Scientific Research Publishing

Journal of Cancer Therapy, 2016, 7, 773-783
http://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Hypofractionated Radiation Therapy for the Treatment of Breast Cancer: Experience of National Institute of Oncology, Rabat, Morocco

A. S. Koné[1], A. Diakité[1], S. Ahid[2,3], I. M. Diarra[1], K. Diabaté[1], R. Abouqal[3], Y. Cherrah[2], N. Benjaafar[1]

[1]Service de Radiothérapie, Institut National d'Oncologie de Rabat, Rabat, Morocco
[2]Laboratoire de Pharmacologie & Toxicologie, Faculté de Médecine et de pharmacie de Rabat, Rabat, Morocco
[3]Laboratoire de Biostatistique, de Recherche Clinique et d'Epidémiologie, Faculté de Médecine et de pharmacie de Rabat, Rabat, Morocco
Email: adamadoc@yahoo.fr, aphousalle@yahoo.fr

How to cite this paper: Koné, A.S., Diakité, A., Ahid, S., Diarra, I.M., Diabaté, K., Abouqal, R., Cherrah, Y. and Benjaafar, N. (2016) Hypofractionated Radiation Therapy for the Treatment of Breast Cancer: Experience of National Institute of Oncology, Rabat. Morocco. *Journal of Cancer Therapy*, **7**, 773-783.
http://dx.doi.org/10.4236/jct.2016.710078

Received: June 20, 2016
Accepted: October 24, 2016
Published: October 27, 2016

Abstract

Hypofractionated radiation therapy has proven effective on locoregional control and tolerance in the adjuvant treatment of breast cancer. The aim of this study is to compare the results of hypofractionated radiation therapy versus conventional radiation therapy in terms of local control and tolerance. It was a retrospective study of patients observations collected from January 2007 to December 2008 in Department of Radiation Therapy in Institut National d'Oncologie de Rabat. The treatment results were evaluated by the rate of locoregional recurrence, distant recurrence and research of late toxicities. Radiotherapy was delivered using the same technique in both groups, by gamma photons of cobalt 60 with an energy of 1.25 MeV. They were 2 groups: the first group treated with standard dose rate and the second group treated by hypofractionated radiation therapy. The mean age of the patients was 42.8 ± 6.9 years old in the standard group and 43.22 ± 7.2 years old in the hypofractionation group. We noted a predominance of infiltrating ductal carcinoma. The majority of patients were pT_2, pN_0 and pN_1. The majority of patients had radical surgery and chemotherapy with anthracyclines in both groups. We noted a statistically significant difference in the irradiation of chest wall between the standard (89.2%) and hypofractionated group (70.3%), with $p = 0.043$. The median duration of radiation therapy was statistically different in both groups: 39 days in the standard and 23 days in the hypofractionated group ($p < 0.001$). The local recurrences were statistically identical to 12 and 24 months ($p = 0.999$). Concerning toxicities, the frequency of adverse event was similar in both groups. Hypofractionated radiation therapy with a total dose of 42 Gy at 2.8 Gy per fraction in 5 fractions weekly is comparable to standard radiotherapy in terms of local control and tolerance and is therefore a very good alternative to standard treatment.

Keywords

Hypofractionated Radiation Therapy, Breast Cancer, Local Control, Tolerance

1. Introduction

The hypofractionated irradiation is currently a good alternative in the adjuvant treatment of breast cancer. It has demonstrated oncological efficacy and good tolerance [1]-[5].

Since the 1990s, the hypofractionated scheme has been proposed by several teams with the aim of exploring a shorter pattern. This hypofractionated radiotherapy reduces the total treatment time by decreasing the number of meetings and increasing the dose per fraction to obtain a biological equivalence of the total dose [6] [7]. Several recent tests have shown that the α ratio/β du breast cancer is low, around 4 Grays; breast adenocarcinoma would therefore offer a significant sensitivity to variations in the dose per fraction. This radiobiological argument strengthens the current interest of hypofractionated breast cancer irradiation [8].

Several trials compared conventional irradiation versus hypofractionated irradiation. Whelan *et al.* compared 42.5 Gy scheme in 16 fractions of 2.65 Gy in 22 days versus 50 Gy classic scheme in 25 fractions of 2 Gy; with a recurrence rate of 6% at 10 years, which was equivalent in both groups [9]. The British trial Yarnorld *et al.* had compared the classic pattern versus two hypofractionated schemes: 39 Gy in 13 fractions in 42, 9 Gy in 13 fractions, with a spread of five weeks in the three arms. Analysis of the results at ten years showed a similar rate of relapse in the three arms [10]. This scheme has proved effective in local control, with a net decrease of treatment duration which is a major benefit in countries where the waiting list is long.

In Morocco, the Radiotherapy Department of the National Oncology Institute (INO) is confronting with a high number of patients awaiting treatment. The majority of patients came from far away to receive their radiation therapy for 5 weeks.

In view of previous clinical trials, the radiation therapy team adopted in 2007, the hypofractionated scheme in order to decongest the treatment posts and to facilitate access of treatment for patients with a shorter regimen of 42 Gy in 15 fractions over 21 days 2, 8 Gy.

The objective of this work is to compare the results of hypofractionated radiotherapy versus conventional radiotherapy in terms of locoregional control and toxicities.

2. Patients and Methods

This is a retrospective study on observations of patients collected from January 2007 to December 2008 at the radiotherapy department of INO in Rabat.

Patients with invasive tumor, without metastasis and who received standard radiotherapy and hypofractionated radiotherapy after surgery and chemotherapy were included in the study. The breast cancer patients who have not received radiotherapy

were excluded from the study.

The treatment results were evaluated by the rate of locoregional recurrence, distant recurrence and research of late toxicities.

Surgical treatment consisted of radical surgery with mastectomy and axillary node dissection or conservative surgery with lumpectomy plus ipsilateral axillary node dissection.

Chemotherapy was administered to all patients with recurrence risk factors. The chemotherapy regimens were either anthracycline-based AC (Adriamycin 6 cycles: 60 mg/m^2 and cyclophosphamide: 600 mg/m^2); FEC (6 cycles of 5-fluorouracil: epuribicine: 100 mg/m^2, cyclophosphamide); or combining anthracyclines and taxanes in sequential 4 AC courses, followed by 4 paclitaxel or 4 AC courses, followed by 4 cycles of docetaxel or 3 courses of FEC followed by 3 docetaxel.

Radiotherapy was delivered using the same technique in both groups, by gamma photons of cobalt 60 with an energy of 1.25 MeV.

The first group (A) receiving radiation therapy according to the standard scheme, with total dose of 50 Gy in a proportion of 2 Gy per fraction in 25 sessions over 5 weeks, associated with a boost on the tumor bed in the case of conservative surgery dose Total 15 - 16 Gy the second group (B) received radiotherapy according to scheme hypofractionated total dose of 42 Gy in a rate of 2.8 Gy per fraction in 15 sessions on 3 weeks associated with an overlay 15 - 16 Gy in case of conservative surgery. The supraclavicular area was irradiated when axillary dissection was positive, the internal mammary chain when the tumor was located in an internal quadrant or metastatic axillary lymph nodes (more than 3) were found during the analysis of the dissection piece.

The axillary irradiation was associated with the supraclavicular when the cleaning was inadequate and positive. The nodal irradiation, when indicated, delivered a dose of 50 Gy in 25 fractions in group A and 42 Gy in 15 fractions in group B. The boost was issued either by interstitial brachytherapy, either by photons or electrons.

Hormone therapy was prescribed in all patients hormone-sensitive. The positivity rate was 10%. Patients received for 5 years or tamoxifen or aromatase inhibitors according to their menopausal status and their financial means.

Monitoring and evaluation were performed in 6 to 12 - 24 months and included: the clinical component through research recurrence of signs of the tumor bed and nodal areas and skin, heart, lung toxicities. Acute toxicities were not exploitable in the patient medical files.

Late toxicities were evaluated according to the SOMA-LENT scale (subjective objective management analytic-late effects of normal Tissues scale (SOMA-LENT) [11].

The radiological component of the evaluation included a mammogram, looking for locoregional recurrence in case of conservative treatment and in the controlateral breast. Chest radiography in search of metastasis and sequelae of radiation therapy.

Statistical Analysis

The variables were expressed as mean and standard deviation or median and interquartile or percentage. Patients who received standard or hypofractionated radiation were

compared by univariate analysis using the χ^2 test or the Fisher exact test for variables-qualitatives and the Student t test for quantitative variables. Distribution distribution of quantitative variables was verified by the Kolmogorov-Smirnov. Mann- Whitney test was used for comparison of quantitative variables that did not have a normal distribution. P value < 0.05 was considered significant.

A propensity score, which is the probability of receiving the hypofractionated radiotherapy, was developed by a multiple logistic regression model including confounding factors vis-à-vis the propensity to receive hypofractionated radiotherapy: age patients, histological type, histological size, number of involved lymph nodes, SBR grade, hormone receptor positivity and surgical resections. Continuous variables, who was linear relation with the logit of the probability of hypofractionated radiotherapy were introduced in the model [12] [13] [14].

One patient of hypofractionated arm was matched to one patient of standard arm nearest propensity score using the method of five to one digit of the propensity score (technical greedy matching): the best match was obtained when the propensity score was identical to the fifth decimal score.

When a match was obtained, the pair hypofractionated/standard radiation therapy was removed from the process. When matching is not possible with an identical score to the fifth decimal place, it was made for an identical score to four decimal places, then three and so on up to a decimal.

If the match was not obtained at that point, the patient who received radiation therapy were excluded. The comparison of groups and evaluation of effects of standard and hypofractionated radiation therapy were performed by conditional univariate logistic regression.

Statistical analysis was performed with SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

117 patients were selected on 329 eligible patients, with 54 in the standard arm and 63 in arm B hypofractionated (**Figure 1**). We noted a statistically significant difference between the two arms on age. The median age was 40.2 ± 7.7 years in the standard arm and 49 ± 9.7 years hypofractionated in the arm with p < 0.001. Other features such as histology, histologic tumor size, histologic node involvement, SBR grade, hormone receptors, surgical limits were comparable between the two arms. The propensity score has to match 37 patients in each arm on the various clinical and pathological features above-mentioned (**Table 1**).

After matching, the median age of patients was 42.8 ± 6.9 years in the standard arm and 43.22 ± 7.2 years in the hypofractionatedarm.

We noted a predominance of invasive ductal carcinomas. The majority of patients had pT2 and pN0 and pN1 (**Table 2**).

Therapeutic characteristics such as surgery and chemotherapy were statistically the same in both groups (p = 0.121 and p = 0.552). Over the majority of patients underwent radical surgery and anthracycline-based chemotherapy in both groups (**Table 3**). Re-

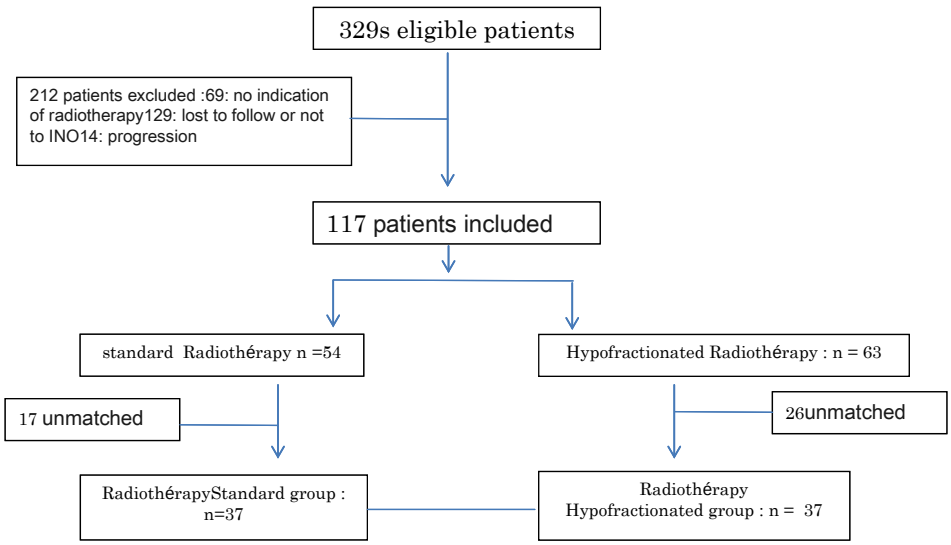

Figure 1. Patients matching.

garding radiotherapy, we observed a statistically significant difference of radiation to the chest wall between the standard arm (89.2%) and hypofractionné arm (70.3%), with p = 0.043. We did not find statistically significant differences in both groups for the irradiation of the lymph nodes, the supraclavicular area and internal mammary chain. The median duration of radiation therapy was statistically different in both groups: 39 days (37 - 44) in the standard arm and 23 days (21 to 27) in the hypofractionated arm (p < 0.001).

We have found no recurrence at 6 months. Local recurrence were statistically identical at 12 and 24 months (p = 0.999).

For late toxicities, we did not find statistically significant difference in both arms; with 83.7% in the standard arm and 86.4% in the hypofractionned arm. The pain was 37.8% and 16.21% respectively in standard and hypofractionated arm; fibrosis was found in 21.6% of patients in the standard arm versus 16.21% in the hypofractionated arm; lymphedema at 16.21% versus 2.7%; atrophy at 5.4% versus 8.1% and cardiac arrhythmia was 2.7% in each arm. No late lung toxicity was observed (Table 4).

According to the SOMA-LENT scale, we found 51.35% and 24.32% of late grades I and II toxicities in the standard arm versus 29.73% and 16.21% in the hypofractionated arm. No Toxicity of grade III or IV have been find in the standard arm, while in the hypofractionated arm, there was only one case of toxicity, grade III with cardiac arrhythmia (Table 5).

4. Discussion

Analysis of the results of this retrospective study showed that adjuvant radiotherapy with a hypofractionated scheme is comparable to the standard regimen in terms of local control and tolerance with a significant reduction in the median duration of radiation between the two arms. Several clinical trials have focused on the evaluation of local

Table 1. Comparison of patients who received standard radiation therapy and hypofractionated radiotherapy before pairing.

Characteristics	Standard N = 37 n (%)	Hypofractionated N = 37 n (%)	*p*
Age (year)*	40.24 ± 7.69	49.03 ± 9.76	<0.001
Histological type			0.418
CCI	49 (90.7)	59 (93.7)	
CLI	5 (9.3)	3 (4.8)	
Other	0	1 (1.6)	
Histological tumoral size (pT)			
			0.357
pT1	9 (18.4)	10 (17.2)	
pT2	25 (51)	37 (63.8)	
pT3	11(22.4)	7 (12.1)	
pT4	4 (8.2)	4 (6.9)	
Number of involved nodes (pN)			
pN0	26 (48.1)	21 (34.4)	0.418
pN1	18 (33.3)	22 (36.1)	
pN2	7 (13)	12 (19.7)	
pN3	3 (5.6)	6 (9.8)	
SBR Grade			
I	4 (8)	9 (15.5)	
II	31 (62)	25 (43.1)	0.131
III	15 (30)	24 (41.4)	
Hormone receptors			
Positives	41 (75.9)	55 (87.3)	
Negatives	13 (24.1)	8 (12.7)	
Surgical limits			
Positives	52 (96.3)	59 (93.7)	0.11
Negatives	2 (3.7)	4 (6.3)	0.416

*: Expressed as mean and standard deviation; CCI: infiltrating ductal carcinoma; CLI: invasive lobular carcinoma; pT: Histological tumor size; pN: Histological lymphadenopathy.

control; Whelan *et al.* showed that 42.5 Gy radiotherapy 16 2.65 Gy fractions in 22 days gave the same results in terms of local control that the vector diagram of 50 Gy in 25 fractions of 2 Gy in 35 days; with a recurrence rate at 10 years 6%, which was equivalent

Table 2. Comparison of patients who received standard radiation therapy and hypofractionated radiotherapy after matching.

Characteristics	Standard N = 37 n (%)	Hypofractionated N = 37 n (%)	*p*
Age (year)*	42.86 ± 6.9	43.22 ± 7.2	0.835
Histological type			0.477
CCI	35 (94.6)	34 (92)	
CLI	2 (5.4)	2 (5.4)	
Other	0	1 (2.7)	
Histological tumoral size (pT)			0.357
pT1	3 (9.4)	7 (18.9)	
pT2	20 (62.5)	23 (62.5)	
pT3	7 (21.9)	4 (10.8)	
pT4	2 (6.3)	3 (8.1)	
Number of involved nodes (pN)			0.138
pN0	17 (45.9)	13 (35.1)	
pN1	12 (32.4)	11 (29.7)	
pN2	6 (16.2)	7 (18.9)	
pN3	2 (5.4)	6 (16.2)	
SBR Grade			
I	2 (5.9)	3 (8.6)	
II	19 (55.9)	18 (51.4)	0.949
III	13 (38.2)	14 (40)	
Hormone receptors			
Positives	27 (73)	31 (83.8)	
Negatives	10 (27)	6 (16.2)	
Surgical limits			
Positives	35 (94.6)	35 (94.6)	0.263
Negatives	2 (5.4)	2 (5.4)	0.999

*: Expressed as mean and standard deviation; CCI: infiltrating ductal carcinoma; CLI: invasive lobular carcinoma; pT: Histological tumor size; pN: Histological lymphadenopathy.

in both groups [2] [3]. The British trial Yarnorld *et al.* had compared the classic pattern versus two regimens hypofractionated 39 Gy in 13 fractions and 42.9 Gy in 13 fractions, with a spread of five weeks in the three arms. Analysis of the results at ten years showed a similar rate of relapse in the three arms [4] [5] [6].

The Start trial A, in 2236 randomized patients with localized breast cancer, three conservative arm after radical surgery or 50 Gy in 25 fractions versus 41.6 Gy in 13 fractions and 39 Gy in 13 fractions with a spreading 5 weeks. There was not a statistically significant difference in the three arms on the risk of recurrence. The Start B trial, randomized after conservative or radical surgery, patients in both arms in 2215: 50 Gy in 25 fractions versus 40 Gy in 15 fractions. Local recurrence at 6 years was 3.3% in the standard arm and 2.2% in the arm with a significant difference. Our results are consistent with those found in these studies.

Table 3. Therapeutic characteristics of patients.

Characteristics	Standard n = 37 n (%)	Hypofractionated n = 37 n (%)	*p*
Surgery			0.121
Radical	30 (81)	24 (65)	
Conservative	7 (19)	13 (35)	
Chemotherapy			
Neo-adjuvant	3 (8)	6 (16.7)	0.275
Adjuvant (protocol)			0.552
Anthracyclins	24 (64)	22 (63)	
Sequential	7 (18.9)	10 (28.6)	
Radiotherapy			
Chest wall	33 (89.2)	26 (70.3)	0.043
Breast + Chest wall	4 (10.8)	19 (27)	0.075
Clavicular aera	21 (56.8)	21 (56.8)	0.999
Axillary-supraclavicular	2 (5.4)	1 (2.7)	0.556
Internal mammary chain	22 (59.5)	15 (40.5)	0.104
Spading (days)	39 (37 - 43)	23 (21 - 27)	<0.001
Boost	8 (21.6)	13 (35)	0.197
Hormone therapy	29 (78.4)	32 (86.5)	0.359

An analysis of Xi *et al.* on radiobiological models showed that the ratio α/β of breast cancer was 2.88 Gy (0.75 - 5.01).

The hypofractionated arms of 2.26 Gy × 20, 10 × 3.34, 3.34 × 10 Gy, 4.95 Gy × 5 or 3.39 Gy × 10 had the same effectiveness as the classic pattern of 2 Gy × 25 [8].

The effective biological dose (Biological Effective Dose, BED) can quickly compare different requirements according to the following formula: BED = nd (1 + d/ (α/β) Using the α ratio/βde 4 Gy, proposed by Yamada *et al.* [14], the effective biological dose was 75 Gy for a prescription of 50 Gy in 25 fractions and 71.4 Gy for our prescription of 42 Gy in 15 fractions Thus the effective biological dose with a prescription of 42 Gy. 15 fractions is approximately 95% of that received by giving 50 Gy in 25 fractions.

In terms of effective dose, the two requirements are equivalent because the treatment in 15 fractions of 2.8 Gy is done on a shorter spreading.

Most studies have evaluated the hypofractionated scheme in patients who received conservative treatment, whereas in our series 7 patients in the standard arm and 13 in the hypofractionated arm had that conservative treatment. In each arm over half of the patients had lymph node involvement than 4 and the irradiation of lymph nodes was done according to the hypofractionated scheme, while in the Canadian trial patients had no lymph node involvement and thus no lymph node irradiation [15]. In tests Standardisation of Breast Radiotherapy (START) A and B, nodal involvement was less than or equal to 3 (N1) and less than 10% of patients underwent radical surgery, only

14 and 7% of patients respectively received a nodal irradiation [16]. Our results imply that the hypofractionated scheme is as effective and tolerated in case of radiation to the chest wall and lymph nodes.

In our study, the boost on the tumor bed was primarily via brachytherapy or by electrons. No studies have tested the overprint on a hypofractionatedscheme. In trying to Whelan there was no overprinting and English tests, she was under the classical scheme.

Acute toxicities were not evaluated in our study. A French prospective trial conducted at the Institut Curie showed a delayed skin reaction occurring within 14 days after the end of irradiation hypofractionated to the total dose of 42.9 Gy in 13 fractions [17].

Our study showed that there was no statistically significant difference in late toxicity in both arms. These same results were found in other studies. An Italian study comparing two arms: 45 Gy in 2.25 Gy/fraction in 85 patients, versus 50 Gy in 2 Gy/fraction in 70 patients; showed that the risk of late toxicity at 12 to 30 months were 5.9% and

Table 4. Evaluation of local control and late toxicity.

	Standard n = 37 n (%)	Hypofractionated n = 37 n (%)	*p*
Followed at 6 months			
Local control	37 (100)	37 (100)	
Followed at 12 months			0.999
Local control	37 (100)	36 (97.3)	
Recidivism	0	1 (2.7)	
Followed at 24 months			0.999
Local control	35(94.6)	36 (97.3)	
Recidivism	2 (5.4)	1 (2.7)	
Pain	14 (37.8)	8 (21.6)	0.127
Fibrosis	8 (21.6)	6 (16.2)	0.553
Lymphedema (arm)	6 (16.2)	1 (2.7)	0.124
Atrophy	2 (5.4)	3 (8)	0.643
Cardiac arrhythmia	1 (2.7)	1 (2.7)	0.999

Table 5. Late toxicities that the SOMA-LENT scale.

	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Arm*	S	H	S	H	S	H	S	H
Pain	12	7	1	0	0	0	0	0
Fibrosis	5	3	4	0	0	0	0	0
Lymphedema (arm)	2	0	1	0	0	0	0	0
Atrophy	0	1	0	0	0	0	0	0
Cardiac arrhythmia	0	0	0	0	1	0	0	0

*S: standard; H: hypofractionated.

29.2% respectively in the hypofractionated arm; 8.7% and 10.6% in the standard arm; but not statistically significant.

Whelan *et al.* had found the late toxicities of grade I and II similar in the both arms and at 5 and 10 years. These data comply with our results; we essentially found similar late toxicities, grade I and II in both arms.

No late lung toxicity had been found in patients, however we noted cardiac arrhythmia grade II was found in a patient's of standard arm, grade III in hypofractionated arm. We have not recovered grade IV toxicity.

Our study shows the low sampling-related limits. Indeed on 117 records selected in total, we had 37 selected in each arm, a total of 74 patients. Acute toxicities were not exploitable in the files where the interests of standardization regarding the postponement toxicities during treatment.

5. Conclusion

The hypofractionated radiotherapy with a total dose of 42 Gy at a rate of 2.8 Gy per fraction, 5 weekly fractions, gives results comparable to standard radiotherapy in local control and tolerance and is therefore a good alternative to standard treatment. Our results suppose that hypofractionated radiation therapy scheme can be as effective and well tolerated on the chest wall and the lymph nodes, but needs to be confirmed in a randomized trial.

Conflict of Interest

The authors declare that they have no conflict of interest in connection with the submitted manuscript.

References

[1] Botti, M., Kirova, Y.M., Dendale, R. and Savignoni, A. (2009) La radiothérapie hypofractionnée en 13 séances, parfaite tolérance ou réaction cutanée décalée? Etude prospective de l'institut Curie. *Cancer/Radiothérapie*, **13**, 92-96. http://dx.doi.org/10.1016/j.canrad.2008.11.009

[2] Whelan, T., MacKenzie, R., Julian, J., *et al.* (2002) Randomized Trial of Breast Irradiation Schedules after Lumpectomy for Women with Lymph Node-Negative Breast Cancer. *Journal of the National Cancer Institute*, **94**, 1143-1150. http://dx.doi.org/10.1093/jnci/94.15.1143

[3] Whelan, T.J., Pignol, J.P., Levine, M.N., Julian, J.A., MacKenzie, R., Parpia, S., Shelley, W., Grimard, L., Bowen, J., Lukka, H., Perera, F., Fyles, A., Schneider, K., Gulavita, S. and Freeman, C. (2010) Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer. *The New England Journal of Medicine*, **362**, 513-520. http://dx.doi.org/10.1056/NEJMoa0906260

[4] Yarnold, J., Ashton, A., Bliss, J., *et al.* (2005) Fractionation Sensitivity and Dose Response of Late Adverse Effects in the Breast after Radiotherapy for Early Breast Cancer: Long-Term Results of a Randomized Trial. *Radiotherapy and Oncology*, **75**, 9-17. ttp://dx.doi.org/10.1016/j.radonc.2005.01.005

[5] Yarnold, J. and Haviland, J. (2010) Hypofractionated Adjuvant Whole Breast Radiotherapy:

Progress and Prospects. *Acta Oncologica*, **49**, 1288-1292.
http://dx.doi.org/10.3109/0284186X.2010.509334

[6] Yarnold, J., Bentzen, S.M., Coles, C. and Haviland, J. (2011) Hypofractionated Whole-Breast Radiotherapy for Women with Early Breast Cancer: Myths and Realities. *International Journal of Radiation Oncology * Biology * Physics*, **79**, 1-9.
http://dx.doi.org/10.1016/j.ijrobp.2010.08.035

[7] Cosset, J.M. (2005) Hypofractionnement en radiothérapie: Le retour? *Cancer/Radiothérapie*, **9**, 366-373. http://dx.doi.org/10.1016/j.canrad.2005.09.013

[8] Qi, X.S., White, J. and Li, X.A. (2011) Is α/β for Breast Cancer Really Low? *Radiotherapy and Oncology*, **100**, 282-288. http://dx.doi.org/10.1016/j.radonc.2011.01.010

[9] START Trialists' Group, Bentzen, S.M., Agrawal, R.K., *et al.* (2008) The UK Standardisation of Breast Radiotherapy (START) Trial A of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: A Randomized Trial. *The Lancet Oncology*, **9**, 331-341.
http://dx.doi.org/10.1016/S1470-2045(08)70077-9

[10] START Trialists' Group, Bentzen, S.M., Agrawal, R.K., *et al.* (2008) The UK Standardisation of Breast Radiotherapy (START) TrialB of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: A Randomized Trial. *Lancet*, **371**, 1098-1107.
http://dx.doi.org/10.1016/S0140-6736(08)60348-7

[11] (1995) LENT/Soma Tables. *Radiation Oncology*, **35**, 17-60.

[12] Guenzi, M., *et al.* (2010) A Biologically Competitive 21 Days Hypofractionation Scheme with Weekly Concomitant Boost in Breast Cancer Radiotherapy Feasibility Acute Sub-Acute and Short Term Late Effects. *Radiation Oncology*, **5**, 111.
http://dx.doi.org/10.1186/1748-717X-5-111
Rosenbaum, P.R. and Rubin, D.B. (1983) The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika*, **70**, 41-55.
http://dx.doi.org/10.1093/biomet/70.1.41

[13] Rubin, D.B. (1997) Estimating Causal Effects from Large Data Sets Using Propensity Scores. *Annals of Internal Medicine*, **127**, 757-763.
tp://dx.doi.org/10.7326/0003-4819-127-8_Part_2-199710151-00064

[14] Yamada, Y., Ackerman, I., Franssen, E., MacKenzie, R.G. and Thomas, G. (1999) Does the Dose Fractionation Schedule Influence Local Control of Adjuvant Radiotherapy for Early Stage Breast Cancer? *International Journal of Radiation Oncology * Biology * Physics*, **44**, 99-104.

[15] Deantonio, *et al.* (2010) Hypofractionated Radiotherapy after Conservative Surgery for Breast Cancer: Analysis of Acute and Late Toxicity. *Radiation Oncology*, **5**, 112.
http://dx.doi.org/10.1186/1748-717X-5-112

[16] Pinnarò, P., *et al.* (2010) Accelerated Hypofractionated Radiotherapy as Adjuvant Regimen after Conserving Surgery for Early Breast Cancer: Interim Report of Toxicity after a Minimum Follow up of 3 Years. *Journal of Experimental & Clinical Cancer Research*, **29**, 9.
http://dx.doi.org/10.1186/1756-9966-29-9

[17] Cutuli, B. and Fourquet, A. (2011) Irradiation hypofractionnée dans le cancer du sein: Pour ou contre? *Cancer/Radiothérapie*, **15**, 445-449.
http://dx.doi.org/10.1016/j.canrad.2011.07.235