.

1. Background

Breast-conserving surgery followed by whole breast irradiation is a standard treatment of early breast cancer. Numerous randomised studies and their metaanalyses have confirmed this procedure to be as effective as modified radical mastectomy.[1–6] These studies used conventional fractionation schemes with total dose of 45–50.4 Gy delivered to the whole breast and fractionated doses of 1.8–2.0 Gy delivered with a 5 days per week schedule. Currently, an additional boost dose of 10–20 Gy is commonly administered to the tumour bed, leading to further improvement of local control.[7,8] Total duration of a conventionally fractionated radiotherapy is 5–7 weeks. The application of postoperative radiotherapy reduces by two-thirds the risk of 10-year local recurrence, thus enhancing the chance for breast conservation and increasing the rate of 10-year survival by 5%.[6] Postoperative radiotherapy is therefore an effective method of eradicating subclinical disease, ensuring local control with acceptable risk of late normal tissue reactions (lungs, heart). However, with conventional fractionation, this modality requires a lengthy hospitalisation

* *Corresponding author at*: Department of Oncology and Radiotherapy, Medical University of Gdańsk, Dębinki 7, 80-952 Gdańsk, Poland. Tel.: +48 58 349 22 70; fax: +48 58 349 22 10.
E-mail address: aczufryn@wp.pl (A. Kacprowska).

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Table 1 – Major patient characteristics in phase III studies of hypofractionated radiotherapy.

Trial (Ref.)	Age ≥ 50 years (%)	pT1-2 (%)	pN0 (%)	Chemotherapy used (%)	High tumour grade (%)
RMH/GOC[14]	70	94	40	14	NR
OCOG[15]	75	100	100	11	19
START A[16]	77	Majority	69	35	28
START B[17]	79	Majority	74	22	23

OCOG, Ontario Clinical Oncology Group; RMH/GOC, Royal Marsden Hospital/Gloucestershire Oncology Centre; START, Standardisation of Breast Radiotherapy; NR, not reported.

or commuting to a hospital for radiotherapy. This may create a major obstacle for patients with disabilities or those who cannot rely on their families' support. In the USA, for instance, an estimated 30% of women after breast-conserving surgery do not receive radiotherapy.[9] The probability of missing radiotherapy is higher with older patients and those living farther away from radiotherapy centres.[10–12] As a result, a part of the patients qualified for breast-conserving treatment opt for mastectomy. Long-lasting radiotherapy is also associated with higher costs and longer waiting lists.

Hypofractionation is a strategy allowing shortening the time of radiotherapy. The method involves higher fraction doses (above 2 Gy) as compared to conventional radiotherapy, so the dose can be delivered in fewer fractions. With such schemes, the total dose is usually lowered. There are radiobiological reasons justifying the use of hypofractionation in breast cancer. The α/β value for breast cancer has been estimated at 4 Gy, whereas the α/β value for soft tissues is approximately 3.5 Gy.[13] Since breast cancer sensitivity to radiotherapy is similar to that of healthy tissues responding with late reactions, high fraction doses may be more efficient in destroying tumour cells. There are concerns, however, that higher fractions may also increase the frequency and severity of late post-radiation reactions. Four large phase III trials have been conducted to compare results of conventional versus hypofractionated radiotherapy following surgery for early breast cancer (Table 1). The purpose of this paper is to present these studies, their main outcomes and conclusions for clinical practice.

2. Hypofractionated radiotherapy protocols in breast cancer

2.1. *Study of the Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC)*

The RMH/GOC study compared two schemes of hypofractionated radiotherapy: 42.9 Gy in 13 fractions and 39 Gy in 13 fractions versus conventional radiotherapy (50 Gy in 25 fractions).[13,14] All the schemes were administered over 5 days. A total of 1410 early breast patients treated with breast-conserving surgery were included in this study. The rates of 10-year local recurrence in the groups receiving 50 Gy, 39 Gy and 42.9 Gy were 12.1%, 14.8% and 9.6%, respectively. The difference between the groups receiving 39 Gy and 42.9 Gy was significant ($p = 0.027$). The cosmetic outcome was evaluated based on photos and physical examination during annual control visits. The photos of both breasts were taken immediately after surgery, then before radiotherapy, annually over 5 years and upon completion of the 10-year treatment. The photos were evaluated independently by two male doctors and one female nurse. The evaluators did not know patients' identity or treatment allocation. Breast changes were compared using a three-level scale (no change/minimal change – 0; small change – 2; large change – 3) in reference to the appearance from the photo taken after surgery. The photographic evaluation showed that after 10 years any changes in breast appearance in the groups that had received 50 Gy, 42.9 Gy and 39 Gy were found in 35.4%, 42.3% and 27.4% of patients, respectively. The difference in breast appearance between the groups receiving 50 Gy and 39 Gy was significant ($p = 0.01$), whereas between the groups receiving 50 Gy and 42.9 Gy it was borderline ($p = 0.05$). After 10-year follow-up, the photographic evaluation showed significant changes in breast appearance in the groups administered 50 Gy, 42.9 Gy and 39 Gy in 5.6%, 10.1% and 3.4% of patients, respectively. The differences between the groups receiving 39 Gy and 42.9 Gy and between the groups receiving 50 Gy and 42.9 Gy were significant ($p = 0.01$), whereas no significant differences were found between the groups receiving 50 Gy and 39 Gy ($p = 0.18$). A clinical assessment made 10 years after radiotherapy showed significant differences between all studied groups ($p < 0.001$). The worst cosmetic effect was observed in the group treated with 42.9 Gy, and the best one in the group administered 39 Gy.

2.2. *Study of the Ontario Clinical Oncology Group (OCOG)*

The OCOG trial, including 1234 patients with early-stage breast cancer who underwent breast-conserving surgery compared a conventional radiation regimen (50 Gy given in 25 fractions over 35 days) with hypofractionated radiation schedule (42.5 Gy in 16 fractions over 22 days).[15] The 10-year rate of local relapse was 6.7% in the standard radiotherapy group versus 6.2% in the hypofractionated radiotherapy group. The subgroup analysis showed that radiotherapy efficacy was similar in both groups regardless of age, tumour size, status of oestrogen receptors and chemotherapy. The hypofractionated radiotherapy scheme was less effective in patients with poorly differentiated breast cancer. Within this group, the 10-year local recurrence in patients administered hypofractionated and conventional radiotherapy was 15.6% and 4.7%, respectively ($p = 0.01$). A good and very good cosmetic result at 10 years was observed in 69.8% and 71.3% of women in both groups, respectively (the difference non-significant). After 10 years of follow-up, no significant differences were found between the groups in the distribution of causes of death including cardiac deaths.

2.3. *The study of the UK Standardisation of Breast Radiotherapy (START) Trial A (START A)*

The START trial compared three schemes of postoperative radiotherapy in patients with early breast cancer subjected to breast-conserving surgery or mastectomy: 50 Gy in 25 fractions, 41.6 Gy in 13 fractions and 39 Gy in 13 fractions.[16] All schemes were delivered over 5 weeks. A total of 2236 patients were entered into the trial. The 5-year rate of local relapse in the groups receiving 50 Gy, 41.6 Gy and 39 Gy was 3.2%, 3.2% and 4.6%, respectively ($p = 0.74$, $p = 0.40$, for the comparisons between 41.6 Gy with 50 Gy and 39 Gy with 50 Gy, respectively). The 5-year probability of disease-free survival in the groups receiving 50 Gy, 41.6 Gy and 39 Gy was 86%, 88% and 85%, respectively, whereas the absolute 5-year survival was 89% for all groups. Changes in breast appearance at 5 years that were self-evaluated as moderate or large were comparable in the groups receiving 50 Gy and 41.6 Gy, and significantly better with regard to skin appearance after 39 Gy than after 50 Gy ($p = 0.004$). The incidence of ischaemic heart disease, rib fractures and symptomatic pulmonary fibrosis during a median follow-up of 5.1 years was low and similar for all the groups.

2.4. *The study of the UK Standardisation of Breast Radiotherapy (START) Trial B (START B)*

The START B trial compared conventional fractionated radiotherapy (50 Gy in 25 fractions over 5 weeks) with a hypofractionated radiotherapy regimen (40 Gy in 15 fractions over 3 weeks).[17] The study included 2215 women treated with mastectomy or breast-conserving surgery for early-stage breast cancer. The 5-year local recurrence rates in the groups receiving 40 Gy and 50 Gy were 2.0% and 3.3%, respectively ($p = 0.21$). The 5-year disease-free survival rates in the groups receiving 50 Gy and 40 Gy were 86% and 89%, respectively, whereas the 5-year overall survival rates were 89% and 92%, respectively. No significant differences were found in patient self-evaluated cosmetic effect, except for better skin appearance after the dose of 40 Gy ($p = 0.02$). The incidence of ischaemic heart disease, rib fractures and symptomatic pulmonary fibrosis during a median follow-up of 6 years was low and similar for both groups. No cases of brachial plexus damage were recorded in patients irradiated to the region of supraclavicular fossa and/or axilla.

2.5. *The UK FAST trial*

The FAST trial is a prospective randomised trial testing two schemes of hypofractionated radiotherapy (28.5 Gy in 5 fractions and 30 Gy in 5 fractions over 5 weeks) versus conventional radiotherapy regimen (50 Gy in 25 fractions over 5 weeks).[18] This study included 900 patients with early breast cancer who underwent conservation surgery. The first analysis of the results after a median follow-up of 28 months showed non-inferiority with respect to local control and cosmetic outcome.[19]

3. Discussion

Results of randomised trials comparing conventional and modestly hypofractionated (13–16 fractions) radiotherapy schemes including a total of 7000 patients have not shown apparent differences in treatment efficacy, incidence of late post-radiotherapy complications or cosmetic effects during a 5–10 year follow-up. The *Ontario* study, due to its long follow-up, provides a particularly strong evidence of non-inferiority of this approach compared with conventionally fractionated radiotherapy. This finding is also supported by the results of the three large completed UK studies. The late outcomes of radiotherapy including just 5 large fractions over 5 weeks remain to be established. Yet there are still some uncertainties about whether hypofractionated schemes can be safely implemented as a routine practice in all patients with breast cancer. Even though entry criteria for the above-mentioned studies were relatively broad, most patients were over 50 years old, had been treated with breast-conserving surgery for pT1–2N0 cancer and had not received irradiation to nodal fields or chemotherapy. These studies used both 2D and 3D techniques and a boost to the tumour bed was not always administered or varied in dose (Table 2). Due to this selective assignment of patients, it is not known whether hypofractionation is equally effective and safe in patients with lymph node metastases, big breasts, receiving chemotherapy or trastuzumab, or those under 50 years of age.

Data from earlier observations show that radiotherapy-related cardiovascular toxicity manifests only after 10 years after treatment.[20] There are concerns, therefore, that the follow-up of 5–10 years may be too short to fully evaluate the safety of hypofractionated radiotherapy for early breast cancer. A long-term follow-up is also required for a full efficacy assessment. For example, in the EORTC trial evaluating the

Table 2 – Radiotherapy parameters in phase III studies of hypofractionated radiotherapy.

Trial (Ref.)	Energy	Planning	Central axis dose homogeneity (%)	Boost (electrons)	Nodal irradiation
RMH/GOC[14]	6 MV	2D or 3D	−5 to +7	14 Gy/7 fr (75%)	SCV ± Ax (21%)
OCOG[15]	^{60}Co, 4, 6 MV	2D	−7 to +7	No	No
START A[16]	6 MV	2D or 3D	−5 to +5	10 Gy/5 fr (61%)	SCV ± Ax (14%)
START B[17]	6 MV	2D or 3D	−5 to +5	10 Gy/5 fr (31%)	SCV ± Ax (7%)

OCOG, Ontario Clinical Oncology Group; RMH/GOC, Royal Marsden Hospital/Gloucestershire Oncology Centre; START, Standardisation of Breast Radiotherapy; 2D, two-dimensional; 3D, three-dimensional; SCV, supraclavicular lymph nodes; Ax, axilla; fr, number of fractions; MV, megavoltage.

role of boost dose in postoperative whole breast irradiation, 10-year results differed from those observed at 5 years.[7,8] Indeed, higher doses to a tumour bed were found to reduce the rate of local relapse not only in younger patients (as observed already after 5 years) but also in the older age group. Therefore, some concerns have been raised that the 5-year follow-up in START A and START B may be too short to fully evaluate treatment efficacy.

Based on the data from the above-presented randomised studies, the American Society for Radiation Oncology has issued recommendations for postoperative whole breast irradiation hypofractionated schemes.[21] It was agreed that: "Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who meet all of these criteria:

- Age $\geq$ 50 years at diagnosis
- Pathologic stage T1-2
- Breast-conserving surgery
- No chemotherapy
- Dose heterogeneity within $\pm$7% limits.

A group of British Columbia experts concluded that hypofractionation should now be considered a new standard for radiation therapy after breast conserving surgery.[22] The Expert Panel at the early breast treatment conference in St. Gallen in 2011 also endorsed accelerated radiotherapy to the whole breast following a breast-conserving surgery as an acceptable procedure, but was divided about the use of this approach in the presence of extensive vascular invasion.[23]

In conclusion, modestly hypofractionated radiotherapy in breast cancer is a valuable alternative to conventional fractionated radiotherapy and existing randomised studies confirm its effectiveness and safety. The follow-up of 5–10 years does not allow, however, the definite exclusion of a possibility of increased risk of late post-radiation reactions pertaining mainly to the heart. These schemes should, therefore, be used with particular caution in young patients with left-sided tumours.

Conflict of interest

None declared.

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