

Emerging Role of Hypofractionated Radiotherapy with Simultaneous Integrated Boost in Modern Radiotherapy of Breast Cancer

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Keywords

Breast cancer · Hypofractionation · Radiotherapy

Summary

Hypofractionated radiotherapy for breast cancer is becoming increasingly important. The scientific background of this development as well as the introduction of the simultaneous integrated boost to the primary tumor region in this context are discussed here.

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Introduction

Current standard whole breast irradiation (WBI) in breast-conserving concepts consists of a total dose (TD) of 50 Gy delivered in 25 daily fractions over a period of approximately 35 days. Alternatively, 50.4 Gy are applied using a daily dose of 1.8 Gy. An additional boost to the primary tumor region at a TD of 12–16 Gy is indicated in the majority of patients, resulting in an overall treatment period of up to 47 days [1–4]. Impressive data of more than 10,000 women in 17 randomized trials with a 15-year follow-up confirm a risk reduction of ipsilateral breast recurrences by a factor of at least 3–4 [5]. This translates into a risk reduction of about 3% for breast cancer deaths in node-negative patients and about 8% in node-positive patients. Moreover, there is plenty of experience concerning treatment-related acute and late toxicity accompanied by excellent cosmetic results [1].

Is There a Rationale for Changing the Established Fractionation Regimens in the Near Future?

Malignant tumor cells and the surrounding healthy tissues differ with regard to their radiation sensitivity. The cells of normal healthy tissues are able to recover from sublethal radiation damage, whereas tumor cells show limited repair. These differences have been investigated intensively and have resulted in distinctive radiotherapeutic treatment regimens in which the daily fraction dose, TD, and adherent treatment schedules have been established [6]. Dose effectiveness in modern radiotherapy is described with the linear-quadratic model (α/β model), predicting radiobiologically equivalent (isoeffective) doses. The α/β value of the linear-quadratic model describes the sensitivity of healthy tissue and tumor cells depending on fractionation and TD. The fractionation sensitivity of any tissue is characterized by its α/β value; the α/β value is a mathematically calculated term derived from the dose-effect curve of the tissue, given in units of Gray (Gy). Generally, the α/β values of healthy tissues for late reactions are low (in the range of 2–3 Gy). In contrast, tumors and early reacting tissues have much higher α/β values in the range of 10 Gy or more [7]. In order to protect the healthy tissue from late radiation effects, irradiation should therefore be administered at low single doses of 1.2–2 Gy.

The linear-quadratic model has been confirmed in a variety of randomized studies, and it is a proven radiobiological fact that the greatest therapeutic window with regard to both local tumor control and late tissue effects is achieved if low doses per fraction are administered. However, the dogma that all tumors have high α/β values has been challenged over the past years. Over the past decade, growing evidence has accumulated that at least some cancers may have exceptionally low α/β values. This has so far been proven

for prostate cancer with an α/β value of about 1.5 Gy. If the α/β value of the tumor is below the α/β value of late-reacting surrounding tissue, treatment with higher doses per fraction is, from a theoretical point of view, advantageous. Therefore, hypofractionation has a well-defined theoretical basis in prostate cancer, and the results of completed and ongoing randomized studies support the notion that at least moderate hypofractionation is feasible in prostate cancer. Moreover, recent data suggest that prostate cancer is probably not the only exception and that some form of hypofractionation may be feasible in certain other cancer entities [8].

Why Was Hypofractionation Introduced in Breast Cancer?

The hypofractionation studies in breast cancer were started at a time when the data on low α/β values in tumors were not yet available. The aim of these breast cancer studies was a more pragmatic one, mainly to decrease the number of visits to the radiotherapy department and to shorten overall treatment time, thereby making adjuvant radiotherapy more convenient for patients. These studies were conducted in countries with centralized radiotherapy structures and long travel distances. It was assumed that a relevant subgroup of patients who were candidates for breast-conserving treatment did in fact choose mastectomy as primary treatment due to the inability to withstand a 6–8-week course of radiotherapy. Therefore, studies were started in the 1990s evaluating an overall shortened treatment time to increase acceptance of adjuvant radiotherapy and reduce costs.

Surprisingly, the latest data from these studies assume an α/β value for breast cancer of 3–3.5 Gy which is similar to that of the surrounding normal healthy tissue [9, 10]. This would mean that fraction size can be changed within a relatively broad range without negative impact on tumor control and late radiation sequelae. Although not expected at the beginning of these trials, the data form a stable theoretical basis for the use of moderate hypofractionation in breast cancer.

Which Studies Support the Effectiveness and Safety of Hypofractionation in Breast Cancer?

So far, 4 randomized trials have examined a hypofractionated schedule as compared to the standard 5-week fractionation schedule for adjuvant WBI.

The UK START pilot trial assessed dose schedules using either 3 Gy/fraction up to a TD of 39 Gy, or 3.3 Gy/fraction with a TD of 42.9 Gy (13 fractions) compared to the standard regimen of 2 Gy/fraction and a TD of 50 Gy [11, 12]. The following START-A randomized 2,236 patients to 1 of 3 treatment arms: 3 Gy/fraction (every second day) to a TD of 39 Gy, 3.2 Gy to a TD of 41.6 Gy, and standard normofractionation [13]. START-B compared the standard schedule with a daily hypofractionated schedule using 40 Gy with a fraction size of 2.66 Gy [14]. It should be noted that in both

START trials 61% of all patients finally received a sequential boost with 10 Gy (2 Gy/fraction). The boost was always administered after hypofractionated breast irradiation.

After 10-years, all treatment concepts showed equivalent outcomes for hypofractionated radiotherapy compared to the traditional schedule, favoring the use of 40 Gy in 15 fractions with a low local recurrence rate of 5.6% [9]. All 3 trials included women with operable T1–3 N0–1 M0 invasive breast cancer and mostly small or medium breast size.

Another trial reproduced these results independently: The Ontario Clinical Oncology Group randomly assigned 1,234 patients to standard WBI or to 42.5 Gy in 16 fractions within 22 days [15]. 1,234 women with invasive breast cancer (< 5 cm, no T3–4, negative margins, node-negative) and without multicentric disease, large breast size, and bilateral breast cancer were included. After 10 years, the risk of recurrence was 6.7% in the standard group and 6.2% in the hypofractionated group. Cosmetic outcome was reported as good or excellent with 71.3% in the standard group and 69.8% in the hypofractionated group. These studies built the clinical basis for an α/β value of breast cancer in the range of 3–3.5 Gy, similar to that of the surrounding healthy tissues (table 1).

Ongoing Controversies Concerning the Hypofractionated Treatment of Breast Cancer

High-Risk Features

The majority of patients in the above mentioned trials had estrogen receptor-positive and HER2-negative tumors. It is well known that patients with high-grade tumors have a higher risk of local recurrence after radiation. It is therefore questionable whether hypofractionated WBI is suitable for all patients [1]. The 10-year update of the START trials including 1,272 women with grade 3 breast cancer showed no difference between hypo- and normofractionation in terms of local recurrence in this group [9], whereas the Ontario trial documented a significantly higher local failure rate in the hypofractionation arm [15], which was somehow considered a statistical fluke. In contrast to the Ontario trial, a sequential boost to the primary tumor site was allowed in the START trials, which may also be a possible explanation for the different treatment results in the high-risk group. Recently, the Ontario group published the results of their analysis of tumor factors predictive for response to hypofractionated versus normofractionated radiotherapy. They stated that tumor grade, histological subtype, and hypoxia did not predict for hypofractionation response, proving that hypofractionation can be safely administered in all breast cancer patients [16].

Young Age

The 2011 ASTRO consensus did not recommend hypofractionation in women < 50 years of age [17] as younger women have a higher risk of local recurrence compared with older patients, and only few younger patients were randomized in those studies at this

Table 1. Study data on hypofractionation in breast cancer treatment [25]

10-year event	RMH/GOC			START A			START B			Canadian		
	Arm, Gy	Result, %	p	Arm, Gy	Result, %	p	Arm, Gy	Result, %	p	Arm, Gy	Result, %	p
Ipsilateral breast tumor relapse	50	12.1	0.027	50	6.7	NS	50	3.8	NS	50	7.4	NS
	42.9	9.6		41.6	5.6		50	5.2		42.5	7.5	
Distant relapse	39	14.8		39	8.1							
	NR			50	14.7	NS	50	16.0	0.014	NR		
All-cause mortality				41.6	16.8		40	12.3				
	NR			39	18.0							
Cosmesis, selected end points				50	19.8	NS	50	19.2	0.042	50	15.6	NS
				41.6	18.4		40	15.9		42.5	15.4	
Toxicity, selected end points				39	20.3							
				telangiectasia						excellent-good		
Toxicity, selected end points	50	18.1	0.065	50	7.2	–	50	5.8	0.032	42.5	69.8	NS
	42.9	18.0		41.6	7.1	0.99	40	4.2		50	71.3	
Toxicity, selected end points	39	12.0		39	3.0	0.003						
				breast edema								
Toxicity, selected end points	50	13.8	0.004	50	13.5	–	50	9.0	0.001			
	42.9	21.5		41.6	11.8	0.24	40	5.1				
Toxicity, selected end points	39	11.5		39	7.3	0.001						
				ischemic heart disease						grade 3 skin		
Toxicity, selected end points				50	1.9		50	2.1		42.5	2.7	NS
				41.6	1.5		40	1.5		50	2.5	
Toxicity, selected end points				39	1.1							
				symptomatic lung fibrosis						grade 3 subcutaneous tissue		
Toxicity, selected end points				50	1.2		50	1.7		42.5	3.6	NS
				41.6	1.1		40	1.7		50	2.5	
Toxicity, selected end points				39	1.0							

NR = Not reported; NS = not significant; RMH/GOC = Royal Marsden Hospital/Gloucester Oncology Center; START A/B = Standardization of Breast Radiotherapy Trial A/B.

time. However, of the 4 major trials, only the Ontario study stratified by age and detected no significant differences in ipsilateral tumor recurrence, although no boost was applied [15]. The 10-year update of the START trials included 1,398 women < 50 years of age and demonstrated the effectiveness of hypofractionation in younger patients, even showing a trend towards an improved effect of hypofractionation in this cohort [9].

Regional Nodal Irradiation

There is only limited experience with hypofractionated regional irradiation due to the small number of women with regional radiotherapy recruited in the reported studies. The safety of the investigated fractionation schemes in view of brachial plexopathy is still

under investigation. In the START trials, the only reported plexopathy occurred with the 41.6 Gy fractionation schedule [9].

Cardiotoxicity

Late cardiac side effects of hypofractionated radiotherapy have only been evaluated to a maximum follow-up of 10 years. Since most radiotherapy-associated cardiac side effects occur after 15 years or more, currently available results must be assessed with caution, especially in women with a long life expectancy and an unhealthy lifestyle. However, no significant cardiotoxicity has been observed in modern normofractionated radiotherapy for breast cancer with current radiotherapy techniques making it now safer than in the past [18]. Recently, Chan et al. [19] reported a 15-year

follow-up of cardiac injury, comparing hypofractionation versus normofractionation in left-sided early-stage breast cancer patients. In 5,334 patients receiving breast or chest wall irradiation, no statistically significant difference in cardiac mortality was detected.

Implementation of a Simultaneous Integrated Boost in Hypofractionated Radiotherapy of Breast Cancer

A boost to the primary tumor site improves local control in all age groups. In R0-resected patients, the local recurrence rate is reduced by 4–6.2% within 10 years [20]. To maintain this important treatment effect in hypofractionated WBI without altering the overall shortened treatment time, 4 studies have been conducted so far in which a simultaneous integrated boost (SIB) was introduced. Scorsetti et al. [21] enrolled 50 women to be treated with an SIB-VMAT (volumetric-modulated arc therapy) approach, applying doses of 40.5 Gy to the whole breast and 48 Gy to the primary tumor bed in 15 fractions. They observed 1 grade 3 and 32 grade 1 skin toxicities, with the latter resolving within 3 weeks of treatment completion. No significant changes in cosmetic outcome were observed 3 and 6 months after radiotherapy. Another protocol delivering 40.5 Gy to the breast and 45 Gy as an SIB in 15 fractions over 19 days was investigated by Chada et al. [22]. The 5-year disease-free survival was 97%, based on a median follow-up of 3.5 years. Acute and late toxicity were low without any grade 3 or 4 skin toxicity after 2 years. A randomized trial by van Parijs et al. [23] compared conventional radiotherapy to hypofractionated tomotherapy with 2.8 Gy/fraction to the whole breast and an SIB of 0.6 Gy/fraction in 15 fractions. The primary purpose of this study was to evaluate whether tomotherapy reduces heart and lung toxicity in this setting. They demonstrated a slight trend in favor of tomotherapy, stating that short-course treatment with SIB is feasible with no severe toxicity. The largest prospective investigation so far, a German multicenter phase II study, treated 141 patients with 40 Gy to the whole breast and an SIB of 48 Gy in 16 fractions. The regimen was well tolerated with no grade 3 or 4 adverse events [24]. According to this trial, hypofractionation with SIB seems to be safe and feasible with unchanged quality of life, even though long-term follow-

up is still missing. The new prospective multicenter 2-arm phase III German HYPOSIB trial will provide data on hypofractionated irradiation with SIB with an overall very much shortened treatment time compared to standard radiotherapy. This non-inferiority trial is designed to recruit 1,162 patients in each arm. The study will randomize all patients with histologically confirmed unilateral invasive breast cancer after breast-conserving surgery with an indication for a boost.

Conclusion

Current clinical results of hypofractionated WBI support its introduction into clinical routine in the near future. Hypofractionation offers an alternative to standard fractionation regimens at least in a subset of patients. There is now a clear radiobiological basis for the use of moderate hypofractionation with a decrease in the number of fractions by about 50%; extreme hypofractionation (e.g. less than 10 fractions) or extremely reduced treatment times (e.g. less than 3 weeks) should, however, be restricted to clinical trials. Moreover, there is limited data on potentially different effects of hypofractionation in subgroups, and it is unclear whether the effects of standard fractionation and hypofractionation are really identical in all tumor subtypes. Delivery of a tumor bed boost in the form of an SIB seems to be safe, feasible, and effective while further reducing the overall treatment time without compromising established excellent overall results. The new HYPOSIB trial will clarify the question of simultaneous boost application and hypofractionation in breast cancer on the basis of a high number of patients. All German radiotherapy facilities are encouraged to participate in the HYPOSIB trial as the study subject is a highly relevant key issue in the development of modern radiotherapy of breast cancer in Germany.

Disclosure Statement

All authors declare no conflict of interests.

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