

ORIGINAL ARTICLE

Two hypofractionated schedules for early stage breast cancer: Comparative retrospective analysis for acute and late radiation induced dermatitis

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Summary

Purpose: To compare two hypofractionated radiation schedules in early breast cancer concerning skin toxicity.

Methods: We retrospectively analyzed 80 patients (group A) versus 54 (group B) who underwent hypofractionated radiotherapy after breast conserving surgery. Group A received 42.75Gy in 15 fractions over 5 weeks (3 fractions/ week) plus 8.55Gy boost to the tumor bed (3 fractions). Group B received 45.05Gy (5 fractions/week) and 7.95Gy boost (3 fractions). Multivariate logistic regression analysis (MVLRA) was conducted for relevant parameters regarding RTOG/EORTC skin toxicity.

Results: Median follow up was 60 months. Median age was 75 years (group A) and 56 (group B). Mean values of

radio-dermatitis were significantly higher in group A vs B until 3 months post RT ($p < 0.001$ and $p = 0.002$, respectively), while 6 months thereafter toxicity was regressed without any significant difference between groups. MVLRA showed a significant ($p < 0.001$) odds ratio for age (2.36, 95%CI:1.11-3.75) and group A (1.31, 95%CI:1.12-1.49).

Conclusion: Schedule B would be preferable in younger women in favor of toxicity. Schedule A could still be applied in elderly patients, unavailable attending daily schedules, with acceptable toxicity.

Key words: breast cancer, radiotherapy, hypofractionated, skin toxicity, retrospective, comparative study

Introduction

Whole breast radiotherapy (RT) after conservative surgery is a well-established standard in breast irradiation [1,2]. However, many randomized trials, have reported on the alternative clinical role of hypofractionated radiotherapy confirming to be at least as safe and effective [3-6]. On the other hand, in several countries, RT resources are quite limited and/or restricted only

to large cities inducing long delays for RT treatment.

Several alternative RT schemes have been used in order to simplify treatment modalities and offer a wider access to patients. [7-29].

The aim of this study was to perform retrospectively a comparative evaluation between two hypofractionated schedules in terms of acute and late toxicity.

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Methods

Research involving human participants

In terms of ethical approval, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the local ethics committee.

Through a multidisciplinary approach under a local tumor board, we used hypofractionated schedules in women with breast cancer, especially in those who are unable to follow many RT sessions due to distant and isolated areas of residence. In our retrospective study, we analyzed the outcome of radio-dermatitis between two hypofractionated schedules. Both hypofractionated schedules as prospective studies have been approved from the local ethical committee, while their clinical outcome has also been reported in previous publications [7,8].

The inclusion criteria for our analysis were stage I-II invasive carcinoma of the breast after lumpectomy, with or without axillary lymph node dissection, with a minimum follow up of 5 years. If there was indication for chemotherapy, the initialization of RT was at least one month after. Patients with secondary cancer or other radiation therapy on the thorax and neck or any anatomically neighboring region were excluded from the study. We finally evaluated patients' data from May 2004 to May 2012. Under this scope, 80 patients in the first schedule (group A) and 54 patients in the second schedule (group B) were included in the analysis. Their median age was 75 years in group A and 56 years in group B. The patients' characteristics are shown in Table 1. The incidence of diabetes mellitus was quite similar between the two groups, by means of 11 out of 80 patients (13.7%) in group A and 7 out of 54 patients in group B (12.9%).

Radiotherapy schedules

All patients underwent a treatment planning computed tomography (CT) scan of 5mm slice thickness in supine position and arms above the shoulder and immobilized. All the data were transferred to the treatment planning system (Plato Sunrise v. 2.7; Nucletron, Veenedaal, Netherlands and Oncentra). The clinical target volume (CTV) was defined as the residual glandular breast tissue (postlumpectomy). In the postlumpectomy setting, imaging of surgical clips was particularly helpful to delineate the tumor bed. Adding another 1 cm margin to account for set up error, the planning target volume (PTV) was created. The heart, ipsilateral lung and contralateral breast were outlined as organs at risk (OAR). Radiation therapy was delivered by using a 6 MV Oncor Impression linear accelerator, Siemens, Germany, equipped with an 82 multileaf collimator (leaf thickness, 1 cm). Group A received 42.75 Gy in 15 fractions within 5 weeks, 3 fractions/week with 2.85Gy/fraction and a boost of 8.55 Gy in 3 fractions [8]. Group B received 45.05 Gy

to the whole breast in 17 fractions and 7.95 Gy boost to the tumor bed in 3 fractions, in an every-day schedule (Monday to Friday) [7].

The biological effective dose (BED) for normal tissues was calculated using the following formula [30]:

$$BED=D [1+d/\alpha/\beta]$$

where D is the total dose, d is the dose per fraction, α and β are the coefficients for the linear and quadratic terms in Linear Quadratic (LQ) model. We considered $\alpha/\beta=4$ for tumor, $\alpha/\beta=10$ for acute skin toxicity and $\alpha/\beta=3$ for late skin toxicity [21].

Calculations of BED for tumor local control were based on the following formula, taking into account for repopulation [8]:

$$BED=D [1+d/\alpha/\beta]-KT$$

where D is the total dose (51.3 Gy for group A, 53 Gy for group B), d is the dose per fraction (2.85 Gy for group A, 2.65 Gy for group B), $\alpha/\beta=4$. T is overall treatment time (40 days for group A, 20 days for group B). The parameter K (Gy/day) is the biological dose per day required to compensate for ongoing tumour cell repopulation, calculated based on Tpot (potential doubling time) and a radiosensitivity coefficient. Thus, $K=\ln 2 / aT_{pot}$. According to published data, Tpot=14 days and $a=0.08$ [31].

The dose was calculated at the isocenter according to International Commission on Radiation Units and Measurements (ICRU point). For quality assurance purpose double exposure portal films were obtained weekly and compared with the corresponding digitally reconstructed radiograph from initial simulation. The dose within the PTV ranged between 95% and 107% of the isocentric dose, according to ICRU recommendations. In all cases, the maximum radiobiological equivalent dose to the heart, ipsilateral lung and contralateral breast were according to the Quantitative Analyses of Normal Tissue Effects in the Clinical Trial for the dose constraints (QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic) [32].

Systemic therapy

Pre-menopausal patients with positive nodes were treated with adjuvant chemotherapy, whereas postmenopausal women received tamoxifen. Node-negative patients with tumors less than 2 cm in diameter required adjuvant systemic therapy when high risk factors were present.

Patient monitoring and follow up

The follow up was monthly for the first 3 months, every 6 months for the next 2 years and yearly thereafter. The follow up evaluation included physical examination, bilateral mammograms and ultrasounds, blood exams, CT scan of the thorax and ultrasound of abdomen annually.

Data analysis

The combined RTOG/EORTC criteria [33] were employed to assess acute and late skin toxicity. The recurrence was estimated in the treated field of radiation therapy.

In this study, the primary endpoint was to compare the acute and late skin toxicity of the two schedules and the secondary to estimate local recurrence rate.

Statistics

Pearson χ^2 test for 2x2 tables was used to test relationships between categorical variables. Mann-Whitney U non-parametric test was used for statistical comparisons between mean values. A p value less than 0.05 was considered as significant. Logistic regression analysis was performed for analyzing the contribution of age, chemotherapy, hormonotherapy and irradiation schedule (Group A vs B) to the development of radiation induced acute skin-toxicity. Logistic regression analysis was conducted in two steps. In step one, univariate logistic regression analysis was estimated individually for each possible factor. In step two, all significant factors from univariate analysis were entered into a forward step-wise multivariate analysis (likelihood ratio criterion, χ^2 model p for entry = 0.05). The whole statistical analysis was performed using the SPSS 8.0 package (SPSS, Inc, Chicago, IL).

Results

As shown in Table 1, the patient characteristics regarding T, N stage, use of chemotherapy or hormonal therapy, were homogeneous, with the exception of median age, which was 75 years in Group A and 56 years in Group B.

The calculated values of BED for either tumor or acute and late responding normal tissues are shown in Table 2.

The calculated BED for tumor control ($\alpha/\beta=4$), if we take into account for repopulation, in group A-schedule was 63.9 Gy vs 71.6 Gy in group B [8]. This demonstrates that schedule B might be more effective in favor of tumor control due to higher biologically effective dose delivered to the tumor bed.

By the calculation of BED for acute and late responding tissues ($\alpha/\beta=10$ and $\alpha/\beta=3$, respectively), group A had quite similar and slightly lower toxicity than schedule B.

Table 1. Patients' characteristics. The two groups of patients were homogeneous with all relevant parameters except age (last column for χ^2 test)

| | Group A | Group B | P |
|-------------------------|---------|---------|-------|
| T1 | 56 | 39 | 0.85 |
| T2 | 24 | 15 | |
| N0 | 59 | 44 | 0.41 |
| N1 | 21 | 10 | |
| Hormonotherapy (yes/no) | 52/28 | 27/27 | 0.11 |
| Chemotherapy (yes/no) | 53/27 | 44/10 | 0.076 |
| Age, years (median) | 75 | 56 | 0.003 |

Table 2. Calculated BED values for the two RT schedules

| | Tumor control ($\alpha/\beta=4$) | Acute ($\alpha/\beta=10$) | Late ($\alpha/\beta=3$) |
|---------|------------------------------------|-----------------------------|---------------------------|
| Group A | 63.9 | 65.92 | 100 |
| Group B | 71.6 | 67 | 99.8 |

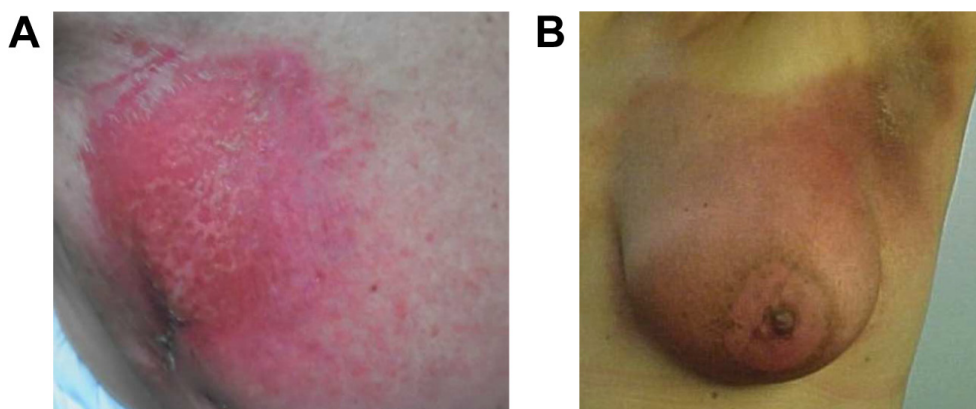


Figure 1. A typical grade III (wet pigmentation) dermatitis in group A and in group B (figure 1A and 1B, respectively).

Table 3. Non parametric test (Mann-Whitney) for mean toxicity score for group A vs group B, regarding several time points as completion of RT and 1, 2,3,6, 12, and 24 months thereafter

| | Group A | Group B | <i>p</i> |
|-------------------|-------------|-------------|----------|
| Time point | Mean (±SD) | Mean (±SD) | |
| Completion | 1.79 (0.41) | 0.43 (0.66) | <0.001 |
| 1 month post RT | 1.19 (0.48) | 0.33 (0.70) | <0.001 |
| 2 months post RT | 0.79 (0.44) | 0.13 (0.39) | <0.001 |
| 3 months post RT | 0.33 (0.47) | 0.09 (0.29) | 0.002 |
| 6 months post RT | 0.16 (0.37) | 0.09 (0.29) | 0.246 |
| 12 months post RT | 0.0 (0.0) | 0.04 (0.19) | 0.084 |
| 24 months post RT | 0.0 (0.0) | 0.0 (0.0) | - |

Table 4. Univariate and stepwise multivariate analysis for toxicity grading score at the completion of radiotherapy. Model fit F=114.3, *p*<0.001, for two degrees of freedom

| Parameter | Univariate analysis | | Multivariate analysis | |
|-------------------------|---------------------|----------|-----------------------|----------|
| | Odds ratio (95% CI) | <i>p</i> | Odds ratio (95% CI) | <i>p</i> |
| Age | 2.64 (1.12-3.96) | <0.001 | 2.36 (1.11-3.75) | <0.001 |
| Hormonotherapy (yes/no) | 1.09 | 0.57 | - | - |
| Chemotherapy (yes/no) | 1.15 | 0.069 | - | - |
| Group A vs B | 1.83 (1.14-2.11) | <0.001 | 1.31 (1.12-1.49) | <0.001 |

Typical grade III dermatitis for group A and B is shown in Figure 1. In Table 3, we have calculated the mean toxicity score at several time points, as at the completion of RT and 1, 2, 3, 6, 12, and 24 months after for the two groups. It is clear, however, that acute toxicity was lower in the Group B patients, with significant difference at 6 months post-RT time of follow up. Late toxicity was also lower in group B, but without significant difference, while practically no toxicity was reported 2 years after RT, in both groups.

In Table 4, at the time of completion of RT, it seems that in univariate as well as in multivariate analysis, there was higher acute skin toxicity associated with the delivery of RT schedule for Group A vs B. Older age was also demonstrated as an unfavorable prognostic factor for acute dermatitis in both univariate and multivariate analysis. Chemotherapy and hormonal therapy were not associated independently with the severity of acute toxicity in multivariate analysis.

There were no recurrences reported within the treatment field for the two groups during the 5-year follow-up.

Discussion

The contribution of adjuvant radiotherapy following breast-conservative therapies for breast cancer is well established due to the results of

various studies on breast cancer. No sub-group of breast cancer patients, even those with low risk disease, has been proved to be able to omit RT and have no impact on local control and DSS [1]. Only in women older than 70 year old with early stage-ER positive breast cancer (stage I) could be treated only using tamoxifen (CALGB9343) [34].

The conventional RT schedule used in clinical practice is the delivery of 50 Gy in 25 fractions of 2Gy/fraction to the whole breast, in an every-day session and additional boost of 10-16 Gy to the tumor bed. In the phase III EORTC trial [35], the delivery of boost dose improved local control, especially in younger women, after 20-year follow up, at the cost of mild fibrosis. This study proposed that the boost can be omitted in women older than 60 years. The multivariate analysis showed that age less than 50 years is a factor that is constantly associated with high risk of relapse in long-term follow-up.

It is clear that the ability to apply hypofractionated schedules of radiotherapy in cancer patients contributes to patients' convenience and quality of life, as demonstrated in relative studies [36]. Additionally, due to the reduction of treatment time, hypofractionation contributes to the shrinking of waiting lists and enables the treatment of a larger number of patients with a given health-care budget, equipment and personnel. It is therefore cost-effective, while relevant studies suggested

that it can result in an increased survival of breast cancer patients in resource constrained economies [37].

However, the adoption of hypofractionation caused several considerations in the past, due to the fear of an increase in late toxicity, by increasing the daily dose, and of a potential increase of rates of local recurrence by reducing the total dose [7]. In fact, by radiobiological aspect, a small increase in the daily dose has only a small impact on toxicity, which can be determined by calculation of biologically effective dose (BED) of adverse events of normal tissues in correlation with BED which is required for local control in breast cancer. This has been calculated in various relevant studies [7,9] and seems to be safe for surrounding tissues. Furthermore, the local control with hypofractionation, with a small reduction of the total dose, can be equally effective as conventional fractionation for tumors with an a/b value less or equal to the surrounding normal tissues. Concerning breast cancer, a/b value is considered to be around 4 [10,38-40]. Moreover, it has been suggested by Ray et al that hypofractionation in breast cancer could improve the therapeutic index [41].

The safety regarding the toxicity and efficacy of hypofractionated schedules in breast cancer has been widely studied with very satisfactory outcomes, in terms of local control. Even the delivery of an additional boost with hypofractionation, is well tolerated with mild acute and late toxicity and a good cosmesis, as it has been demonstrated in recent studies of Sanz [42] and Yu et al [43]. A meta-analysis of 13 studies and 8189 patients performed by Valle et al concluded that hypofractionation does not compromise local control or long-term cosmesis, while it could even reduce acute toxicity compared with conventional fractionation [44].

However, the ideal schedule of hypofractionated radiotherapy is yet to be proven and a variety of different schedules has been tested in the past. Starting from Whelan et al (ONTARIO Clinical Group) [11,12] to START A and B [4-6] studies demonstrated the efficacy of hypofractionation in local control and the reduction in telangiectasia and oedema vs conventional schedules after 10-year follow-up. Beyond FAST trial [45], there have been many attempts to establish an ideal combination of daily dose, total dose and overall treatment time.

In the present study, we conducted a retrospective comparison of two hypofractionated schedules in a fairly homogeneous group of 134 patients. The two groups of patients were homogeneous with all relevant parameters (T, N stage, use of chemo- or hormonal therapy), except age, as in group A the median age was 75 years and in group B 56 years.

By calculating BED for tumor control ($\alpha/\beta=4$) for both groups, we could assume superiority of group B, as BED was higher than in group A (71.6 vs 63.9), taking into account the repopulation. However, in our study, both groups demonstrated excellent local control, as there was no relapse during the follow-up period in any of the groups. Relevant studies of hypofractionated schedules showed that stage and hormonal status are factors significantly associated with local recurrence in multivariate analysis [2,45]. These factors have not been studied independently in our study in correlation to local relapse, as there was no relapse reported, but patient population was homogeneous with these parameters. Probably, a longer follow-up would lead to safer conclusions about local control.

By calculating BED for acute responding tissues ($\alpha/\beta=10$) for the two groups, as relevant to probability of acute dermatitis (Table 2), we could assume that group B would demonstrate equal or slightly higher acute toxicity than group A (BED 67 vs 65.92, respectively). In fact, the results of our study demonstrated the opposite. Acute toxicity after the completion of RT was lower in Group B than in Group A patients, with statistically significant difference. Beyond that, calculation of BED for late responding tissues ($\alpha/\beta=3$), as an indicator of late toxicity, implies that this would be equal for both groups (BED =100 for group A vs 99.8 for group B). Yet, the results of our study demonstrated that also late toxicity was lower in group B than in group A. Finally, two years after RT, there was practically no toxicity reported in both groups.

Could there be a reason for these unexpected clinical results regarding toxicity in the two groups? DeSantis et al tried to determine risk factors associated with acute and late toxicity of hypofractionated RT in 537 patients who also received chemotherapy [46]. In univariate analysis, factors such as delivery of a boost, diabetes and chemotherapy were statistically significant for late fibrosis, but the multivariate analysis demonstrated no association with any factor. Acute toxicity was statistically significantly higher in larger breast volume, dose inhomogeneities and larger boost volumes in univariate analysis, but in multivariate analysis, only the delivery of a boost was a statistically significant factor. This study concluded that only the delivery of additional boost could be a predictor of toxicity and that chemotherapy had no impact on acute or late toxicity [46]. In our study, all patients in both groups received additional boost dose at the tumor bed, even though breast and boost volumes were not studied independently, and patient population was homogeneous with delivery or not of chemotherapy in the two groups, while the incidence of

diabetes differed and was slightly higher in group A than in group B (13.7 vs 12.9%). Could this be an explanation?

Additionally, in our study older age was clearly associated with higher rates of acute dermatitis in univariate and multivariate analysis. Since an association between age and skin toxicity has not been reported yet in the literature, in any multivariate analysis of hypofractionated breast RT, we could assume that these results could be attributed to other relevant to older age factors, such as diabetes. Diabetes has been reported as an unfavorable prognostic factor for toxicity, especially late subcutaneous fibrosis, in univariate [46] and multivariate [47] analysis of hypofractionated RT. The increasing incidence of diabetes among older women, could explain the increasing toxicity we reported among elderly patients in group A, even though it was quite similar between the two groups (13.7 vs 12.9%) and eventually has not been evaluated independently in our study.

Ortholan et al reported that tumor size was a significant factor for toxicity in multivariate analysis. In our study, tumor size was not independently studied as a factor related to toxicity, but our patient population was homogeneous with T stage between the two groups [48].

Ciammella et al have also correlated the delivery of additional boost with late skin toxicity and diabetes as statistically significant factors associated with poor prognosis for late subcutaneous fibrosis ($p=0.0283$) [49]. Furthermore, adjuvant chemotherapy (anthracycline-based) was a precursor for increased late subcutaneous toxicity and poor cosmetic outcome in multivariate analysis ($p=0.0409$) in this study [47]. In our study, chemotherapy and hormonal therapy were not associated independently with the severity of acute toxicity in multivariate analysis. This is consistent with other studies that demonstrate no impact of chemotherapy on acute or late toxicity [46]. In our study, chemotherapy was administered at least one month before RT in both groups, not explaining the increased toxicity in group A.

The fact that there is an obvious difference in median age of the two groups of our study, could be of clinical interest, when it comes to treatment of elderly patients. Our study has proven acceptable toxicity in the group A schedule of elderly patients, even though worse than in group B. In the literature, relevant hypofractionated schedules have been reported in the treatment of breast cancer in older women [2,48,49]. The weekly delivery of 6-6.5 Gy fractions to a total dose of 30-32.5 Gy in women with median age 78 years, showed mild

acute toxicity and acceptable late toxicity with excellent long-term local control. This study [48], after a 5-year follow-up concluded that such schedules can be applied in elderly patients who have difficulty attending every-day sessions due to old age or comorbidity. Similar RT schedules have even been proposed as radical treatment combined with hormonal therapy in elderly women not fit for surgery, with acceptable toxicity and local control [50]. Even in studies of nonagenarians (>90 years old), hypofractionation is reported to have acceptable toxicity [51].

Conclusion

In conclusion, we could support that the RT schedule B is superior regarding acute and late toxicity and therefore could be the best option in irradiating younger women, where the group A schedule could be an acceptable alternative treatment for older women with difficulties attending to every-day schedule (assuming they do not belong to the category of early-stage(I)- ER positive breast cancer, aged > 70 years, who can omit RT completely, according to current guidelines) [34]. Relevant studies, such as by Jaggi et al, have already reported that, even though hypofractionated RT has been proven safe and efficient, it has been adopted with increasing rates only in older women with smaller tumors [52].

We should also keep in mind that, in clinical practice, the treatment finally applied in older patients (>80 years old) often differs from the guidelines and there is connection between age and guideline concordance, a fact that has been already reported in a recent study [53]. This fact outlines the need for further evaluation of parameters regarding quality and appropriateness of treatment in older patients, as it is highlighted in this study. What is beyond doubt is that both hypofractionated schedules that have been proposed in the present study, could contribute to the convenience of patients, quality of life and could be proven cost-effective, increasing the final percentage of breast cancer patients treated, especially in resource-constrained economies.

It is still to be investigated whether older age could be a prognostic factor for acute toxicity in hypofractionated RT, as it is suggested by our results, or whether this is only associated with comorbidities of elderly patients, such as diabetes.

Conflict of interests

The authors declare no conflict of interests.

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