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The role of boost in hypofractionated irradiation after breast-conserving surgery

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ABSTRACT

Adjuvant radiotherapy after surgical treatment constitutes an indispensable part of breast-conserving therapy (BCT) in early breast cancer. The standard dose to the whole breast in BCT is 50 Gy delivered in 2 Gy fractions, with or without a boost dose to the tumour bed. A decreased risk of local recurrence, particularly in younger patients, as a result of a boost dose has been confirmed in a large randomised trial. Recently, mildly hypofractionated schedules of radiotherapy are being used more frequently in BCT. The indications and form of boost radiotherapy in hypofractionated schedules have not been fully determined. This article reviews randomised trials addressing hypofractionated radiotherapy in BCT, and particularly the role of a boost dose. We also present current recommendations in these areas.

Key words: breast cancer, breast conserving therapy, hypofractionated radiotherapy, boost dose

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Introduction

Breast-conserving therapy (BCT) has been the standard of care in patients with early breast cancer since more than 30 years. It involves surgical tumourectomy together with histological evaluation of axillary lymph nodes and adjuvant radiotherapy to the whole breast with the possibility of an additional boost to the tumour bed. Overall survival rates of patients treated with either BCT or radical mastectomy are comparable, and the use of adjuvant radiotherapy after tumourectomy significantly decreases the risk of loco-regional relapse and death due to breast cancer [1–4]. The reduction in local recurrence risk by adding a boost, particularly in younger patients, following the whole breast irradiation with 50 Gy was confirmed in a large randomised trial [3, 4]. The standard dose of breast radiotherapy during BCT was 50 Gy (45–50.4 Gy) delivered in 25 fractions. Recently, shortened schedules of radiotherapy to the whole breast have most commonly been used during BCT, and their efficacy is comparable with conventional fractionation [5–8]. Radiobiological aspects, finances,

and patients' convenience support the use of higher fraction doses.

We presented four randomised clinical trials with hypofractionated radiotherapy to the whole breast as a part of BCT published so far, as well as the role of boost during radiotherapy. We also presented international and the Polish guidelines for this topic.

Randomised trials with hypofractionated radiotherapy to the whole breast

The response to radiotherapy of normal breast tissue as well as breast cancer cells depends on the dose of fraction and sensitivity of cells to the change of fraction dose is described by the α/β ratio [9]. As the α/β ratio lowers so the cells' sensitivity increases with this change. It is currently assumed that the α/β ratio for breast cancer is approximately 4 Gy, and for late-responding tissues (skin, subcutaneous tissue, muscles, and ribs) it is slightly above 3 Gy [10]. Similar radiosensitivity of breast cancer

cells and late-responding tissues supports the possibility of using of higher fraction doses.

Hypofractionated schedules of radiotherapy during BCT were evaluated in four previously published phase III randomised clinical trials: the Canadian Ontario Clinical Oncology Group (OCOG) [5] and three British studies: the Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) [6], Standardisation of Breast Radiotherapy A (START A) [7], and Standardisation of Breast Radiotherapy B (START B) [8] (Table 1). Patients enrolled to these trials had slightly different relapse risk factors. All four trials indicated comparable efficacy of hypofractionated and conventional radiotherapy with the dose of 50 Gy in terms of local and regional recurrences as well as cosmetic outcomes. The risk of local recurrence was significantly higher as compared with other schedules

of fractionation in one arm of the RMH/GOC study only, when the dose of 39 Gy was used in 13 fractions [6]. START B showed significantly lower distant relapse rate and lower general morbidity in patients receiving hypofractionated radiotherapy (40 Gy in 15 fractions) compared with standard radiotherapy (7.5% and 10.5%, and 7.9% and 10.9%, respectively). Good and very good cosmetic effects were achieved by 58–74% of patients in individual trials, and hypofractionated schedules were associated with significantly lower risk of oedema and induration (hardness) of the breast as well as telangiectasia [8].

It should be underlined that the majority (70–79%) of patients participating in the mentioned trials were above the age of 50 years. A stratification according to patients' age was used barely in the Canadian trial that enrolled only 305 patients aged below 50. It was also

Table 1. Phase III clinical trials with hypofractionated radiotherapy in breast conserving therapy (BCT) for early breast cancer

| Study (ref.) | OCOG [5] | RMH/GOC [6] | START A [7] | START B [8] |
|--|---|---|---|---|
| Number of patients | 1234 | 1410 | 2236 | 2215 |
| Recruitment (years) | 1993–1996 | 1986–1998 | 1999–2002 | 1999–2002 |
| Primary/secondary endpoint | Local recurrence/distant relapse, death, cosmetic effect, late toxicity | Late cosmetic effect/local recurrence, distant relapse, second primary cancer | Loco-regional recurrence, late cosmetic effect, quality of life/DFS, OS, second primary cancer, financial aspects | Loco-regional recurrence, late cosmetic effect, quality of life/DFS, OS, second primary cancer, financial aspects |
| Staging | pT1-2N0M0 | pT1-3N0-1M0 | pT1-3aN0-1M0 | pT1-3aN0-1M0 |
| Age ≥ 50 years (%) | 75 | 70 | 77 | 79 |
| Poorly differentiated cancer (G3) | 19% | Not presented | 28% | 23% |
| Follow-up after treatment | 10 years | 9.7 years (median) | 9.3 years (median) | 9.9 years (median) |
| Radiotherapy schedules | | | | |
| — study arm | 42.5 Gy/16 fr/22 days | 42.9 Gy/13 fr/35 days 39 Gy/13 fr/35 days | 41.6 Gy/13 fr/35 days 39 Gy/13 fr/35 days | 40 Gy/15 fr/21 days |
| — control arm | 50 Gy/25 fr/35 days | 50 Gy/25 fr/35 days | 50 Gy/25 fr/35 days | 50 Gy/25 fr/35 days |
| Proportion of patients with boost | — | 75% | 61% | 43% |
| Systemic treatment | | | | |
| — chemotherapy | 11% | 14% | 35% | 22% |
| — hormonotherapy* | 41% | 76% | 79% | 87% |
| Local recurrence | | | | |
| — study arm | 6.2% | 9.6% 14.8% | 3.5% 5.2% | 2.2% |
| — control arm | 6.7% | 12.1% | 3.6% | 3.3% |

*Mainly tamoxifen, only a few patients received aromatase inhibitors

OCOG — Ontario Clinical Oncology Group; RMH/GOC — Royal Marsden Hospital and Gloucestershire Oncology Centre; START — Standardisation of Breast Radiotherapy; DFS — disease-free survival; OS — overall survival

the only trial including patients with no involvement of lymph nodes (pN0). In the remaining trials patients with axillary lymph nodes metastases accounted for 26–60% of the analysed groups. 11–35% patients enrolled to clinical trials received adjuvant chemotherapy. The majority of patients received anthracycline-containing regimens, and in rare cases taxoides (25% and 13% in START A, and 1% and 0.4% in START B trial, respectively). None of the patients was treated with trastuzumab or any other targeted therapy.

In the Canadian study only, a subgroup analysis considering classical clinical factors (age, tumour size, steroid receptors status, histological grade, postoperative use of chemotherapy/hormonotherapy) demonstrated significantly higher risk of local recurrence in patients with high grade cancer (G3) receiving hypofractionated radiotherapy [5]. During 10 years of follow-up 15.6% of patients in this group experienced local recurrence compared to 4.7% of patients irradiated with the use of conventional fractionation [5]. In this study, patients with G3 tumours comprised only 19% of the entire group. START A and B trials, with slightly higher percentages of patients with G3 tumours, did not reveal a such correlation. A high-grade tumour status had no impact on local treatment effectiveness also in the large retrospective study that included patients who underwent shortened schedules of radiotherapy during BCT [11]. Multivariate analysis of data from the Canadian study has revealed that the molecular tumour subtype is the only independent risk factor of local recurrence [12]. After a median follow-up of more than 12 years the 10-year cumulative recurrence risk in patients with luminal A and basal subtype of breast cancer was 4.6%, with luminal B at 7.9%, and HER2-positive breast cancer at 16.9% ($p < 0.01$).

Treatment toxicity was not increased by the higher fraction doses, also in patients receiving chemotherapy or concomitant hormonotherapy with aromatase inhibitors [13, 14]. Hypofractionated radiotherapy in women with breast volume more than 1.5 L was associated with the lower risk of moist desquamation as compared to the standard radiotherapy [15]. In the Canadian study, after 10 years of follow-up there were no differences between arms according to the causes of death, including cardiovascular. Similarly, in comparable groups in the START trials the incidence of ischaemic heart disease, fractures of ribs, and symptomatic pulmonary fibrosis were similar.

During the St. Gallen Conference in 2013 concerned the treatment of early breast cancer the vast majority of experts agreed that shortened schedules of radiotherapy (40 Gy in 15 fractions or 42.5 Gy in 16 fractions) should be the standard of care in the majority of patients, regardless of a boost to the tumour bed [16]. This opinion was supported during the next St. Gallen Conference in 2015 [17].

The role of boost in hypofractionated radiotherapy of breast cancer during BCT

The risk of local recurrence in patients with breast cancer, who underwent BCT accounts for 10% after 10 years, and continues the following years. The majority of recurrences appear in the direct surroundings of the tumour, and cancer cells can be found even at a distance of 4 cm from the primary tumour [18, 19]. This observation supported the increase of irradiation dose to the tumour bed. There are different forms of a boost in clinical practice [20]. The most common type is external beam irradiation after teletherapy to the whole breast. The application of intensity-modulated radiotherapy (IMRT) allows to deliver a boost concomitantly with the whole breast irradiation (so-called concomitant boost) [21–24]. Intra-operative administration of a boost directly after breast tumourectomy shortens total treatment time and decreases the risk of so-called geographical mistake during delineation of the tumour bed. In a retrospective analysis by the International Society of Intraoperative Radiation Therapy (ISIRT) 99.2% of 1109 patients receiving intra-operative electron boost with the dose of 10 Gy had local control (median follow-up exceeded 72 months) [25].

The role of a boost in conventional whole breast irradiation was evaluated in a large clinical trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC), which enrolled 5318 patients with stage T1-2 N0-1 M0 breast cancer [3, 4]. Patients with axillary lymph nodes metastases accounted for only 20% of the entire population, and 30% of the patients received adjuvant systemic treatment. In this study patients after breast conserving surgery and whole-breast irradiation with 50 Gy were randomly assigned to receive boost with the dose of 16 Gy in eight fractions to the tumour bed or to be observed. In the majority of patients (90%) the boost was administered by external electron beam and the remaining patients were boosted with brachytherapy. The volume irradiated during brachytherapy included the tumour bed with the margin of 1.5 or 3 cm (either patients after complete tumourectomy or with extensive intraductal component, respectively). The administration of the boost was associated with the lower rate of local recurrence after 10 years of follow-up (6.2% vs. 10.2%, respectively) [3]. The greatest effect was observed in the group of patients under 50 years of age. Recently published long-term results of this study showed that after a median follow-up of slightly more than 17 years the 20-year risk of local recurrence was 12% in the group of patients receiving boost, as compared to 16.4% in the control group ($p < 0.0001$) [4]. The benefit from the boost administration were noted in all age groups; however,

it was the greatest in the patients under 40 years of age and decreased with increasing age. The use of the boost did not influence the overall survival (59.7% and 61.1%) and the risk of distant relapse (26% and 24.8%), and it was associated with the higher risk of excessive fibrosis of the breast (5.2% in the group of patients receiving boost as compared to 1.8% in the control group; $p < 0.0001$).

In the only one randomised clinical study evaluating the influence of a boost following shortened radiotherapy to the breast a significant decrease in risk of local recurrence after boost administration was also showed, particularly in young patients [26]. This study included 1024 patients with T1-2 N0-1 M0 ductal breast cancer with tumour size up to 3 cm, and the majority of patients (more than 80%) underwent lumpectomy with negative excision margin. The average age was 53 years, and patients at the age above 40 years accounted for 90%. In this study patients after irradiation to the whole breast with the dose of 50 Gy in 20 fractions, corresponding to an equivalent dose of 2 Gy per fraction (EQD2) 55 Gy for α/β ratio 3, were randomly assigned to the group receiving electron boost with the dose of 10 Gy in four fractions or to the group with observation alone. 23% and 20% of patients, respectively, had poorly differentiated cancer, and adjuvant chemotherapy and hormone therapy were used in 21% and 23%, and 31% and 29% in the arm without and with the boost, respectively. After a median follow-up of more than three years the 5-year risk of local recurrence in both groups was 4.5% and 3.6%, respectively ($p < 0.044$). The use of the boost was associated with higher risk of telangiectasia (12.4% and 5.9%), although the cosmetic effect in the patients' assessment, was similar. The long-term results of this study have not been published yet.

Among all of the clinical trials with hypofractionation presented above a boost was not used only in the Canadian study. In the remaining trials a boost was used with electrons, but the percentages of patients with a boost varied between studies. In the RMH/GOC study the dose of the boost was 14 Gy in seven fractions, specified on isodose 90%. In the START studies it was 10 Gy in five fractions, specified on 100%. A meta-analysis of the factors potentially influencing treatment outcomes showed that the use of a boost in patients receiving hypofractionated radiotherapy did not increase the toxicity of treatment, also in the subgroup of patients with high breast volume [8].

There are a few data published to date concerning the application of intra-operative boost in patients with shortened schedules of radiotherapy to the breast. In an Italian study that included 211 patients, the intra-operative electron boost in a single dose of 12 Gy preceding teletherapy to the entire breast with a dose of 37.05 Gy in 13 fractions, acute toxicity grade 1, 2, and 3 was observed in 67.6%, 28.6% and 3.8%

of patients, respectively [27]. Grade 1–2 late toxicity occurred in 98.2% patients, and grade 3–4 was seen in two cases. The authors did not present the data about local recurrence. In 2011 started the HIOB (Hypofractionated Whole-Breast Irradiation following Intra-Operative Electron Boost) study in which patients receive intra-operative boost with electron beam in a single dose of 10 Gy followed by teletherapy to the whole breast with a dose of 40.5 Gy in 15 fractions [28]. After a median follow-up of 13 months there were neither local recurrences nor grade 3 complications.

Experts' recommendations

According to the American Society for Radiation Oncology (ASTRO) guidelines, the use of hypofractionated radiotherapy during BCT could be considered in patients at the age of 50 years or older, with tumour size of less than 5 cm, without metastases to axillary lymph nodes, and chemotherapy-naïve [29]. The ASTRO Expert Panel did not agree to a common statement regarding indications for a boost in patients receiving hypofractionated radiotherapy to the whole breast. They stated that these indications are independent of the fractionation schedule of external irradiation to the whole breast. The National Comprehensive Cancer Network (NCCN) experts recommend a boost with the dose of 10–16 Gy with 2–2.5 Gy per fraction in the high-risk group of patients, e.g. at age under 50 years and with G3 tumours [30]. According to the British National Institute for Health and Care Excellence (NICE) recommendations, a boost following radiotherapy with the dose of 40 Gy in 15 fractions is indicated in patients with increased risk of local relapse; however, neither the dose nor the fractionation schedule was defined [31]. Similarly, experts employed in the European Society of Medical Oncology (ESMO) recommend a boost in patients with unfavourable factors of local recurrence risk, e.g. age under 50 years, G3 tumour, extensive DCIS, vascular invasion, as well as positive resection margin [32]. The Polish Society of Clinical Oncology recommends administration of a boost with the dose of 10–15 Gy to the tumour bed in the majority of patients receiving conventional (50 Gy in 25 fractions) as well as hypofractionated radiotherapy (40 Gy in 15 fractions; EQD2 45 Gy for α/β ratio 3, which is currently the preferred method) [33].

Summary

Implementation of a boost to the tumour bed in addition to conventional radiotherapy to the whole breast is associated with a significant decrease of local recurrence risk, particularly in younger patients.

Nevertheless, this approach does not influence overall survival and increases breast fibrosis. The role of boost in hypofractionated irradiation to the whole breast during BCT is not fully determined. To-date this topic has not been evaluated in a randomised clinical study with a large group of patients, with adequately long follow-up, and currently used schedules, in particular 40 Gy in 15 fractions. According to experts' opinions, in daily clinical practice a boost should be considered in patients with higher local recurrence risk, particularly at age below 50 years and with G3 tumours, regardless of the whole breast fractionation schedules.

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