REVIEW

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BREAST CANCER RADIOTHERAPY - CHANGES IN FRACTIONATION SCHEMES THROUGH DECADES

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Summary

Traditionally, as a standard dose fractionation schedule, adjuvant radiotherapy for breast cancer has been performed using prescribed doses of 46–50 Gy divided into daily fractions of 1.8–2 Gy. Overall, radiotherapy treatment took 5 weeks. In the 1990s, schedules using higher daily doses (2.5–3 Gy), a smaller number of fractions (hypofractionation), and a reduced overall prescribed dose started in the context of clinical trials. First results revealed an equivalent cosmetic effect of hypofractionated protocols compared to standard fractionation, and after longer follow-up, hypofractionation was connected with better control of the disease. Hypofractionation started to be considered the new treatment standard. Results of newer clinical trials confirm the efficacy and safety of adjuvant breast cancer radiotherapy lasting 5 working days using daily fractions of 5.2 Gy in certain subgroups of breast cancer patients.

KEYWORDS: *breast cancer; adjuvant radiotherapy; hypofractionation*

INTRODUCTION

Breast cancer adjuvant radiotherapy reduces the risk of local recurrence and distant metastases and prolongs the overall survival (OS) of patients. The abovementioned was confirmed in several meta-analyses exploring the data of thousands of patients included in a number of randomized clinical trials(1,2). Adjuvant breast cancer radiotherapy is still an area of investigation, as we reported in our previous review papers(3,4). Different radiotherapy techniques, different target volumes (partial breast irradiation *vs.* whole breast irradiation), and different fractionation schedules are being investigated. In the majority of clinical trials, radiotherapy was performed using standard fractionation schemes: daily doses of 2 Gy, a total dose of 50 Gy, and an overall treatment time of five weeks.

The rationale for that scheme comes from radiobiology, which assumes that the α/β ratio of tumors is around 10 and the α/β ratio of healthy tissue is around 3, concluding that healthy tissues are sensitive to fraction size. Therefore, radiation with smaller daily doses is performed to enable the protection of healthy tissues. However, radiobiology findings suggest that the α/β ratio of breast cancer is smaller and is assumed to be around 3–4, being closer to the α/β ratio of surrounding healthy tissues. That makes breast cancer as sensitive to fraction size as healthy tissues, and the use of smaller fraction doses protects both breast cancer and healthy tissues. This knowledge about radiobiology enabled the introduction of the idea of hypofractionated radiotherapy using daily doses higher than 2 Gy. The key questions were how much the daily dose can be increased and how much the overall prescribed dose should

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be decreased in order to maintain radiation's efficacy and safety(5).

MODERATE HYPOFRACTIONATION

In 1990s clinical trials Ontario, START A and START B were performed, comparing moderate hypofractionation with daily doses of 2.7–3 Gy and standard fractionation schemes.

The Ontario trial included patients with breast cancer who underwent a tumorectomy and had negative axillary lymph nodes. The clinical target volume was breast only, and the experimental regimen was 16x2.66 Gy (42.56 Gy). After 10 years of follow-up, local relapse rates were 6.7% in the group with standard fractionation and 6.2% in the group treated with a hypofractionated regimen. A good or excellent cosmetic outcome has been observed in 71% of patients upon standard fractionation and in 70% of patients receiving 16x2.66 Gy. In conclusion, hypofractionation was proven to be non-inferior to standard fractionation(6).

The START A trial randomized patients with breast cancer stage pT1-3 N0-1 in the following treatment groups according to radiation schedules: 25x2 Gy (50 Gy), 13x3 Gy (39 Gy), or 13x3.2 Gy (41.6 Gy). The overall treatment time for all three regimens was five weeks. 85% of patients underwent tumorectomy; 35% of patients received adjuvant chemotherapy, and 79% of patients received tamoxifen. In 14% of patients, the target volume included regional lymph nodes, and 61% of patients also received a boost dose on the tumor bed. Breast induration, breast swelling, and telangiectasia occurred significantly less often in patients receiving 39 Gy compared to patients receiving 50 Gy. No notably different cosmetic effect has been observed between the doses of 41.5 and 50 Gy. Efficacy and cosmetic results after 5-year follow-up confirmed the hypothesis that both breast tissue and adjacent health tissue are equally sensitive to fraction size(7).

Patients included in the START B trial were given either 25x2 Gy during five weeks or 15x2.67 Gy (40 Gy) during three weeks. 92% of patients underwent tumorectomy; 22% of patients received adjuvant chemotherapy, and 87% of patients received tamoxifen. In 7% of patients, the target volume included regional lymph nodes, and 43% of patients also received a boost dose on the tumor bed. After a median follow-up of 9.9 years, no significant difference in the rate of local relapse has been observed; it has occurred in 4.3% of patients receiving 40 Gy and in 5.5% of patients receiving 50 Gy. Patients receiving 40 Gy had significantly less breast shrinkage, breast swelling, and telangiectasia(8).

Upon publication of these results, the gradual introduction of hypofractionated protocols in clinical practice started. Implementation was significantly accelerated with the COVID-19 pandemic in early 2020, when shorter treatment times were desirable.

RADIOTHERAPY USING DAILY FRACTIONS HIGHER THAN 5 Gy

Patients older than 50 years with breast cancer sized 3 cm or more and negative axillary lymph nodes were included in the FAST trial. The clinical target volume was breast-only. Boost doses on tumor beds were not allowed. Patients were given either 25x2 Gy, 5x6 Gy (once weekly, total dose of 30 Gy), or 5.7 Gy (once weekly, total dose of 28.5 Gy). Primary outcome was change in breast appearance on photography taken after 2 and 5 years, and secondary outcomes were local disease control and physician assessment of normal tissue effects (NTE), including breast shrinking, breast indurations, telangiectasias, or breast oedema (9). After 10 years of follow-up, no significant difference in NTE between the 5x5.7 Gy and 25x2 Gy protocols was observed. However, NTEs were more frequent with the 5x6 Gy regimen. According to the trial's results, 5x5.7 Gy applied once a week is radiobiologically comparable with standard fractionation in terms of normal tissue effects. Local recurrence has been observed in 11 patients: in 3 patients that received 50 Gy, in 4 patients that received 30 Gy, and in 4 patients that were given 28.5 Gy. Ninety-six patients died: 30 in the group that received 50 Gy and 33 in both groups, the 30 and 28.5 Gy(9).

The FAST forward trial evaluated irradiation with daily doses higher than 5 Gy compared to the 15x2.67 Gy regimen, which has become standard(10). The primary outcome was local disease recurrence. The trial included 4100 patients with

Table 1.

Summary of data from clinical trials

Clinical trial (reference)	Investigated schedule (overall dose)	Control schedule	Overall treatment time		Therapeutic effect	Cosmetic effect
			Investigated schedule/s	Control schedule		
Ontario (6)	16x 2.66 Gy (42.5 Gy)	25x 2 Gy (50 Gy)	22 days	35 days	No difference	No difference
START A (7)	13x 3 Gy (39 Gy) and 13 x 3.2 Gy (41.6 Gy)	25x 2 Gy (50 Gy)	5 weeks, both schedules	5 weeks	No difference between three schedules	Better for 13x3 Gy, no difference between 13x3.2 Gy and 25x2 Gy
START B (8)	15x 2.67 Gy (40 Gy)	25x 2 Gy (50 Gy)	3 weeks	5 weeks	No difference	Better for 15x2.67 Gy
FAST (9)	5x 6 Gy once weekly (30 Gy) and 5x 5.7 Gy once weekly (28.5 Gy)	25x 2 Gy (50 Gy)	5 weeks, both schedules	5 weeks	No difference between three schedules	Worse for 5x6 Gy, no difference between 5x5.7 Gy and 25x2 Gy
FAST forward (10)	5 x 5.2 Gy (26 Gy) and 5 x 5.4 Gy (27 Gy)	15 x 2.67 Gy (40 Gy)	5 working days	3 weeks	No difference between three schedules	Worse for 5x5.4 Gy, no difference between 5x5.2 Gy and 15x2.67 Gy

breast cancer stage pT1-3N0-1. Patients in experimental arms received either 5x5.2 Gy (26 Gy) or 5x5.4 Gy (27 Gy). The target volume consisted of the breast or thoracic wall. Lymph node irradiation was not allowed. The median age of the patients was 60 years. About 15% of patients were younger than 50 years old. There was no difference between left and right breast cancer frequencies. Most of the patients underwent a lumpectomy. About 6% of patients in each arm had a mastectomy. Mastectomy with reconstruction was performed on less than 1% of the patients.

In about 80% of patients in each trial group, lymph nodes were negative for the presence of tumor (pN0 stage of the disease). The median tumor size was 16 mm. About 90% of tumors were ER-positive. About 10% of patients in each group had HER2-positive tumors. A quarter of patients received adjuvant chemotherapy. Neoadjuvant chemotherapy was given to 3–4% of patients. More than 95% of patients received hormonal therapy. A boost dose on the tumor bed was given to 25% of patients, with the most frequent regimens being 5x2 Gy or 8x2 Gy. In conclusion, the majority of patients had low-risk disease. However, even in patients with a higher risk of tumor recurrence, no difference in efficacy between the fractionation schemes has been observed.

Acute side effects were less frequent with shorter radiation schemes; they appeared earlier during the irradiation course and resolved sooner. After 5 years of follow-up, no statistically significant difference between the 3 fractionation schemes has been observed in terms of local disease recurrence, distant relapse, or death of any cause.

There was no significant difference between 40 Gy in 15 fractions and 26 Gy in 5 fractions regarding cosmetic effect. However, in patients receiving 27 Gy in 5 daily fractions of 5.4 Gy, breast shrinking, breast induration, tumor bed induration, and breast/thoracic wall swelling occurred significantly more often. The aforementioned is indicative of the very narrow therapeutic window of this approach. Namely, an absolute difference in fraction size of only 4% resulted in a significant difference in the frequency of late side effects(10).

In terms of efficacy and safety, the 5x5.2 Gy protocol proved to be non-inferior to the 15x2.67 Gy protocol, which is the current standard. Publication of this trial in early 2020 correlated with the COVID-19 pandemic, which accelerated the implementation of the 5x5.2 regimen in clinical practice. That enabled a treatment duration of 5 days only, compared to 15, reducing the number of visits to radiotherapy units and also reducing the risk of COVID-19 infection in patients and staff(11).

The final results of the FAST forward nodal trial are awaited. That is a sub-study of the FAST forward trial that is exploring the efficacy and safety of 5x5.2 Gy and 5x5.4 Gy compared to 15x2.67 Gy in 470 patients with breast cancer undergoing irradiation of both breast and lymph nodes. After 3 years of follow-up, the frequency of arm swelling was 10% in the group of patients receiving 15x2.67 Gy, 7% in the group receiving 5x5.2 Gy, and 13% in the patient group receiving 5x5.4 Gy. After 2 years of follow-up, lymphoedema was observed in 8% of patients receiving 40 Gy, 12% of patients receiving 26 Gy, and 11% of patients receiving 27 Gy(12).

Clinical trial data are summarized in Table 1.

CONCLUSION

Adjuvant radiotherapy for breast cancer using a daily dose higher than 2 Gy is strongly supported by radiobiological data. Implementation of radiation schemes lasting 15 working days instead of 25 working days, once their non-inferiority has been proven, has made radiotherapy simpler and more convenient for patients. It has also increased the availability of radiotherapy.

Adjuvant radiotherapy given in only five working days contributes even more to both convenience and treatment availability. However, so far, we have just the data confirming its efficacy and safety in patients with low-risk breast cancer who underwent lumpectomy and in whom no lymph node irradiation is necessary. It should be mentioned that these procedures have a very narrow therapeutic window. A quality control system has to be established prior to its implementation in everyday practice.

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Sažetak

RADIOTERAPIJA RAKA DOJKE - PROMJENE U SHEMAMA FRAKCIONIRANJA KROZ DESETLJEĆA

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Tradicionalno se, kao standardna shema frakcioniranja, adjuvantna radioterapija raka dojke provodila dozom od 46 do 50 Gy podijeljenom u dnevne frakcije od 1,8 do 2 Gy. Ukupno trajanje radioterapije iznosilo je 5 tjedana. 1990-ih se unutar kliničkih studija započelo sa zračenjem većim dnevnim dozama (2,5 do 3 Gy), uz smanjenje broja frakcija zračenja (hipofrakcioniranje) te smanjenjem ukupne doze zračenja. Prvi rezultati su pokazali ekvivalentan kozmetski učinak hipofrakcioniranog zračenja u odnosu na standardno frakcioniranje, a nakon duljeg praćenja pokazana je i bolja kontrola bolesti uz hipofrakcionirano zračenje. Hipofrakcioniranje je potom postupno postalo standard liječenja. Rezultati novijih kliničkih studija potvrđuju učinovitost i sigurnost adjuvantne radioterapije raka dojke u trajanju od 5 radnih dana dnevnim dozama od 5,2 Gy za određene podskupine bolesnica.

KLJUČNE RIJEČI: *rak dojke; adjuvantna radioterapija; hipofrakcionirano zračenje*