Two Different Hypofractionated Breast Radiotherapy Schedules for 113 Patients with Ductal Carcinoma *In Situ*: Preliminary Results

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Abstract. *Aim: To assess local control and cosmetic outcomes for two different hypofractionated radiotherapy schedules after breast-conserving surgery for ductal carcinoma in situ (DCIS). Patients and Methods: A total of 113 breast-conserving operated patients with DCIS were treated from August 2006 to August 2011: 41 women received 46 Gy in 20 fractions of 2.3 Gy four times a week, for five weeks; the other 72 patients received 39 Gy in 13 fractions of 3 Gy four times a week for 3.5 weeks. Both schedules involved a concomitant boost to the tumor bed, with dose adjustment according to the surgical margins. Results: The median follow-up is 30.5 months. Overall, the treatments were well-tolerated. The most common acute effect was erythema: grade 1 in 56.1% and 31.9% in the longer and in the shorter hypofractionated treatment, grade 2 in 9.8% and 0% of cases respectively. Late toxicity of fibrosis occurred at grade 1 in 19.6% and 15.3% respectively and at grade 2 in 0% and 2.8%. Conclusion: These results suggest that patients with DCIS can be safely treated with a shorter radiotherapy regimen.*

Screening mammography has increased the diagnosis of ductal carcinoma *in situ* (DCIS) from 3-5% in the 1970s and 1980s to 25-30% today (1). Randomised clinical trials demonstrated that adjuvant breast radiotherapy (RT) reduces the risk of recurrence in DCIS following breast-conserving surgery (BCS) (3, 4). The standard radiation treatment is administered in 25 fractions over five weeks and such a number of visits to the RT center can impact on the quality of life of patients. Moreover, this prolonged schedule does not allow for optimum use of human and technological resources of the center. Recent randomized trials justify the routine use of hypofractionation for adjuvant whole-breast radiotherapy in women with early breast cancer, but there are currently no prospective data addressing this schedule for DCIS (5). At our center, all patients with breast cancer receive hypofractionated radiotherapy (HFRT). In this analysis, we review preliminary data for local control and cosmetic outcomes for a cohort of patients treated with two different HFRT schedules at our center following BCS for DCIS.

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Patients and Methods

We analyzed a sample of 113 BCS, breast cancer patients treated at our Department from August 2006 to August 2011 with two different adjuvant RT schedules for DCIS. The median age was 67 (range=35-85) years. The patient and tumor characteristics are listed in Table I. Surgery consisted of a wide excision. In cases of occult invasion risk, high-grade lesions, palpable node or extended microcalcifications, sentinal lymph node biopsy was implemented (6, 7). Margins were microscopically evaluated and scored as free when exceeding a tumor-free width of 2 mm and as involved when width was less. DCIS was graded into three categories (well, intermediately, and poorly differentiated). The patients were evaluated and classified according to the presence of comedo subtype with or without necrosis. Intraoperative specimen X-rays were performed to confirm complete excision of micro-calcifications.

We used two different RTs to progressively introduce shorter HFRT schedules, starting with the older women (over 60 years) and extending to the younger patients. In addition we used four fractions per week to administer palliative single doses, to perform weekly dosimetry and other technical requirements on the fifth day (Wednesday). According to clinical characteristics (performance status, age, breast volume and shape), after primary surgery, the appropriate schedule was selected for each patient: 41 women, younger than 60 years, were assigned to receive 46 Gy in 20

Table I. *Patients' characteristics*.

Characteristic	Patients, n (%)
Age	
<70 years	88 (77.8)
≥70 years	25 (22.2)
Breast laterality	
Left	60 (53)
Right	53 (47)
Grade	
G1	24 (21.2)
G2	67 (59.3)
G3	22 (19.5)
Tumor estrogen receptor status	
Negative	21 (18.6)
Positive	92 (81.4)
Tumor progesterone receptor status	
Negative	24 (21.2)
Positive	89 (72.8)
Histological type	
Comedo subtype with necrosis	3 (2.7)
Comedo subtype without necrosis	16 (14.2)
No comedo subtype with necrosis	94 (83.1)
Marginal status	
≥2 mm	96 (85)
<2 mm	17 (15)
Microcalcifications	
Present	99 (87.6)
Absent	14 (12.4)
Menopausal Status	
No	12 (10.6)
Yes	101 (89.4)
Adjuvant hormonal therapy	
No	102 (90.3)
Yes	11 (9.7)

fractions of 2.3 Gy four times a week for five weeks. The remaining 72 patients received 39 Gy in 13 fractions of 3 Gy four times a week for 3.5 weeks. Both schedules involved a concomitant boost to the tumor bed, with the dose adjusted according to the surgical margins (Table II). Using the linear-quadratic cell survival model, we calculated biologically equivalent doses (BEDs) for the breast and boost volumes. We assumed an α/β ratio of 4 Gy for tumor response, 10 Gy for acute-responding normal tissues, 1.7 Gy for late-responding tissues (fibrosis) and 2.5 for vascular damage (8). We used doses and fractionations derivered from the BED, $BED=(nd)\ (1+d/\alpha/\beta)$, where n is the number of fractions, d is the dose per fraction, and α/β is the tissue-specific parameter.

All the patients provided informed consent and started the RT within three months after surgery. All patients underwent 3D-conformal RT. Computed tomography (CT) from the level of the larynx to the level of the upper abdomen, including both lungs, with a scan thickness and index of 5 mm was performed for each patient positioned on a wing-board with both arms raised above the head. The whole-breast clinical target volume included the glandular breast tissue of the ipsilateral breast and the whole-breast planning target volume was generated, adding an isotropic margin of 0.5 cm in all directions except towards the skin. The identification of the lumpectomy cavity was helped by the presence of surgical clips and surgery-induced changes. Two-five tangential beams with different energies and wedges were planned. A multi-leaf collimator (MLC) was used to spare organs at risk (OAR) according to individual anatomy. A boost plan was created using two or more photon beams. Wedge and MLC shielding were selected in order to obtain a 95% isodose encompassing both the whole-breast and boost PTV. A cumulative dose volume histogram was created to evaluate dose distribution.

Table II. *Radiotherapy schedules*.

RT schedules 230 cGy × 20 fr (41/113) Dose cc boost		RT schedules 300 cGy × 13 fr (72/113) Dose cc boost	
120 cGy × 5 fr	28 (68.3%)	120 cGy × 5 fr	2 (2.8%)
150 cGy × 5 fr	5 (12.2%)	100 cGy × 3 fr	56 (77.8%)
300 cGy × 5 fr	1 (2.4%)	100 cGy × 4 fr	7 (9.7%)
No cc boost	7 (17.1%)	No cc boost	7 (9.7%)

RT: Radiotherapy; cc: concomitant.

Acute skin toxicity was assessed during each week of radiation treatment according to the Radiation Therapy Oncology Group (RTOG) scale (9), while late toxicity was assessed 180 days after radiation therapy using the Common Terminology Criteria for Adverse Events (CTCAE) which incorporated the LENT SOMA scale (10). Patients were followed-up every six months for the first two years then every 12 months for the subsequent years. Mammograms were performed annually, unless warranted by an intercurrent finding.

Results

A total of 113 patients with a median age of 67 (range=37-85) years were treated and the current results are reported for a median follow-up of 30.5 (range=6-65) months. All patients completed the planned RT schedule without any interruptions or delays in therapy. Overall, the treatments were well-tolerated. The analyzed acute toxicities include breast erythema, edema and pain. The most common acute effect was erythema: G1 was found in 56.1% and 31.9% ($p<0.05$) respectively in the two radiation schedules (230cGy x 20fr *vs*. 300cGy x 13); G2 in 9.8% and in 0% ($p<0.05$) while no G3-G4 were found and no erythema was showed in 34.1% and 68% of the patients respectively ($p<0.05$). Edema and pain were reported during and some weeks after the treatment in 4.9% and in 6.9% of cases, respectively without any statistical significant value. Late toxicities, defined as occurring after six months from the

Table III. *Acute toxicity recorded according to therapy.*

Acute toxicity			
	230 cGy × 20 f (41/113)	300cGy × 13 f (72/113)	*p*-Value[a]
Erythema			
G0	14/41 (34.1%)	49/72 (68.1%)	0.004
G1	23/41 (56.1%)	23/72 (31.9%)	0.01
G2	4/41 (9.8%)	0/72 (0%)	0.006
G3-G4	0/41 (0%)	0/72 (0%)	NA
Edema and pain			
Yes	2/41 (4.9%)	5/72 (6.9%)	0.66
No	39/41 (95.1%)	67/72 (93.1%)	0.66

NA, not applicable. [a]χ^2 test.

Table IV. *Late toxicity reported according to therapy.*

Late toxicity			
	230 cGy × 20 f (41/113)	300 cGy × 13 f (72/113)	*p*-Value[a]
Fibrosis			
G0	33/41(80.5%)	59/72 (81.9%)	0.85
G1	8/41 (19.5%)	11/72 (15.3%)	0.56
G2	0/41 (0%)	2/72 (2.8%)	0.28
G3-G4	0/41 (0%)	0/72 (0%)	NA
Scar retractin			
Yes	6/41 (14.6%)	13/72 (18%)	0.64
No	35/41(85.4%)	59/72 (82%)	0.64
Teleangiectasias			
Yes	0/41 (0%)	0/72 (0%)	NA
No	41/41 (100%)	72/72 (100%)	NA

NA, not applicable. [a]χ^2 test.

Table V. *Cosmetic results.*

Cosmetic results			
	230 cGy × 20 f (41/113)	300cGy × 13 f (72/113)	*p*-Value[a]
Excellent	25/41 (61%)	27/72 (37.5%)	0.02
Good	15/41 (36.6%)	29/72 (40.3%)	0.70
Accetable	0/4(0%)	10/72 (13.9%)	NA
Poor	1/41 (2.4%)	6/72 (8.3%)	0.21

NA, not applicable. [a]χ^2 test

end of RT course, included breast fibrosis, scar retraction, skin telangiectasias and hyperpigmentation. G1 fibrosis occurred in 19.6% and 15.3% in the two different schedules and G2 in 0% and 2.8% of cases, respectively. There were no statistically significant differences in the two radiation schemes. G3 and G4 fibrosis were not seen; 80.4% and 81.9% of patients respectively did not show any degree of fibrosis. Scar retraction was registered in 14.6% of the less hypofractionated schedules and in 18% of the shorter one, without statistically significant differences. No patients showed skin teleangiectasias and hyperpigmentation. Only two patients reported mild breast pain after treatment, which did not require any medical treatment. The acute and late toxicities are reported in Tables III and IV. The aesthetic outcome in the two different schemes was judged excellent in 61% and 37% ($p<0.05$), good in 36.6% and 40.3% (NS), acceptable in the 0% and 13.9% (NS) and poor in 2.4 and 8.3% (NS) of cases. Although selected patients treated with the less hypofractionated schedule showed a greater recognition of excellent aesthetic results compared to those of the stronger hypofractionated group it does not seem to correlate with an increased fibrosis, nor with an excess of scarring or telangiectasias. Evaluating all the treated patients, the esthetic result was poor in only 6% (7/113), considering not only RT effects but also the impact of surgery on the breast profile. Table V reports the cosmetic outcome for the two different RT schedules. The incidence of acceptable and poor esthetic results was higher in the most strongly hypofractionated group (2.4% *vs.* 22.2%), but considering the assessment of individual case we were able to ascribe the majority of the unfavorable cosmetic outcomes to surgical treatment: three patients underwent a margin re-excision, one patient had a keloid from previous surgery and one patient presented scar retraction before starting RT. It seems there was no detectable difference with regard to use of hormonal therapy in the overall distribution of cosmetic outcomes.

We noted only one relapse, developed after three years from the end of treatment. The patient was treated with mastectomy and is now without any evidence of disease. Given the natural history of DCIS, only a longer observation of the patients treated can assess long-term efficacy.

Discussion

Our experience with two radiobiologically equivalent postoperative HFRT schemes, with the addition of a weekly concomitant boost to the tumor bed, suggests that this approach is feasible in patients with DCIS, both in terms of esthetic outcome and local control. At a median follow-up of 30.5 (range=6-65) months, only one patient has developed local

recurrence (0.8%). Our data appear to be in agreement with those of the literature (range from 5%-10% at 5 years) (11-13). The results of several randomized trials justify the routine use of hypofractionation for adjuvant whole-breast radiotherapy in women with early breast cancer (5). The American Society for Radiation Oncology produced several recommendations for HFRT. Data were sufficient to support the use of whole-breast HFRT for patients with early-stage breast cancer aged 50 years or older, with stage pT1-2 pN0, not receiving chemotherapy and treated with a radiation dose homogeneity within ±7% in the central axis plane. For other patients, the task force could not reach agreement either for or against the use of whole-breast HFRT, which nevertheless should not be interpreted as a contraindication to its use (14). It may be hypothesized that this approach is a feasible option for treatment of patients with DCIS. Constantine *et al*. demonstrated the feasibility of treating the whole breast for DCIS with a hypofractionated regimen (2.8 Gy per fraction in 15 fractions, without boost) with modest acute and late toxicity and with a good cosmetic outcome (good to excellent in 91% of the patients) (15). Ciervide *et al*. treated 145 patients with DCIS with two different HFRT schemes in two different trials: the New York University NYU 01-51 Trial (16) prescribed 42 Gy (2.8 Gy in 15 fractions) to the whole breast and the NYU 05-181Trial (16) prescribed 40.5 Gy (2.7 Gy in 15 fractions) with an additional daily boost of 0.5 Gy to the surgical cavity. The reported cosmetic outcome was satisfactory: 91% good-to-excellent and only 9% fair-to-poor (16). With a median follow-up of five years, they found 4.1% ipsilateral local recurrences, comparable to that reported from the National Surgical Adjuvant Breast and Bowel Project trials that employed 50 Gy in 25 fractions of radiotherapy for DCIS (17). Williamson *et al*. compared local control in women treated with conventional (50 Gy in 25 fractions) or hypofractionated (42.4 Gy in 16 fractions or 40 Gy/16 plus 12.5 Gy boost) whole-breast irradiation after BCS for DCIS, with a median follow-up of 3.76 (range=0.1-8.9) years. Actuarial risk of recurrence at four years was 7% with whole-breast HFRT and 6% with the conventional schedule (p=0.9) (18).

Conclusion

These results suggest that patients with DCIS can be safely treated with a shorter regimen of radiotherapy and our preliminary records appear to be in agreement with the literature data, showing that even for this type of low-risk cancer, quality of life can be improved and the use of resources of the RT center can be optimized.

References

1 Kerlikovske K: Epidemiology of ductal carcinoma *in situ*. J Cancer Inst Monogr *41*: 139-141, 2010.

2 Weaver DL, Rosenberg RD, Barlow WE, Ichikawa L, Carney PA, Kerlikowske K, Buist DS, Geller BM, Key CR, Maygarden SJ and Ballard-Barbash R: Pathologic findings from the Breast Cancer Surveillance Consortium: Population-based outcomes in women undergoing biopsy after screening mammography. Cancer *106*: 732-742, 2006.

3 Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, Avril A, Sylvester R, Mignolet F, Bartelink H and Van Dongen JA: EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet *355*: 528-533, 2000.

4 Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, Fisher ER, Wickerham DL, Deutsch M, Margolese R, Dimitrov N and Kavanah M: Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol *16*: 441-452, 1998.

5 Yarnold J, Bentzen SM, Coles C and Haviland J: Hypofractionated whole-breast radiotherapy for women with early breast cancer: Myths and realities. Int J Radiat Oncol Biol Phys *79(1)*: 1-9, 2011.

6 Tuttle TM, Shamliyan T, Virnig BA and Kane RL: The Impact of Sentinel Lymph Node Biopsy and Magnetic Resonance Imaging on Important Outcomes Among Patients With Ductal Carcinoma In Situ. J Natl Cancer Inst Monogr *41*: 117-120, 2010.

7 Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, Cochran AJ, Cody HS 3rd, Edge SB, Galper S, Hayman JA, Kim TY, Perkins CL, Podoloff DA, Sivasubramaniam VH, Turner RR, Wahl R, Weaver DL, Wolff AC and Winer EP: American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol *23*: 7703-7720, 2005.

8 Corvò R, Ricchetti F, Doino D, Torielli P, Agostinelli S, Cavagnetto F, Giannelli F, D'Alonzo A, Vagge S, Belgioia L and Guenzi M: Adjuvant hypofractionated radiotherapy with weekly concomitant boost for women with early breast cancer: The clinical experience at Genoa University. Anticancer Res *30(11)*: 4749-4753, 2010.

9 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31*: 1341-1346, 1995.

10 LENT/Soma Tables [No authors listed]. Radiat Oncol *35*: 17-60, 1995.

11 Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M; UK Coordinating Committee on Cancer Research; Ductal Carcinoma *in situ* Working Party; DCIS trialists in the UK, Australia, and New Zealand: Radiotherapy and tamoxifen in women with completely excised ductal carcinoma *in situ* of the breast in the UK, Australia, and New Zealand: Randomised controlled trial. Lancet *362*: 95-102, 2003.

12 Bijker N, Meijnen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, Julien JP, Gennaro M, Rouanet P, Avril A, Fentiman IS, Bartelink H and Rutgers EJ: Breast-conserving treatment with or without radiotherapy in ductal carcinoma-*in situ*: Ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853da study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol *24*: 3381-3387, 2006.

13 Holmberg L, Garmo H, Granstrand B, Ringberg A, Arnesson LG, Sandelin K, Karlsson P, Anderson H and Emdin S: Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma *in situ* of the breast. J Clin Oncol *26*: 1247-1252, 2008.

14 Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, Julian TB, Marks LB, Todor DA, Vicini FA, Whelan TJ, White J, Wo JY and Harris JR: Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys *74(4)*: 987-1001, 2009.

15 Constantine C, Parhar P, Lymberis S, Fenton-Kerimian M, Han SC, Rosenstein BS and Formenti SC: Feasibility of accelerated whole-breast radiation in the treatment of patients with ductal carcinoma *in situ* of the breast. Clin Breast Cancer *8(3)*: 269-274, 2008.

16 Ciervide R, Dhage S, Guth A, Shapiro RL, Axelrod DM, Roses DF and Formenti SC: Five Year Outcome of 145 Patients With Ductal Carcinoma In Situ After Accelerated Breast Radiotherapy. Int J Radiation Oncol Biol Phys *83(2)*: 159-164, 2012.

17 Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, Land SR, Margolese RG, Swain SM, Costantino JP and Wolmark N: Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst. *103(6)*: 478-488, 2011.

18 Williamson D, Dinniwell R, Fung S, Pintilie M, Done SJ and Fyles AW: Local control with conventional and hypofractionated adjuvant radiotherapy after breast-conserving surgery for ductal carcinoma *in situ* Radiother and Oncol *95*: 317-320, 2010.

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