Hypofractionated irradiation in elderly patients with breast cancer after breast conserving surgery and mastectomy: Analysis of 205 cases

Mélanie Doré1*, Bruno Cutuli2, Patrice Cellier3, Loïc Campion1 and Magali Le Blanc1

Abstract

Background: Several randomized trials and meta-analyses confirmed a wide benefit of radiotherapy (RT), both after breast conserving surgery (BCS) and mastectomy. However, many elderly women don’t receive RT. Hypofractionated (HF) RT allows « simplified » and more accessible treatments with equivalent results to classic RT in three large randomized trials. However, there are few available data on HF-RT for nodal irradiation, as well as for the boost.

Methods: We evaluated patients treated for IBC by HF-RT between 2004 and 2012 in two regional cancer centres. We used an original scheme delivering 45 Gy in 15 fractions three times a week, both after BCS or mastectomy, with or without nodal irradiation. After BCS, a 9 Gy boost in 3 fractions was delivered. Local, regional and distant recurrences were assessed, as well as acute and late cutaneous, cardiac or pulmonary toxicities.

Results: 205 patients were analysed, 116 after BCS (57 %) and 89 after mastectomy (43 %). Median age was 81 years (range: 52-91); 44 % had axillary nodal involvement (pN+). The Nottingham Prognostic Index (NPI) scored 0, 1, 2 and 3 in 10 %, 27 %, 44 % and 19 % of the cases. A nodal HF-RT was delivered in 65 patients (32 %) and boost in 98 patients (84 % of BCS) by 9 Gy/3 fr scheme. Fifty (24 %) patients underwent chemotherapy and 156 (75 %) hormonal treatment. With a 49-month median follow-up, 3/116 (2.6 %) patients and 4/89 (4.5 %) had local recurrence (LR) after BCS and mastectomy, respectively. The overall 5-year LR rate was 4.4 %. In univariate and multivariate analysis, LR risk factors were: high NPI (HR 5.46; p = 0.028), and triple negative tumour (HR 9.78; p = 0.006). Only 8 (4.5 %) patients had grade III skin toxicity; 29 (14 %) late fibrosis and 16 (8 %) telangiectasia. No pulmonary or cardiac toxicity was observed.

Conclusion: Our HF-RT scheme (with or without nodal irradiation) confirms in elderly patients the data from randomized trials, both after BCS or mastectomy. Toxicity seems very acceptable but requires a longer follow-up. A larger evaluation is still ongoing in several other centres in France.

Keywords: Breast cancer, Hypofractionated radiotherapy, Elderly, Breast-conserving surgery, Mastectomy, Local recurrence, Toxicity, Nodal irradiation

* Correspondence: meladore@gmail.com
1Radiation Oncology Department, Institut de Cancérologie de l’Ouest, Nantes, France
Full list of author information is available at the end of the article

© 2015 Doré et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
In Western countries, breast cancer (BC) is the most common female cancer, and occurs frequently in women older than 70 [1]. In two large national surveys performed in France (1155 patients) and Italy (3532 patients) in 2001–2002, BC rates in women older than 70 were 20.4 and 18.5 %, respectively [2, 3]. This rate reached almost 30 % in another Swiss study including 4820 patients treated from 2003 to 2005 [4].

The benefit of post-operative irradiation was widely confirmed by several studies, randomized trials [5, 6] and meta-analyses (EBCTCG) [7], both after breast conserving surgery and mastectomy, but many studies showed a clear undertreatment in older patients for various reasons (e.g. difficult access to radiotherapy centres, comorbidities). This fact induces higher local recurrence (LR) rates and increases long-term mortality [8, 9]. Thus, the International Society of Geriatric Oncology’s recent guidelines strongly recommend the use of post-operative RT in the same conditions as in a younger population, whenever possible [1]. In order to facilitate the access to radiotherapy centres and to simplify treatment modalities, several schemes of «hypofractionated» RT (HFRT) have been developed for 15–20 years, especially in UK and Canada [10–12]. Other French centres have been using «empirically» shortened schemes for many years [13–15]. However, due to a lack of data of the randomized trials on HFRT and mastectomy, HFRT and lymph node irradiation (LNI), and HFRT and chemotherapy, the use of a shortened scheme is not recommended yet in those situations.

Methods
Data collection
We assessed 205 postmenopausal patients treated by HFRT for a non-metastatic BC in two regional cancer centres (Nantes and Angers) between June 2004 and June 2012 both after breast conserving surgery (BCS) or mastectomy.

For each patient, a file detailed the following items: BC family history, age at menopause, hormone replacement therapy (HRT), comorbidities, type of surgery (lumpectomy/mastectomy), RT modalities (volumes/dose), chemotherapy and/or hormonal therapy.

The following histopathological features were also assessed: tumour size, axillary nodal involvement (ANI), histological subtype (ductal, lobular, mixed), SBR (Scarff, Bloom and Richardson) grading, excision quality, presence of vascular or lymphatic emboli, Her-2 oncoprotein over-expression and hormone receptor status (HR). The «Nottingham Prognostic Index» (NPI) score was calculated taking into account tumour size, ANI and SBR grading. The study was in accordance to the declaration of Helsinki in its latest version.

Radiotherapy techniques and dose equivalence
HFRT was delivered 4–8 weeks after surgery or 4–6 weeks after chemotherapy. A 45 Gy total dose in 15 fractions (3 per week) was delivered to the whole breast (with or without a 9 Gy boost in 3 fractions) or chest wall, by two opposed tangential fields (4–10 MV photons). The boost was delivered by an anterior field (9–12 Mev electrons) or by two reduced tangential fields. In case of nodal irradiation (supraclavicular fossa (SCF), axilla or internal mammary chain (IMC)), the same dose was delivered (45 Gy/15 fr, 3 fr/week). SCF and axilla were treated by a 10 MV photon direct field (with or without a complementary posterior field for axilla according to dosimetry), and IMC by a direct field using a combination of photons and electrons. Assuming that α/β = 3.5, the Biological Equivalent Dose (BED) of 45 Gy/15 fr scheme was 52 Gy using the iLQ version 1.0 Calculator (by SFjRO, French Society of Young Radiation Oncologist).

Toxicity assessment and follow-up
During the treatment, a weekly consultation was performed by a radiation oncologist. The acute skin toxicity was assessed by the CTCAE scale (Common Terminology Criteria for Adverse Events). After treatment, the patients were assessed twice a year in order to evaluate the oncological outcome and possible toxicities (fibrosis, telangiectasias, rib fractures, heart or lung sequelae). An annual mammogram was performed as well as other exams in case of clinical symptoms.

Statistics
The continuous variables were described by the median [extreme values] and/or the mean ± standard deviation. The qualitative variables were described by the distribution of their modalities. The evolutive variable (local recurrence-free survival) was defined as the period between the date of initial surgery and the date of local recurrence of the date of last news without local recurrence. It was calculated using the Kaplan-Meier method. The groups in question were compared using Student’s test (or the Mann-Whitney non-parametric test if necessary) for continuous variables and by Pearson’s Chi² test (or Fisher’s exact test if necessary) for qualitative variables. The local recurrence-free survival curves were compared using the logrank test for the variables in classes and using the univariate Cox model for continuous variables. The prognostic variables at the univariate stage in addition to those with p < 0.15 were entered in the multivariate Cox’s semi-parametric regression model. The analyses were performed in bilateral formulation and the p-value of significance was set at 5 %. The software used was Stata 13.1 (StataCorp, College Station, Texas 77845 USA).
Results

Patients characteristics
Median age was 81 years (range: 52–91) with 94 % over 70 years; 45 patients (22 %) had BC family history; among all patients, only 18 (9 %) received HRT (median duration: 8 years). Among comorbidities, we observed heart failure, severe respiratory disease or severe neurologic or osteoarticular disease in 12, 5 and 32 % of the cases, respectively. BC was discovered clinically in 61 % of the cases; 56 % of BC were in the left side.

Histopathological characteristics of the entire population are described in Table 1. Histological median tumour size was 20 mm (3–70); 177 (86 %) were infiltrating ductal carcinomas (IDC), 14 (7 %) infiltrating lobular carcinomas (ILC), 4 mixed types and 10 other types; 90 patients (44 %) had ANI. Among 144 evaluated cases, 32 (22 %) had vascular emboli. Finally, 24 (12 %) tumours were triple-negative (ER-, PgR-, Her-2-) and 18 had Her2 over-expression (9 %).

| Table 1 | Histopathological features of the population |
|---------|--------------------------------------------|
|          | Number of patients | Percent |
| pT       |                            |         |
| 1        | 85                        | 41,5    |
| 2        | 87                        | 42,5    |
| 3        | 15                        | 7,5     |
| 4        | 11                        | 5,5     |
| not specified | 7                    | 3       |
| pN       |                            |         |
| 0        | 115                       | 56      |
| 1 (1–3 nodes) | 63                  | 31      |
| 2 (4–9 nodes) | 20                  | 10      |
| 3 (≥10 nodes) | 7                   | 3       |
| HR positive (ER+ and /or PgR+) | 172   | 84      |
| HR negative | 33                     | 16      |
| HER2 overexpression | 18               | 9       |
| Triple Negative tumor | 24             | 12      |
| SBR grading |                          |         |
| I        | 37                        | 18      |
| II       | 107                       | 52      |
| III      | 61                        | 30      |
| NPI class |                          |         |
| 0        | 20                        | 10      |
| 1        | 56                        | 27      |
| 2        | 90                        | 44      |
| 3        | 39                        | 19      |

HR hormonal receptor, ER estrogen receptor, PgR progesterone receptor, SBR Scarff Bloom et Richardson grading, NPI Nottingham prognostic index

Treatment modalities
Eighty-nine patients (43 %) underwent mastectomy and 116 (57 %) breast conserving surgery. For both groups, the median follow-ups were 53 and 47 months ($p = 0.37$), respectively. Table 2 summarizes radiotherapy modalities for both groups. Globally, 65 patients (32 %) underwent lymph node irradiation and 98 out of 116 (84 %) received boost after whole breast irradiation. Among 50 (24 %) patients undergoing chemotherapy (CT), 18 received a TC (Taxotere-Cyclophosphamide) protocol, 11 FEC 50 (5FU, Epirubicin, Cyclophosphamide) protocol, 9 EC 100-Taxotere and 12 others. Among 156 (75 %) patients undergoing hormonal treatment (HT), 150 received aromatase inhibitors and 6 Tamoxifen.

Local recurrences
After a 49-month median follow-up, seven local recurrences (LR) occurred: 3 out of 116 (2.6 %) patients treated by BCS and 4 out of 89 (4.5 %) treated by mastectomy. The overall 5-year LR rate was 4.4 %. One patient with LR after BCS had synchronous metastases and three patients with LR after mastectomy developed metastases in the subsequent 4 months. All the patients received chemotherapy (CT).

Table 3 details LR risk factors both in univariate and multivariate analysis. In univariate analysis, significant LR risk factors were high NPI (HR 5.46, $p = 0.028$), triple-negative tumour (HR 9.78, $p = 0.006$), with a trend for ANI (HR 6.97, $p = 0.073$). In multivariate analysis, only triple-negative tumours remained significant ($p = 0.021$) and high NPI was borderline ($p = 0.058$).

Regional and distant failures
Five nodal recurrences (NR) occurred: four in axilla and one in supraclavicular fossa. Two of these NR occurred after nodal irradiation. The overall 5-year NR rate was 3.6 %. Twenty-five patients developed metastasis with a 28-month median delay: 10 bone, 4 lung and 1 liver; 10 patients had multiple sites involved.

| Table 2 | Radiotherapy modalities among patients treated by mastectomy and breast conserving surgery (BCS) |
|---------|---------------------------------------------------------------|
|          | Mastectomy | BCS                |
| n (%)    |             |                    |
| LNRT n = 65 (32 %) | 89 (43 %)  | 116 (57 %)   |
| Supraclavicular fossa (SCF) | 40       | 24               |
| Internal mammary chain (IMC) | 16       | 6                |
| axilla   | 5          | 3                |
| Boost irradiation | 4 (4.5 %) | 98 (84 %)   |

 LNRT lymphnodal irradiation with multiple fields possible
*multiple fields possible
Survival rates and death causes
The 3- and 5-year specific survival rates were 94 and 91.3 % respectively. Forty-two (20.5 %) patients died, including 15 by metastases, 24 by intercurrent disease and 3 of second cancer.

Toxicities
Table 4 shows the early and late skin toxicity rates according to treatments.
Twenty-nine (14 %) patients had no acute skin toxicity; 133 (65 %), 35 (17 %) and 8 (4 %) had respectively grade I, II and III cutaneous toxicity (radio-epithelitis). Among 8 patients with grade III toxicity, only one underwent chemotherapy. Four patients with grade III toxicity required a 7–10 days stop during the treatment.
Thirty (14.6 %) patients had late fibrosis and 17 (8 %) telangiectasias. Telangiectasias was correlated to occurrence of grade II-III radio-epithelitis during the treatment (grade I: 5.6 % versus grade II-III: 19 %, Fisher's test, \( p = 0.011 \)). No cardiac or pulmonary toxicities were observed, neither were plexopathy or rib fractures.

Discussion
BC in elderly women is an increasingly important issue, representing about 25 % of all BC [1–4]. Unfortunately, there are relatively few data on this population, because most of the trials exclude women over 70. However, several studies reported a clear “undertreatment”, both for locoregional and systemic treatment in elderly women, increasing the LR and death risks [9, 16–18]. Moreover, many physicians believe that BC in elderly is a “less aggressive” disease than in young women. This is true when compared to women under 40, but not with 40–69-year-old patients [19, 20]. Finally, distance from and/or rarity of radiotherapy centres and comorbidities are additional difficulties to optimize RT use in the elderly.
This is one of the main reasons of the development of “alternative/concentrated” RT schemes also called hypofractionated (HF) [21]. After many radiobiological analyses [22], several schemes were proposed, especially in UK and Canada. Three randomized trials confirmed equivalent results on local control and specific mortality between classical and HF-RT [10–12, 21] (Table 5).

### Table 3 Local recurrence risk factors

| Variable | Univariate analysis | Multivariate analysis |
|----------|---------------------|-----------------------|
|          | HR (95 % CI)        | \( p \) | HR (95 % CI) | \( p \) |
| Mastectomy | 1.61 (0.36–7.19) | 0.534 | - | - |
| RT duration >42d. | 0.50 (0.06–4.15) | 0.521 | - | - |
| ANI (pN+) | 6.97 (0.83–58.2) | 0.073 | - | - |
| Delay between surgery and RT >42 d. | - | 0.371 | - | - |
| SBR III | 2.95 (0.65–13.40) | 0.161 | - | - |
| Triple negative | 9.78 (1.90–50.29) | 0.006 | 7.19 (1.35–38.17) | 0.021 |
| Chemotherapy | 6.81 (1.30–35.76) | 0.023 | - | - |
| Age | 1.03 (0.90–1.19) | 0.638 | - | - |
| NPI (overall) | 1.98 (1.08–3.65) | 0.028 | 1.94 (0.98–3.86) | 0.058 |
| NPI 3 (vs 0-1-2) | 5.46 (1.21–24.64) | 0.027 | - | - |

\( RT \): radiotherapy, \( ANI \): axillary nodal involvement (pN+), \( SBR \): Scarff, Bloom and Richardson grading, \( NPI \): Nottingham prognostic index, \( d \): days

### Table 4 Skin toxicity

| Toxicity | Breast | Chest wall | SCF\(^a\) | IMC\(^b\) |
|----------|--------|------------|-----------|-----------|
|          | Boost / No boost | | | |
| Acute | | | | |
| Skin | Grade 1 | 54 (55 %) | 9 (50 %) | 70 (79 %) | 29 (45 %) | 14 (64 %) |
| | Grade 2 | 25 (26 %) | 5 (28 %) | 5 (6 %) | - | 1 (5 %) |
| | Grade 3 | 6 (6 %) | 2 (11 %) | - | 1 (2 %) | - |
| Late | | | | |
| Skin | Fibrosis | 24 (24 %) | 3 (17 %) | 3 (3 %) | - | - |
| | Telangiectasias | 13 (13 %) | 1 (6 %) | 3 (3 %) | - | - |
| | hyperpigmentation | 7 (7 %) | - | 1 (1 %) | - | - |

\(^a\): Supravclavicular fossa
\(^b\): Internal mammary chain
The Canadian trial HF-RT arm delivered 42.5 Gy in 16 fractions over 22 days [12], and included only women treated by BCS. The English START A Trial HF-RT arm delivered 41.6 Gy or 39 Gy in 13 fractions and 35 days, and included 85 % of BCS and 15 % of mastectomy [11].

In the subsequent START B Trial experimental arm, 40 Gy in 15 fractions and 21 days were delivered, 92 % after BCS [10]. These schemes are now validated by the French guidelines on infiltrating BC [23] for postmenopausal women with pT1N2N0 lesions and positive hormone receptors.

However, other schemes were used almost exclusively in elderly patients, often with many comorbidities. A single dose of 6.5 Gy per fraction each week (total: 5 or 6 fractions) was used at least in three reports [13–15, 24].

In France, another “empirical” approach was used in order to simplify treatment for elderly, with 42 or 45 Gy in 14 or 15 fractions over 4–5 weeks both after BCS or mastectomy. From a radiobiological point of view, assuming a 3.5 α/β ratio for breast cancer, the biological equivalent dose (BED) of our scheme is approximately 52 Gy (classical fractionation) and 64 Gy if boost was applied. To our knowledge, our study is the first one evaluating this 45 Gy/15 fr/35 days scheme (+/− 9 Gy/3 fr. Boost), especially after mastectomy. It should be noted that in the START A and B trials 336 (15 %) and 177 patients (8 %) underwent mastectomy, but the data on nodal RT (supraclavicular fossa ± axilla, but never IMC) in these patients remain unclear, without technical details and no specific choice criteria. In a series from Thailand, 148 patients treated by mastectomy received HFRT, using an almost identical scheme to the Canadian Trial. With a 39-month follow-up, the local control rate was 86 %, without toxicity differences in comparison with 77 patients treated by a conventional scheme [25].

Despite a relatively short follow-up, our results seem to be consistent with the literature data, leading to an approximately 0.8 % LR rate a year [26, 27]. Acute cutaneous toxicity was acceptable with less than 5 % of grade 3 reaction. No long-term toxicity, particularly cardiac toxicity, was detected, whereas 56 % of the irradiations involved the left-hand side. Our results may be partly explained by a short hindsight, since cardiac toxicity is known to appear at a late stage. In the START trials, 0.8–1.4 % symptomatic pulmonary fibrosis, 1.3–1.5 % rib fractures and 2 % ischemic heart diseases were observed [10, 11]. In a study from Pakistan comparing three HFRT schemes, the cardiac toxicity was approximately 5 %, but the treatments were delivered only by Cobalt photons [28].

To date, there have been no recommendations relating to lymph node area irradiation in a hypofractionated schedule. Indeed, this was not performed in the Canadian trial or in the retrospective trial of Dragan [24], whereas lymph node irradiation was performed in 13.2 and 7.4 % of the patients in the START A and B trials respectively according to each centre’s policy. In our study, HFRT of the axilla, internal mammary chain and supraclavicular area were performed in 4, 11 and 31 % of the cases respectively. Nodal irradiation slightly increased the long-term cardiac death in several older studies, but the rates decreased widely with the use of modern RT techniques, such as clearly shown in the Danish trials widely using electrons to treat chest wall and more particularly IMC [29]. There was no significant influence of fraction dose [30]. In our series, no cardiac or pulmonary toxicities were observed, whereas 66 patients (32 %) underwent nodal irradiation. Unfortunately, we have no precise data on lymphoedema occurrence, but the few available literature data do not report any increased lymphoedema incidence among the patients treated by HFRT [31].

In our study, 84 % of the patients treated by BCS underwent a 9 Gy/3 fr boost, whereas there are no data on this modality in the literature, especially in women over 70. Due to the very low rate of LR, the impact of boost is not evaluable; as to skin toxicity, the rate is similar to those patients without boost, as well as for

| Reference | Type | Cohort (HF) | HF | Mastectomy | Boost | Lymph node RT | 5-year LR |
|-----------|------|-------------|----|------------|-------|--------------|-----------|
| Whelan [12] | P. | 622 | 42.5 Gy/16 fr | 0 % | 0 % | 0 % | PFS 97.2 % |
| Owen [35] | P. | 940 | 42.9 Gy/13 fr | 0 % | 75 % | 21 % | 7 % |
| Start A [11] | P. | 1487 | 41.6 Gy/13 fr | 15 % | 61 % | 13.2 % | 3.2 % |
| Start B [10] | P. | 1110 | 40 Gy/15 fr | 8 % | 43.8 % | 7.4 % | 2 % |
| Cutuli [2] | R. +CA | 133 | 32.5 Gy/5 fr | 0 % | 55 % | 48 % | 3.7 % |
| Ortholan [14] | R. | 150 | 32.5 Gy/5 fr | 28.5 % | 33,00 % | 32 % | - |
| Kirova [15] | R. +CA | 50 | 32.5 Gy/5 fr | 0 % | 0 % | - | - |

P prospective randomized, R retrospective, + CA with control arm, Gr gray, fr fractions, PFS progression-free survival, LR local recurrence

---

Doré et al. Radiation Oncology (2015) 10:161
Conclusions

Finally, our study confirms a good local control rate by HFRT in elderly women without severe toxicities similar to those observed in classical RT, even in case of nodal irradiation. These results confirm the results reported by others, including long-term data from meta-analysis [2, 10, 11, 14, 15, 33–35]. The impact of locoregional recurrence is clinically and psychologically important, even in elderly people [1], and except in case of very heavy comorbidities, an optimal treatment should be proposed in those women, including in case of LR risk factors boost after WBI. Our scheme is quite simple, similar to others used in randomized trials and seems very feasible and adaptable for many elderly patients.

A prospective survey on this RT modality is currently under evaluation in several other centres in France. However, HFRT must strictly comply with the optimal radiotherapy guidelines, both for breast and node irradiation, in order to avoid “hot spots” with a possible risk of long-term side effects, especially when associated to chemotherapy [36, 37].

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MD collected and analysed patient data. BC and ML participated in the design and coordination of the study. LC performed the statistical analysis. All authors drafted the manuscript and read and approved the final manuscript.

Acknowledgements

The authors would like to thank Mrs Diane PENET for her translation skills.

Author details

1Radiation Oncology Department, Institut de Cancérologie de l’Ouest, Nantes, France. 2Radiation Oncology Department, Institut de Cancérologie de Courlauray, Reims, France. 3Radiation Oncology Department, Institut de Cancérologie de l’Ouest, Angers, France.

Received: 14 January 2015 Accepted: 26 June 2015

References

1. Biganzoli L, Wildiers H, Oakman C, Marotti L, Lodd S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13:e148–60.

2. Cutuli B, Cottu PH, Guastalla JP, Mechin H, Costa A, Jourdian R. A French national survey on infiltrating breast cancer: analysis of clinico-pathological features and treatment modalities in 1159 patients. Breast Cancer Res Treat. 2006;9555–64.

3. Cazzaniga ME, Mustacchi G, Pronzato P, De Matteis A, Di Costanzo F, Floriani L et al. Adjuvant systemic treatment of early breast cancer: the NORA study. Ann Oncol. 2006;17:1386–92.

4. Joerger M, Thürlimann B, Savidan A, Frick H, Rageth C, Lütolf U, et al. Treatment of breast cancer in the elderly: a prospective, population-based Swiss study. J Geriatr Oncol. 2013;4:39–47.

5. Veronesi U, Caccinelli N, Mariani L, Grego M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347:1227–32.

6. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233–41.

7. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378:1707–16.

8. Bouchardy C, Rapiti E, Fioretta G, Lairesse P, Neyrou-Caspar I, Schäfer P, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol. 2003;21:3580–7.

9. Smith BD, Haffty BG, Hurria A, Galusha DH, Gross CP. Postmastectomy radiation and survival in older women with breast cancer. J Clin Oncol. 2006;24:4901–7.

10. START Trialists’ Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371:1098–107.

11. START Trialists’ Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371:431–41.

12. Whelan TJ, Pignol J-P, Levine MN, Julian JA, Mackenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513–20.

13. Cutuli B, De Lafontan B, Vitali E, Costa L, Aristei C, Marchal C, et al. Breast conserving treatment (BCT) for stage III breast cancer in elderly women: analysis of 927 cases. Crit Rev Oncol Hematol. 2009;71:79–88.

14. Ortholan C, Hannoun-Lévi J-M, Ferrero J-M, Largillier R, Courdi A. Long-term results of adjuvant radiotherapy in elderly patients. Int J Radiat Oncol Biol Phys. 2005;61:154–62.

15. Kirova YM, Campana F, Savignoni A, Laik F, Muresan M, Dandere R, et al. Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2009;75:76–86.

16. Dragun AE, Huang B, Tucker TC, Spanos WJ. Disparities in the application of adjuvant radiotherapy after breast-conserving surgery for early stage breast cancer: impact on overall survival. Cancer. 2011;117:2590–8.

17. Van Leeuwen BL, Rosenkrantz KM, Feng LL, Bedosian I, Hartmann K, Hunt KK, et al. The effect of under-treatment of breast cancer in women 80 years of age and older. Crit Rev Oncol Hematol. 2017;103:1–20.

18. Crivellari D, Price K, Gelber RD, Castiglione-Gertsch M, Rudenstam C-M, Lindner J, et al. Adjuvant endocrine therapy compared with no systemic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV. J Clin Oncol. 2003;21:4517–23.

19. Singh R, Hellman S, Heimann R. The natural history of breast carcinoma in the elderly: implications for screening and treatment. Cancer. 2004;100:1807–13.

20. Daidone MG, Coradini D, Martelli G, Veneroni S. Primary breast cancer in elderly women: biological profile and relation with clinical outcome. Crit Rev Oncol Hematol. 2003;45:513–25.

21. Haviland JS, Owen JR, Devar JA, Agrawal RN, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy.
hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086–94.

22. Yamold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol. 2005;759–17.

23. French guidelines for infiltrating breast cancer. In: Cancer du sein infiltrant non métastatique - Questions d'actualités. INCa; 2012. http://www.e-cancer.fr/soins/recommandations/cancers-du-sein. Accessed Jul 2012.

24. Dragun AE, Quillo AR, Riley EC, Roberts TL, Hunter AM, Rai SN, et al. A phase 2 trial of once-weekly hypofractionated breast irradiation: first report of acute toxicity, feasibility, and patient satisfaction. Int J Radiat Oncol Biol Phys. 2013;85:e123–8.

25. Pinitpatcharalert A, Chitapanarux I, Euathrongchit J, Tharavichikul E, Sukthomya V, Lorvidhaya V. A retrospective study comparing hypofractionated radiotherapy and conventional radiotherapy in postmastectomy breast cancer. J Med Assoc Thai. 2011;94:s94–102.

26. Truong PT, Bernstein V, Lesperance M, Speers CH, Olivotto IA. Radiotherapy omission after breast-conserving surgery is associated with reduced breast cancer-specific survival in elderly women with breast cancer. Ann J Surg. 2006;191:749–55.

27. Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst. 2006;98:681–90.

28. Shahid A, Athar MA, Asghar S, Zubairi T, Murad S, Yunas N. Post mastectomy adjuvant radiotherapy in breast cancer: a comparison of three hypofractionated protocols. J Pak Med Assoc. 2009;59:282–7.

29. Deantonio L, Gambaro G, Beldì D, Masini L, Tunesi S, Magnani C, et al. Hypofractionated radiotherapy after conservative surgery for breast cancer: analysis of acute and late toxicity. Radiat Oncol Lond Engl. 2010;5:112.

30. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366:2087–106.

31. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006;7:467–71.

32. Cutuli B, Fournet A. Hypofractionated whole breast irradiation: pro and cons. Cancer-Radiothérapie. 2011;15:445–9.

33. Smith BD, Bentzen SM, Correa CR, Hahn CA, Hardenberg PH, Ibbott GS, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;81:59–88.