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ORIGINAL ARTICLE

The potential role of hypofractionated accelerated radiotherapy to cosmesis for stage I-II breast carcinoma: a prospective study

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Summary

Purpose: *To evaluate the acute and late effects as well as the cosmetic results of an accelerated hypofractionated radiotherapeutic schedule in breast cancer irradiation.*

Methods: *Fifty-four patients with stage I-II invasive breast cancer receiving postoperative radiotherapy (RT) after lumpectomy and axillary node dissection were studied. All patients received RT with 6 MV linear accelerator with a total tumor dose of 53 Gy (Equivalent dose-EQD2- 60 Gy), 2.65 Gy per fraction, in 20 fractions. Acute and late effects as well as cosmetic results were assessed using the European Organization for Research and Treatment of Cancer and Radiation Therapy Oncology Group (EORTC-RTOG) Cosmetic Rating System.*

Results: *By the end of RT 66.7% of the patients developed no toxicity, while 24.1% showed grade 1 and 9.3% grade 2 acute skin toxicity. After 6 months 90.7% of women showed grade 0 late toxicity while 100% of women recovered completely 2 years after RT. There was no local or distant recurrence during 5-year follow up.*

Conclusion: *The accelerated hypofractionated schedule appears to be an acceptable alternative to the traditional longer RT schedules, without late toxicity.*

Key words: accelerated irradiation, breast cancer, cosmetic results, stage I-II

Introduction

Breast conserving surgery is commonly recommended as the primary treatment for early breast cancer. Randomized controlled trials have demonstrated that breast irradiation after lumpectomy reduces the local recurrence rates and increases the likelihood of breast conservation [1-3]. Although the role of breast irradiation is widely accepted, there is no uniformly accepted optimal fractionation schedule [4,5]. Several different RT schedules have been used in randomized trials that established the efficacy of breast irradiation. Studies have been reported with acceptable local control rates and minimal acute and late morbidity [6-8].

The aim of the present study was to evaluate the effectiveness of hypofractionated accelerated RT and the related cosmesis to the irradiated breast. The primary endpoint was the time to relapse and the second endpoint was the assessment of acute and late skin toxicity.

Methods

Patient and tumor characteristics

In this prospective study included were women with stage I-II invasive carcinoma of the breast after lumpectomy and axillary lymph node dissection. If adjuvant chemotherapy was indicated, it had to be completed before the start of RT.

The exclusion criteria were: mastectomy, presence of Paget's disease, presence of autoimmune conditions, previous diagnosis of cancer of the thorax, previous diagnosis of breast cancer and operation with bad overall cosmetic outcome, diagnosis of previous or concomitant malignancies or skin disease, breast too large to permit satisfactory RT, presence of psychiatric or addictive disorders, and patients enrolled in another clinical trial. All patients signed informed consent for study inclusion.

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Radiation therapy schedule

Patients were treated with a 6 MV linear accelerator. All patients received RT with a total prescription dose of 53 Gy (EQD2 60 Gy), 2.65 Gy per fraction, in 20 fractions, over 25 days. No attempt was made to treat peripheral lymphatics. RT was delivered daily, from Monday to Friday.

CT scans images (10 mm slice thickness) were acquired and transferred to the treatment planning system. Patients were treated in supine position with both arms raised above the shoulder and immobilized. The treatment volume was irradiated by two opposed tangential fields. The medial border was located at the midsternal line. The lateral border was at the midaxillary line to include the breast with a 2 cm margin and to limit the amount of lung at the central plane to < 2.5 cm. The superior border was located at the horizontal line drawn through the supersternal notch, and the inferior border was located at a horizontal line 1-2 cm below the inframammary fold. Wedge compensation was used to ensure a uniform dose distribution throughout the target volume. The dose was prescribed at a point midway along the central plane, two thirds of the distance from the skin to the base of the tangent fields. The dose range was kept between 95 and 107% of the prescribed dose. Portal films were obtained in the treatment position with therapeutic beam to confirm adequate coverage.

Systemic therapy

During the time period of this study, only patients with axillary nodal metastases received adjuvant systemic treatment. Premenopausal patients received 6 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy i.v. every 21 days, while postmenopausal patients received tamoxifen 20 mg daily for 5 years.

Follow up and outcome measures

After completion of RT, patients were assessed every month for the first 3 months and then every 6 months. At each follow up visit, they provided a medical history and underwent physical examination. Cosmetic outcome was assessed at 6, 12, 18 and 24 months after baseline. The outcome measures were breast cosmesis, late radiation toxicity and disease recurrence. Clinical and laboratory exams that suggested recurrent disease were fully investigated. The criterion for local disease recurrence was recurrent tumor within the treated field.

The cosmetic outcome was assessed according to the EORTC-RTOG grading system [9, 10] (Tables 1, 2).

The responsible doctor compared the treated breast with the untreated one and graded a number of items including breast size and shape, location and shape of the areola, skin color, breast edema, appearance of the surgical scar, telangiectasia and the overall cosmetic result.

Data analysis

The patient medical records were reviewed and information was collected concerning patient's age, tumor size, nodal status, distance between resection

Table 1. RTOG/EORTC acute radiation toxicity scoring system

Organ/tissue (Grade)	0	1	2	3	4	5
Skin	No change over baseline	Follicular, faint or dull erythema/epilation/ dry desquamation/ decreased sweating	Tender or bright erythema; patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds; pitting edema	Ulceration; hemorrhage; necrosis	Death

Table 2. RTOG/EORTC late radiation toxicity scoring system

Organ/tissue (Grade)	0	1	2	3	4	5
Skin	None	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration	Death
Subcutaneous tissue	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis	Death

margin and tumor, and presence of multifocal disease in the resected material. Relapse free interval (RFI) of the treated breast was assessed using the Kaplan-Meier method. The area under curve (AUC) was also assessed in terms of the mean grading value for skin toxicity.

During treatment, the maximal monitored RTOG toxicity grade for each patient was recorded as the radiation-induced acute toxicity score. AUC assessment for the skin toxicity was carried out according to the trapezoid function:

where, x is the weeks of treatment after baseline, *y* is the toxicity grade according to the RTOG criteria, and

$$AUC = \sum_{i=1}^{n} \frac{(x_n - x_{n-1}) \cdot (y_{n-1} + y_n)}{2}$$

n is a certain time point of the measurements. AUC represents the area under the curve for the time course of dermatitis during the whole treatment schedule and is calculated as 1.6418.

The statistical correlation between the acute and late skin toxicity was assessed with the Fisher's exact test and the Spearman's correlation test. Statistical analysis was performed with the SPSS version 10 software (Chicago, IL).

Results

Tumor characteristics

Baseline tumor characteristics are shown in Table 3.

Table 3. Tumor baseline characteristics

Characteristics	*N*	*%*
Tumor size (cm)		
0-1.9	39	72.2
2-4.9	15	27.8
Lymph nodes		
Negative	44	81.5
Positive	10	18.5
TNM stage		
I	44	81.5
II	10	18.5

Acute radiation toxicity

By the end of RT 66.7% of the patients showed no skin toxicity, while 24.1% showed grade 1 and 9.3% grade 2 toxicity. Three months after the end of RT, 90.7% of patients displayed grade 0 toxicity (Table 4). The gradual restoration of the irradiated breast to normal condition is shown in Figures 1, 2 and Table 4. The recovery from the acute skin radiation toxicity is shown in Table 5.

Late radiation toxicity

Six months after completion of RT 90.7% of women showed grade 0 skin toxicity. After one year grade 0 toxicity was found in 96.30% of the patients and grade 1 in 3.70%. In 18 months grade 0 toxicity was found in 98.14% and grade 1 in 1.85% of the patients. All patients recovered completely 2 years after RT. Results of late skin radiation toxicity are shown in Table 6. Table 7 shows the correlation between acute and late skin toxicity.

Recurrence

There were neither local recurrence nor distant metastasis during 5-year follow up.

Discussion

RT is an integral part of the management of breast carcinoma for all kinds of breast conserving operations.

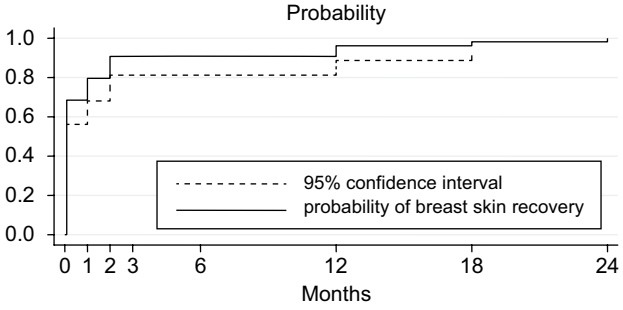

Figure 1. Probability of complete skin recovery of the breast in 54 patients.

Table 4. Acute radiation toxicity in 54 patients

	Completion of RT		*1 month post RT*		*2 months post RT*		*3 months post RT*	
Grade	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
0	36	66.7	42	77.8	48	88.9	49	90.7
1	13	24.1	7	13.0	5	9.3	5	9.3
2	5	9.3	4	7.4	1	1.9	0	0
3	0	0.0	1	1.9	0	0.0	0	0.0
Total	54	100.0	54	100.0	54	100.0	54	100.0

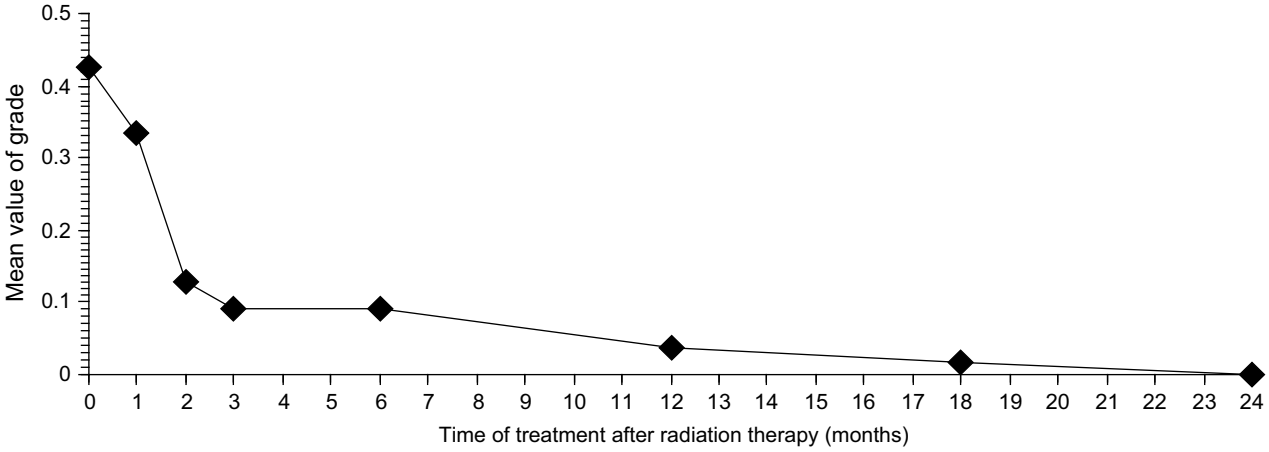

Figure 2. Area under the curve for skin toxicity in 54 patients.

Table 5. Area under the curve for skin toxicity

Mean value of grade	0.42593	0.33333	0.12963	0.09259	0.092593	0.037037	0.01852	0
Time post RT (months)	0	1	2	3	6	12	18	24

Table 6. Late radiation toxicity in 54 patients

	6 months post RT		*12 months post RT*		*18 months post RT*		*24 months post RT*	
Grade	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
0	49	90.7	52	96.3	53	98.1	54	100.0
1	5	9.3	2	3.7	1	1.9	0	0.0
2	0	0.0	0	0.0	0	0.0	0	0.0
3	0	0.0	0	0.0	0	0.0	0	0.0
Total	54	100.0	54	100.0	54	100.0	54	100.0

Table 7. Acute and late toxicity in 54 patients

	Late toxicity					
	0		*1*		*Total*	
Acute toxicity	*N*	*%*	*N*	*%*	*N*	*%*
0	36	100.0	0	0.0	36	100.0
1	13	72.2	5	27.8	18	100.0
Total	49	90.7	5	9.3	54	100.0

Fisher's exact test: p=0.003, Spearman correlation test: p=0.003

There is no standard prescribed daily and total tumor dose for irradiating the breast. A typical course of RT lasts for 6 weeks in postoperative patients. Conventionally, 1.8-2 Gy daily fractions have been used in the treatment of breast cancer, stemming from the concern that fraction sizes > 2 Gy might increase the likelihood of late side effects on healthy tissues. Normal tissue late toxicities, such as breast fibrosis and skin telangiectasia, have been defined for studying the sensitivity of various tissues to different dose and fractionation schedules.

Fisher et al. used 50 Gy in 25 fractions to the whole breast plus 12 Gy boost irradiation to the primary tumor site [1]. Liljegren et al. used 54 Gy in 27 fractions [2], Clark et al. 40 Gy in 16 fractions [3], Barry et al. 30 Gy in 5 fractions within 10 days [4], Yamada et al. 46 Gy to the whole breast followed by a boost of 14 Gy to the tumor bed [5], and Olivotto et al. used 44 Gy in 16 daily fractions [7]. The schedule that is commonly used today in clinical practice is 50 Gy in 25 fractions to the whole breast, administered daily, Monday to Friday, over 35 days in fractions of 2 Gy per day, without boost irradiation to the primary tumor site, or with 10-16 Gy boost to the tumor bed.

Two important randomized trials have evaluated the issue of hypofractionation in breast cancer. The first randomized trial by Whelan et al. [6] studied 1,234 patients with early-stage, lymph node-negative breast cancer after lumpectomy, in whom they compared two fractionation schedules (42.5 Gy in 16 fractions and 50 Gy in 25 fractions) with 2.6 Gy and 2 Gy dose per fraction, respectively. Baseline cosmesis at the start of RT (83.8% in the short-term arm and 82.6% in the long-

term arm) was comparable with the postradiation therapy cosmesis. Their study supported the use of a shorter RT course for patients with the most favorable infiltrating ductal carcinomas.

Studies for low risk patients [6-8] have produced similar recurrence rates (2.8, 3.5 and 6%) as the standard 50 Gy in 2 Gy fractions over 35 days (3.2% recurrence rate in 5 years). Whelan et al. [6] reported a 5-year local RFS of 96.8% after 50 Gy in 25 fractions of 2 Gy/fraction, and 97.2% after 42.5 Gy in 16 fractions of 2.67 Gy (no statistical difference).

Radiobiological modeling can be used to compare different fractionation schedules by determining the biologically effective dose (BED). BED is regarded as a measure of the true biological dose delivered by a particular combination of dose per fraction and total dose to a given tissue characterized by a specific α/β radiobiological ratio value which is an inverse measure of the fractionation sensitivity of the tissue in question.

The tumor control BED values were determined using a α/β value of either 4 Gy, which has been suggested for breast carcinoma [11-14] or 10 Gy, which is the approximate value used for most tumors [15]. A α/β value of 2 Gy has been reported in one study [16] but such a low value of α/β has not been considered in the international bibliography. No studies dealing with hypofractionated RT in breast conserving therapy used boost to the tumor bed [7,8,17].

It is not yet clear whether a repopulation factor is required in cancers other than squamous cell or transitional cell carcinomas, for both of which there is evidence of accelerated repopulation. There is probably no significant time factor in breast cancer subjected to adjuvant RT after tumor excision [18].

BED calculations were also performed for normal tissue side effects such as breast fibrosis, skin telangiectasia (late reacting tissues) and erythema (acute reacting tissue) using an α/β value based on those reported in previous studies [11,15,19,20]. These values were 2.5, 4.0 and 8.0, respectively. The BEDs computed are listed in Table 8. Concerns that have been raised in the literature about rapid fractionation schedules related to two issues: the association of a large dose per fraction with the increased risk of late normal tissue toxicity and the reduction in total dose and potential for decreased effect on tumor control [16,21]. The first concern arises from reports in older, retrospective case series [22]. These studies were poorly controlled. They used older RT techniques. The RT was delivered with large daily fractions (≥3 Gy) without reduction in the overall total dose. Radiobiological models predict that normal tissue toxicity is not increased when the increase in fraction size is modest and the total dose is reduced. Similar models also suggest that rapid schedules may be equally efficacious if the reduction in total dose is accompanied by a shorter overall treatment time [15] or if the tumor is more sensitive to a larger daily dose. This approach is supported by data from randomized trials that compared hypofractionated RT with more conventional RT in women with early breast cancer [23,24]. In the trials by Powell et al., Bates et al., and Baillet et al. [22-24] no difference was detected in late radiation toxicity or local recurrence.

In the present study RT was delivered by a modern approach and important outcomes concerning local recurrence, long term cosmesis and toxicity were assessed in a rigorous fashion. Approximately 98.1% of the patients demonstrated a good or excellent cosmetic outcome at 18 months and 100% of women recovered completed 2 years after RT. Our follow up demonstrated a 5-year local RFF of 100% after total dose of 53 Gy.

Our results support the use of a shorter fractionation schedule for women with stage I-II breast cancer treated by lumpectomy.

The results are not applicable to women with very large breasts. RT may cause skin telangiectasia and thickening of subcutaneous tissue that may adversely affect the cosmetic outcome of the treated breast. The irradiation of such women has been associated with poor cosmetic results, even with conventional fractionation, and alternative techniques may be considered [25].

The hypofractionated schedule appears to be an acceptable alternative to the traditional longer schedules, with an excellent or good overall cosmetic outcome. The results of this study have important implica-

Table 8. BED values (Gy) of commonly employed fractionation schedules

Reference	*Fractionation schedule* *Daily dose × no. of fractions*	*Tumor control* *α/β=10 Gy*	*α/β=4 Gy*	*Breast fibrosis* *α/β=2.5 Gy*	*Telangiectasia* *α/β=4 Gy*	*Erythema* *α/β=8 Gy*
Rosenstein et al. [12]	2 Gy × 33	79.2	99	118.8	99	82.5
Rosenstein et al. [12]	2 Gy × 30	72	90	108	90	75
Zygogianni et al. [13]	2.65 × 20	67	88.1	109.2	88.1	70.6
Kurtz et al. [20]	2.67 × 15	50.7	66.8	82.8	66.8	53.4
Kurtz et al. [20]	3.3 × 13	57.1	78.3	99.5	78.3	60.6

BED: biologically effective dose

tions for women with breast cancer and the health care system. Previous research suggests that the inconvenience of prolonged daily treatments makes a substantial contribution to the decreased quality of life experienced by women with breast cancer treated with RT [25]. A shorter fractionation schedule will lessen the burden of treatment for patients, many of whom may also receive adjuvant chemotherapy and will have important quality of life benefits with respect to convenience, and less time away from home and work. The shorter schedule will also permit more efficient use of resources, in that up to 50% more women can be treated with existing equipment and personnel.

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