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Hypofractioned Radiation Therapy in the Treatment of Partial Breast: 30 Gy in Five Consecutive Fractions

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ABSTRACT

Background and Purpose: Recent prospective studies have explored the partial breast irradiation (PBI) for patients with early-stage breast cancer using different technical approaches. The purpose of this study is to explore feasibility, tumor control and acute and late toxicity of a specific hypo-fractionated 3D-CRT when treating postmenopausal patients with early breast cancer with partial breast irradiation, using five fractions in five consecutive days. **Materials and Methods:** Ten patients, aged ≥ 70 underwent breast conservative surgery for invasive breast carcinoma with a complete microscopic resection; no lymphovascular invasion was found and negative axillary node status was assessed. Metal clips were positioned in the surgical bed at the time of surgery. All of the patients provided an informed consent for breast irradiation. Seven patients received Tamoxifen. Of the ten patients, five were treated for left breast disease, and five for right breast disease. The dose fractionation schedule was 3000 cGy delivered to the isocenter in 5 fractions (600 cGy/fr) using 6 MV photons. According to the linear quadratic model and a α/β ratio of 4 Gy this prescription is equivalent to 50 Gy in a standard 2-Gy fractionation schedule. Patients were treated in the supine position. A comercial breast board was used as immobilization device in order to keep the arms of the patient raised. The clinical target volume (CTV) was drawn with a uniform 1-cm three-dimensional margin around the surgical clips. The CTV was limited to 3 mm from the skin surface and 3 mm from the lung-chest wall interface. A three-dimensional margin was added to the CTV to obtain the planning target volume (PTV). The ipsilateral and controlateral breast, the ipsilateral and controlateral lung, heart and spinal cord were contoured as organs at risk (OAR). The treatment was developed using Precise Plan Treatment Planning System and four no-coplanar fields. The constraints used have been: uninvolved breast (ipsilateral breast-PTV): $V_{15} \leq 50\%$; heart: $V_3 \leq 10\%$; ipsilateral lung: $V_{10} \leq 20\%$; controlateral lung: $V_5 \leq 10\%$ and controlateral breast: maximum dose ≤ 1 Gy. We required PTV coverage of ≥90%. Patient set-up was verified every day before treatment using portal images. No tumour bed boost was delivered. Clinical assessments of early normal tissue reaction were carried out every day during radiotherapy and 10 days after the end of the treatment. After radiotherapy, we visited all patients every 3 months during the first 2 years and every six month thereafter. Frontal and lateral pictures of the breast were taken on the first day of treatment (baseline), at the end of treatment, 10 days after the end of treatment and at the first follow-up. Any change in breast appearance compared with the baseline picture was scored on a four-point RTOG for acute and late radiation morbidity scoring scale. **Results:** No local or distant recurrences were observed and then confirmed by mammograms performed every year and breast ultrasound performed every six months. For acute and late toxicity, only 2 patients developed acute effects at the end of the treatment. **Conclusion:** The clinical outcomes observed in ten patients demonstrate a good feasibility of the schedule adopted both in terms of tumour control and acute and late toxicity, with good cosmetics results. Long term follow-up and a large number of patients will be needed for full evaluation.

Keywords: Breast Cancer; Partial Breast Irradiation; Hypofractioned

1. Introduction

In the past decades, a major change has occurred in the local management of breast cancer, from a mutilating therapeutic approach to a conservative approach with osmetic and functional aims. The use of conservative surgery combined with whole-breast irradiation has been established as a valid alternative to mastectomy. The

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conservative approach consists in the removal of the tumor, followed by 5 - 7 weeks of daily whole breast irradiation (total dose of 50 Gy delivered to the entire breast and 10 - 16 Gy boost delivered to the tumor bed). A disadvantage of this approach is the increase of the non-breast-cancer-related morbidity due to irradiation of non-target tissue [1,2] and the prolonged duration of treatment.

Observation from earlier studies demonstrated that distant recurrences, in quadrants other than that originnally involved by the tumour, occur infrequently (range, 0.6% - 6%) [3-13].

A strategy that aims at improving the therapeutic ratio and at reducing treatment duration, in women with relatively low risk of local tumour relapse, involves limited high-radiation doses to the index quadrant and reduces doses to breast tissue remote from the tumour bed [14,15]. Radiobiological analysis of clinical data has shown that breast adenocarcinomas have an α/β ratio of 4 Gy, like late reacting normal tissues. Consequently, hypo-fractionation in breast cancer may have a reasonable radiobiological support. Recent prospective studies have thus explored the techniques of only treating the tumor bed of the breast, *i.e.* partial breast irradiation (PBI), for patients with early-stage breast cancer using different technical approaches [16-24]. These studies have investigated the use of low-dose-rate and high-dose-rate brachytherapy and the use of External-Beam Radiotherapy (EBRT) for partial breast irradiation.

The purpose of this study is to evaluate feasibility, tumor control and acute and late toxicity of a specific hypo-fractionated 3D-CRT in the treatment of partial breast in postmenopausal patients with early breast cancer, using five consecutive 6 Gy fractions.

2. Material and Methods

2.1. Patients

Sarting on January 2008 ten patients, out of all those who underwent breast conservative surgery for invasive breast carcinoma, received postoperative radiotherapy delivered to the index quadrant only after having provided full written informed consent. The inclusion criteria are listed in **Table 1**. All of the patients enrolled in the study were in postmenopausal status, age ranged from 70 to 84 years (median 76 years). Eight patients had Stage I invasive ductal carcinoma and two patients had Stage I invasive lobular carcinoma. Tumour size ranged between 10 mm and 20 mm, with a median of 14 mm. Seven patients had positive estrogenic receptors and received Tamoxifen, no patients received chemotherapy. All patients underwent lumpectomy with negative surgical margins. The surgeons were requested to place clips at the borders of the surgical bed, using a minimum of six clips. The presence of surgical clips represented a selection criteria to avoid geographic misses. Of the ten patients, five were treated for left breast disease, and five for right breast disease. The main patients' characteristics are listed in **Table 2**. Clinical assessments of early normal tissue reaction were carried out every day during radiotherapy and after 10 days from the end of the treatment. After radiotherapy, all of the patients underwent a clinical examination every 3 months during the first two years and every six months subsequently. Median follow-up from the end of irradiation was 21.1 months (range, 10 - 48 months).

Bilateral mammogram, and bilateral breast ultrasound were obtained once a year during follow-up. An echocardiogram was obtained in patients with left breast cancer. Frontal and lateral pictures (depending on the tumour

Table 1. Inclusion criteria.

Age > 70 aa
Patological stage pT1 pN0
Surgical margin negative (>2 mm)
Clips placed in tumor bed
Full informed consent from patient
No lymphovascular invasion
Unifocal
Intraductal component < 25%
ER and PgR positive
ER = Esrogen Receptor; PgR = Progesteron Receptor

Table 2. Baseline patient characteristics (n = 10).

Characteristics	Patients
Breast side	#
Right	5
Left	5
Tumor estrogen receptor status	#
Positive	10
Negative	0
Tumor progesterone receptor status	#
Positive	10
Negative	0
Tumor Her-2 status	#
Score 0	3
Score 1	2
Score 2	2
Score 3	1
Unknown	2

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site) of the breast were taken on the first day of treatment (baseline), at the end of the treatment, after 10 days from the end of the treatment and at the first follow-up visit (**Figure 1**). Any changes in breast appearance were compared with the baseline picture and was scored on a four-point RTOG for acute and late radiation morbidity scoring scale.

2.2. Patient Positioning and Image Acquisition

Patients underwent Computed Tomography (CT) imaging in supine position with a commercial breast board immobilization device in order to keep their arms raised. CT scanning was performed with a 0.5 cm scan spacing. The scans extended to completely cover the involved breast, lungs, and a 5 cm margin in the cranial and caudal directions.

2.3. Treatment Planning

The prescribed dose to the 95% isodose was 3000 cGy in 5 fractions (600 cGy/fr) in 5 consecutive days. All patients were treated in the supine position. The treatment was developed using Precise Plan Treatment Planning System® (Elekta, Crowley, United Kingdom) and four no-coplanar 6 MV photon fields were used (Elekta Precise® Linear Accelerator, Crawley, United Kingdom).

The planning volumes were defined as follows: the gross target volume (GTV) was contoured on the surgical clips placed during surgery, the clinical target volume (CTV) was draobtained with a uniform 1 cm three dimensional margin around the surgical clips (GTV) and the planning target volume (PTV) was defined as the CTV plus a uniform 1 cm three dimensional margin. The PTV was limited to 3 mm from the skin surface and 3 mm from the lung-chest wall interface. As organ at risk (OAR) we considered the ipsilateral and contralateral breast, the ipsilateral and controateral lung and the heart. The heart was contoured from the first CT slice below the pulmonary artery to the apex inferiorly. Both lungs were contoured in their entirety (**Figure 2**).

The constraints used are listed in **Table 3**. Less than 20% of the ipsilateral lung had to receive 30% of the prescribed dose ($V_{10} \leq 20\%$); less than 10% of the contralateral lung had to receive 15% of the prescribed dose ($V_5 \leq 10\%$); less than 10% of the contoured heart volume had to receive 10% of the prescribed dose ($V_3 \leq 10\%$); maximum dose to the controlateral breast was <1 Gy. We also attempted to maintain the 50% volume of the ipsilateral breast (IB) minus planning target volume (PTV) (IB-PTV), to receive less than 50% (15 Gy) of the prescribed dose. Patient set-up was verified every day

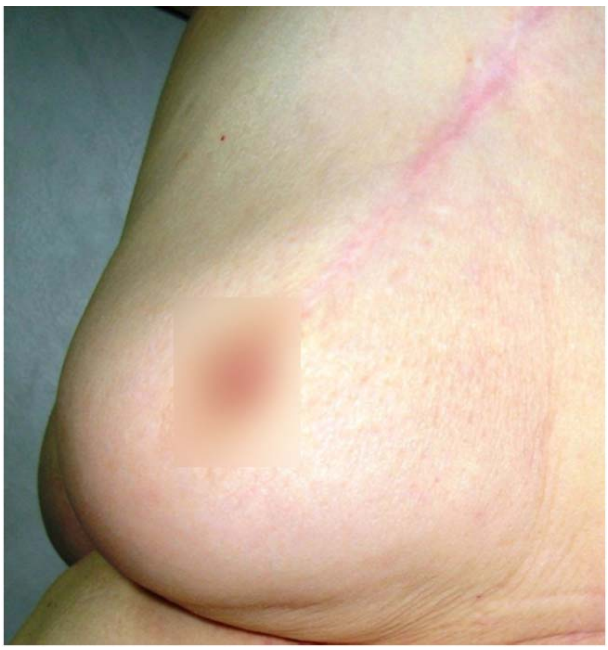

Figure 1. Photo captured 12 month after the end of radiotherapy.

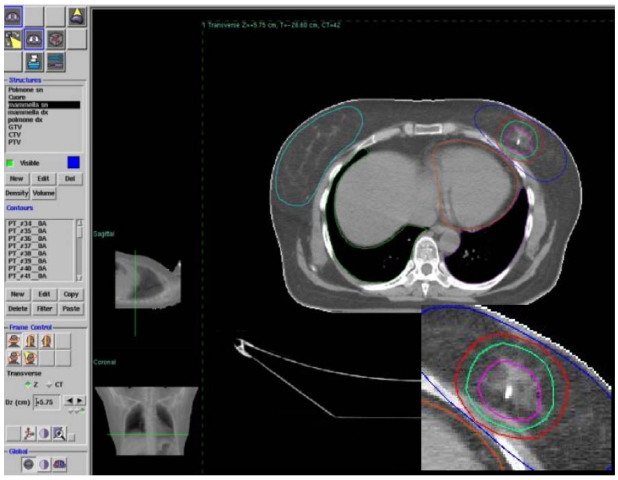

Figure 2. Target and organ at risk (OAR) conturing. Pink is the Gross Tumor Volume (GTV); Light green is the Clinical Target Volume (CTV); Red is the Planning Target Volume (PTV); Blue is the ipsilateral breast; Cyan is the controlateral breast; Orange is the heart; Violet is the ipsilateral lung; Green is the controlateral lung.

Table 3. Constraints for OAR.

OAR	Constraints
Ipsilateral Lung	$V_{10} < 20\%$
Controlateral Lung	$V_5 < 10\%$
Heart	$V_3 < 10\%$
Ipsilateral Breast-PTV	$V_{15} < 50\%$
Controlateral Breast	<1 Gy

OAR = organs at risk; PTV = planning target volume

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before treatment, using orthogonal portal images (Gantry 0˚ and 90˚, coach 0˚) and 2 portal images of the treatment beams.

3. Results

The target coverage was acceptable for all patients. The dose-volume constraints of OARs were always respected. Only in 1 patient the uninvolved breast dose-volume constraint was not respected given that the 82% of uninvolved breast volume received more than 15 Gy (**Table 4**). This was probably due to the anatomic position of the tumour (supero-internal quadrant) and to the small volume of the breast (435 cc).

We observed grade 1 acute skin toxicity (Radiation Therapy Oncology Group scale) developing during the first week after the end of treatment in 2 patients (20%). No patients had late skin toxicity. No difference was observed between patient who received or not Tamoxifen. No patients experienced a reduction in left ventricular ejection fraction or in forced expiratory volume. To date no local recurrence was observed.

4. Discussion

In the far past years the treatment for breast cancer was mastectomy while actually the gold standard for patients with early-stage breast cancer is conservative with a cosmetic and functional surgical approach followed by radiotherapy to increase local control and overall survival [25]. The standard radiation therapy treatment has a duration of 5 - 7 weeks and the delivered dose is 50 Gy in 25 daily fractions delivered to the entire breast plus 10 Gy boost to the tumour bed. This approach has the disadvantage of prolonged duration, which can be a serious inconvenience for patients that have to travel every day for a prolonged period to the radiation therapy centre, especially for the elderly ones. Several clinical trials have demonstrated that shorter radiation schedules, justified by radiobiological models, delivering larger doses per fraction in shorter periods of time [26-30] offer equivalent local control and same acute and late toxicity compared to the standard radiation therapy courses. Whelan *et al.* [27] examined whether a 22-day radiation therapy fractionation schedule was as effective, on the local control, as the traditional 35-day schedule in 1934 women with invasive breast cancer who underwent BCS with pathologically clear resection margins and negative axillary lymph nodes. Patients were randomly assigned to receive 42.5 Gy in 16 fraction over 22 days or 50 Gy in 25 fraction over 35 days to the whole breast. With a median follow-up of 12 years no differences in local recurences, disease free or overall survival rates and cosmetic results were recorded. They concluded that the more convenient 22-day fractionation schedule appear to be an acceptable alternative to the 35-day schedule. The START A (Standardization of Breast Radiotherapy) from the UK trial has shown that 41.6 Gy in 13 fractions or 39 Gy in 13 fractions are similar to the standard treatment (50 Gy in 25 fractions) in terms of local-regional tumour control and late normal tissue effects [28]; this results are consistent with those of the START B trial, which has shown that a radiation schedule of 40 Gy in 15 fractions offers equivalent results to the standard schedule of 50 Gy in 25 fractions [29]. Livi *et al.* [30] evaluated the incidence of loco-regional recurrence and the cosmetic results in a group of 539 patients with breast cancer treated with a hypo-fractionated schedule after conservative surgery. The dose delivered was 44 Gy (2.75 daily fraction) and the tumour bed boost was 10 Gy (Electron beam). They obtained a low local relapse and good tolerance (76.4% patients showing grade 0 - 1 late toxicity, 20.9% patients grade 2 and 2.5% patients grade 3; no patients with grade 4 toxicity was observed). All this fraction regimen do not represent the limits of hypofractionation for whole breast radiotherapy. The UK FAST trial [31] randomized 915 women 50 years old or older with node-negative tumours, following breast conservative surgery, to receive whole breast radiotherapy delivered using 3D dosimetry to a total dose of 50 Gy in 25 fractions (control) versus 28.5 Gy or 30 Gy in 5 once-weekly fractions of 5.7 Gy or 6.0 Gy with no tumour bed boost. The first analysis showed good results in terms of late normal tissue responses and tumour control. A schedule of 30 Gy in 5 fractions over 15 days to the

Table 4. DVH analysis: OAR doses.

OAR	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Hearth: dose to 10% volume	0.5 Gy	1 Gy	0.5 Gy	1 Gy	2 Gy	0.5 Gy	1 Gy	0.1 Gy	1 Gy	1 Gy
Ipsilateral Lung: dose to 20% volume	1 Gy	4 Gy	2 Gy	1.5 Gy	4 Gy	1 Gy	2 Gy	1 Gy	1 Gy	2 Gy
Controlateral Lung: dose to 10% volume	0.1 Gy	0.4 Gy	0.1 Gy	0.1 Gy	1 Gy	0.1 Gy	0.1 Gy	0.1 Gy	0.1 Gy	0.1 Gy
Controlateral Breast: dose to whole organ	0.2 Gy	0.6 Gy	0.5 Gy	0.1 Gy	0.9 Gy	0.1 Gy	0.1 Gy	0.1 Gy	0.1 Gy	0.3 Gy
Ipsilateral Breast-PTV: dose to 50% volume	4.5 Gy	4 Gy	27 Gy	10 Gy	7 Gy	12 Gy	14 Gy	5 Gy	6 Gy	10 Gy

DVH = dose-volume histogram; OAR = organ at risk.

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whole breast, using 3D dosimetry, reported very mild acute reactions and acceptable 2-year outcome in terms of change in breast appearance compared to a matched sample of patients treated to 50 Gy in 25 fractions [32].

Observations that the vast majority of ipsilateral breast recurrences occur in close proximity to the lumpectomy cavity have led to question the opportunity of elective partial breast irradiation (PBI), treating only the tumor bed. Baglan KL *et al.* [21] presented a 3D-CRT technique for partial breast irradiation in supine position. The prescribed dose was 34 Gy in 5 patients and 38.5 Gy in 4 patients, delivered in 10 fractions twice daily over 5 consecutive days. They reported an excellent patient tolerance with minimal acute toxicity. No skin changes were noted during treatment, and at the initial 4 - 8-week follow-up examination, only mild localized hyperpigmentation and/or erythema were observed. Formenti S. *et al.* [22] reported the clinical and dose-volume histogram results in 47 patients accrued to a 3D-CRT accelerated partial breast irradiation (APBI) protocol in the prone position. The prescribed dose was 30 Gy at 6 Gy/fraction delivered in 5 fractions within 10 days. The lung and the heart were spared by treating in the prone position. Acute toxicity was mild (Grade 1 - 2 erythema). With a median follow-up of 18 month only grade 1 late toxicity occurred, and no patient developed local recurrence. Livi L. *et al.* [23] compared, in a randomized phase III clinical trial, conventional (tangential field) fractionated whole breast treatment (Arm A, 128 patients) with accelerated partial breast irradiation plus intensity-modulated radiotherapy (Arm B, 131 patients). For patients in Arm B (PBI) the prescribed dose was 30 Gy in 5 fractions, 6 Gy/fraction. The rate of Grade 1 and Grade 2 acute skin toxicity was respectively 22% and 19% in Arm A (Radiation Therapy Oncology Group scale). The tolerance in Arm B was excellent with only 5% Grade 1 and 0.8% Grade 2 acute skin toxicity. With a median 9.6 years of follow-up Antonucci *et al.* [24] compared a group of patients treated with APBI vs a similar group of patients treated with whole breast irradiation to determine the potential differences in local recurrence rates according to the volume breast tissue irradiated. The cumulative incidence of ipsilateral breast tumour recurrences at 10 years was 5%. On matched-pair analysis, the rate of ipsilateral breast tumour recurrences was not significantly statistically different between the patient groups. These data suggest the potential efficacy of APBI in selected low-risk patients. Different studies [33-38] demonstrate that breast cancer has the same radiobiological behaviour of late reacting normal tissue (α/β ratio of 4 Gy), late effects (fibrosis and telangiectasia) have α/β ratio of 2 Gy and 4 Gy respectively, and acute reaction (erythema and desquamation) 8 Gy and 11 Gy respectively. To compare the fractionation schedule of 30 Gy delivered in 5 consecutive days with the conventional fractionation of 50 Gy delivered in 32 days, the Biologically Effective Dose (BEDs) has to be calculated assuming cell repopulation during treatment. The BEDs formula taking into account cell repopulation is the follow:

$$\mathrm{BED} = nd\left[1 + d/(\alpha/\beta)\right] - \left[\ln 2/\left(\alpha T_{pot}\right)(T - T_k)\right].$$

were n is the number of fraction, d is the dose per fraction, α/β is a tissue-specific and effect-specific parameter associated with the linear-quadratic model, T is the overall time of radiotherapy (days, with first day counted as day 0), T_k is the Kick-off time of repopulation in the tissue of interest (21 days) [26,39,40], α is the radiosensitivity coefficient of non recoverable damage (0.35) [34, 41] and T_{pot} is the potential doubling time of cancer repopulation cells (3 days) [42,43]. This correction for cell proliferation causes the tumour standard treatment BED values to decrease by 3 Gy (from 75 Gy to 72 Gy). The BED values of PBI schedule were calculated with the standard equation:

$$\mathrm{BED} = nd\left[1 + d/(\alpha/\beta)\right].$$

considering that the treatment is accomplished within a period that is shorter than the lag period. **Table 5** lists the BEDs for tumour control, the early responses (erythema and desquamation), and the late responses (telangiectasia and fibrosis). The BEDs for normal tissue acute effects were generally lower for the 30 Gy hypo-fractionated schedule than for the standard 50 Gy treatment, indicating that the risk of radiation-induced complications should be lower in the PBI schedule.

According with the literature experience [22,23,31,32] and to our very preliminary results we want to increase our experience of a 30 Gy (6 Gy/fraction) fractionation schedule delivered in 5 consecutive days, with three-dimensional conformal radiotherapy (3D-CRT), without considering an intermediate time period in order to have a complete cellular recovery between fractions (>24 h). The proposal of such a simpler and less expensive technique, compared to Intensity Modulated Radiotherapy

Table 5. Biologically effective doses (BED).

	α/β (Gy)	Standard (50 Gy)	Hypofractionated (30 Gy)
Erythema	8	63	53
Desquamation	11	59	46
Teleangectasia	4	75	75
Fibrosis	2	100	120
Tumor	4	75	75
Tumor*	4	72	75

*Taking into account cell proliferation during course of treatment.

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(IMRT), with an excellent coverage of the target volume and excellent results in term of dose-volume histogram for OARs for all patients (**Table 4**), seems feseable but deserves more experience and long term results before beeing delivered to a larger population of patients.

5. Conclusion

The clinical results observed in ten patients demonstrated a good feasibility of the schedule adopted both in terms of tumour control rate and acute and late toxicity, with good cosmetics results. Encouraged by the protocol study of the University of Florence [23] (where the age inclusion criteria is >40 y), we propose to go on with this study delivering this schedule to patients younger than 70 years in order to achieve a larger number experience.

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