

Extreme weekly hypofractionation in breast cancer in elderly

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Abstract: Breast cancer is the second cause of cancer death worldwide. One-half of new cases are diagnosed in elderly patients, with a growing global life expectancy and with age being a major risk factor for breast cancer. Radiation therapy is one of the main treatments as adjuvant treatment whenever possible and as definitive if not. Daily conventional fractionation over 5 weeks is costly and lengthy, and alternatively weekly hypofractionation could be a good option in elderly patients with comorbidities, social problems and who live far from the treatment center. The purpose of this article is to review weekly hypofractionated schedules in elderly patients published in literature, in terms of locoregional recurrence (LRR) and side effects. There are eleven studies on the topic with different treatment schedules, 87.1% of lesions were adjuvant treatments and 12.9% definitive treatments, with a range of LRRs between 0% and 16% depending on several factors. The number of acute side effects as grade 3 or grade 4 was very low, being less than 15% in all series. The most significant late side effect was fibrosis in a range between 15.1% and 39.2%. Extreme weekly hypofractionated radiation therapy seems to be a safe treatment without significant side effects.

Keywords: Aged; breast neoplasms; radiation dose hypofractionation; radiotherapy; once weekly; weekly

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Introduction

Breast cancer is the most commonly diagnosed form of cancer and the leading cause of cancer death in women, and globally, the second worldwide (1). The most significant risk factor for the development of a breast cancer is age, and the diagnosis is increasing in elderly patients. In the United States, almost one-half of new breast cancers diagnosed arise in elderly patients, and approximately one third occur in patients older than 70 years (2). Although the prognosis is better than in younger patients, radiation therapy is absolutely necessary as adjuvant treatment after lumpectomy or after mastectomy when there is node disease, to improve local control, regional control and overall survival (OS) (3,4). In spite of this, it is well known that elderly patients receive fewer treatments than young women, whether surgery, radiotherapy or systemic treatments (5).

Historically, the most frequent schedule of adjuvant radiation therapy worldwide, consisted in a total dose of 50 Grays (Gy), delivered in 25 fractions of 2 Gy per day, 5 days a week during 5 weeks, with or without a subsequent boost.

Nowadays, some studies have shown that a moderate hypofractionated treatment consisting of 15–16 fractions, have been associated with equivalent long-term results than conventional schedule (6,7). In the United Kingdom, a moderate hypofractionated treatment in 15 fractions is the standard of care in early breast cancer (8), although for the American Society for Radiation Oncology, there is not enough evidence when regional radiation is indicated (9). START A and B studies, suggest that the α/β ratio of breast cancer ranges from 3 to 5 Gy, similar to surrounding normal tissues, which seems to imply that breast cancer would benefit from higher doses per fraction, according to linear quadratic model (6,7,10).

According to the favourable results from randomized clinical trials of moderate hypofractionation, more extreme schedules have been investigated such as weekly hypofractionation. It is especially important in elderly patients to improve their life expectancy and quality of life because they have more problems to receive the best treatment, perhaps given that they have more comorbidities, social support and difficulties in transportation to attend radiation sessions. The purpose of this article is to review the results of once-weekly hypofractionated schedules in elderly patients published in literature, in terms of locoregional recurrence (LRR) and acute and late toxicity.

Methods

This study is a review of literature realized on MEDLINE via PubMed, Embase and ClinicalKey. Search strategy included MeSH terms and free text due to the small number of published articles. No restrictions on language were used. We searched weekly or once weekly, hypofractionated, radiotherapy and breast cancer with a restriction in age, including the term aged. Articles related with only hypofractionated boost or moderately hypofractionation were excluded. Abstracts related to the topic were excluded. Finally, a total of eleven articles were selected for this review.

Results

The results in the eleven published series of cases or in the arms related to extreme weekly hypofractionated radiation therapy have been collected in the following summary. Globally a total of 87.1% of lesions were treated with adjuvant radiation therapy and 12.9% as definitive radiation therapy, both of them with or without a boost. Only 8.9% of patients received a boost, 73.3% of patients did not receive a boost and in other 17.7% it was not specified. There are two prospective randomized studies, three prospective single-arm studies and six retrospective nonrandomized studies. Summary of results in *Table 1*.

Rostom *et al.* in 1987, retrospectively analyzed 84 patients, with a total of 86 lesions. The average age was 69.2 years. Fifty-three had biopsy only, 13 underwent lumpectomy without axillary dissection, 16 underwent

modified radical mastectomy and 2 experienced wall recurrences after mastectomy. Stage I-II in 37 patients and stage III–IV in 47 patients. No one received adjuvant systemic therapy. They received 39 Gy in 6 weekly fractions of 6.5 Gy. Seven patients received an electron boost to residual tumour with a 3-fraction schedule of 3.2 Gy applied on alternate days. Supraclavicular and axillary nodes were treated in all patients with the ipsilateral internal mammary in 32 patients. Three-year OS was 50% with 33 deaths related to the disease. LRR was not correctly reported. Acute skin reactions were G1 and G2 in 39 patients, G3 in 3 patients. Delayed radiation effects like fibrosis appeared in 13 patients and telangiectasia in 6 patients. In most of patients, cosmetic was good or excellent (11).

In 1990, Baillet *et al.* presented an intermediate analysis of a prospective randomized study, including 125 patients with an average age of 53 years, treated with a schedule to deliver 23 Gy in 4 fractions of 5 Gy for the first two sessions and another two fractions of 6.5 Gy, administered in 17 days. There were 94 patients' stage T1 or T2 patients and 31 stage T3 or T4 patients. Nodes were clinically positive in 30% of patients. Forty-five patients were treated with lumpectomy plus an additionally brachytherapy boost of 20 Gy. Fifty-two patients underwent a mastectomy and 28 patients received neoadjuvant chemotherapy and exclusive radiation therapy. Node irradiation was not reported. At 5 years, 7% patients developed LRR, and the OS was 86.5%. Secondary effects were fibrosis in 14 patients, telangiectasia in 10 patients and brachial lymphoedema in 5 patients (12).

In 1995, a retrospective analysis was published by Maher *et al.*, including 70 patients with a median age of 81 years, who received a total dose of 32.5 Gy to the involved breast and another two fractions as a boost, onceweekly administered. No surgery was performed in any patient. Everybody received hormone therapy. A total of 39% of patients underwent node irradiation with a total dose of 27.5–30 Gy. Thirty-eight patients were stage T1 or T2, thirty-one patients were stage T3 or T4 and a patient was unknown. At 3 years, the local control was 86%. The 16% developed LRR. The OS was 87% and the disease specific survival was 88%. Treatment was well tolerated by 87% of patients. Acute radiodermatitis was developed in only 7 patients (10%) as grade 2 and in 2 patients (3%) as grade 3. Fibrosis was developed in 39% (27 patients) (13).

A prospective single-arm study was developed by Ortholan *et al.* in 2005. One hundred fifty patients with a total of 151 lesions and a median age of 78 years, received a total of 32.5 Gy delivered in 5-weekly fractions of 6.5 Gy

Trial, year	Design	Elegibility criteria	Age, years	Number of patients/ lesions	Surgery	НТ/СНТ (%)	Dose (Gy)	Fractions (Fx)/ number of patients	BOOST/number F	ollow-up (years)	Local and regional recurrence	Dermatitis I G1–2	Dermatitis G3-4	Late toxicity (fibrosis)
Rostom et al. 1987	Retrospective	2	69.2ª	84/86	Lumpectomy 13; mastectomy 18; No surgery 53; 2 NR	HT 4.8; CHT 0	39	6.5 Gy×6 Fx/84	ON	ო	К	45.3%	3.5%	15.1%
Baillet <i>et al.</i> 1990 ^t	Prospective, randomized	T1-4, N -/+	53 ^ª	125	Lumpectomy 45; mastectomy 52; no surgery 28	HT NR; CHT 22.4	23	5.75 Gy×4 Fx/125	ON	Ŋ	%2	NR	ЧN	11.2%
Maher <i>et al.</i> 1995	Retrospective	T1-4, N0-2	81	20	No surgery	HT 100; CHT 0	32.5	6.5 Gy×5 Fx/26	+6.5 Gy×1 Fx/44	ю	16%	10%	3%	39%
Ortholan <i>e</i> i <i>al.</i> 2005	Prospective, single-arm	T14, N01	78	150/151	Lumpectomy 108; mastectomy 43	HT 91.3; CHT 2.7	32.5	6.5 Gy×5 Fx/100	+6.5 Gy×1 Fx/30; +6.5 Gy ×2 Fx/16; +15 Gy×1 Fx (BQT)/4	ى ا	2.3%	27.8%	%0	39.1%
Courdi <i>et al.</i> 2006	Retrospective	T1-4, N0-1	83	115/124	No surgery	HT 98.3; CHT 10.4	32.5	6.5 Gy×5 Fx/23	+6.5 Gy×1 Fx/7; +6.5 Gy ×2 Fx/69; +6.5 Gy×3 Fx/25	Ω	15%	27.4%	%0	37.1%
Martin <i>et al.</i> 2008 ^b	Prospective, single-arm	<3cm, N0	>50	30	Lumpectomy	HT NR; CHT 0	30	6 Gy×5 Fx/30	ON	м	%0	30%	13.3%	N
Kirova <i>et al.</i> 2009	Retrospective	T1-2, N0-1	80	50	Lumpectomy	HT 60–78; CHT 0	32.5	6.5 Gy×5 Fx/50	ON	Q	6%	RN	%0	33%
FAST Trialist group, 2011	Prospective, randomized	<3 cm, N0	62.8	613	Lumpectomy	HT 88.7; CHT NR	28.5/30	5.7 Gy ×5 Fx/305; 6 Gy×5 Fx/308	ON	ო	0.33%	23.2%	0.8%	23.8%
Rovea <i>et al.</i> 2015	Retrospective	T1 mic-4, N0-2	80	291/298ª	Lumpectomy	HT 77.9; CHT 2.7	30/32.5	6 Gy×5 Fx/57; 6.5 Gy×5 Fx/241	ON	Q	2%	27.4%	1.3%	39.2%
Dragun <i>et al.</i> 2017	Prospective, single-arm	0-II, N -/+	59	158	Lumpectomy	HT 73.4; CHT 28.5	28.5/30	5.7 Gy×5 Fx/78; 6 Gy×5 Fx/58	+6 Gy×1 Fx/22; +2.7 Gy×3 Fx/3°; +2 Gy×5 Fx/3°	ი	1.3%	N	22.8% ^d	RN
Sanz <i>et al.</i> 2018	Retrospective	In situ-IV, recurrence, N -/+	62	486	Lumpectomy 382; mastectomy 97; no surgery 7	HT 78.6; CHT 13.4	30/37.5	5 Gy×6 Fx/45; 6.25 Gy ×6 Fx/441	+1-2 Fx/NR	വ	3.3%	81.1%	12.8%	27.2%
^a , age: mec which the I Gy, Gray.	lian age except a patients who hav	average age in ve received bo	studies oost belo	s. In the stur ong has not	dy published by M : been reported; ^d	artin <i>et al.</i> patien acute effects ha	its were (older than 50 year reported as grade	rs, but median or r e 2 or greater. NR,	nean age not repor	is NR; ^b , twice ted; HT, horm	-weekly sch one therapy	redules;°, th /; CHT, chen	e group to 1otherapy;

each one. There were 120 stages T1 or T2, 12 stages T3 or T4 and 19 unknown patients. Lumpectomy was realized in 108 patients and mastectomy in other 43 patients. Boost was administered with brachytherapy in 4 patients and with external beam radiotherapy as one more fraction of 6.5 Gy in 30 patients and as 2 more fractions in 16 patients. Node areas were treated in only 48 patients (32%). Hormone therapy as neoadjuvant or adjuvant was received for 137 patients (90.8%). Adjuvant chemotherapy was administered in only 4 patients. At 5 years, LRR was developed by 2.3%. The OS was 71.6% and the disease specific survival was 89.1%. Acute side effects as dermatitis was developed as grade 1 in 28 patients and grade 2 in 14 patients, with no grade 3 reactions. Fibrosis was developed in 54 patients. Chronic pain was developed in 7 patients (14).

In the same institution as the previous study developed by Ortholan, Courdi et al. presented in 2006 a prospective series of 115 patients with a median age of 83 years and with a total of 124 lesions. None underwent surgery. Eighty-three patients were stage 1 and 2 and forty one were stage 3 and 4. The treatment schedule was delivered in 5 weekly fractions of 6.5 Gy that was administered in a total of 23 lesions, and followed for a boost of one more session in 7 lesions, two more sessions in 69 lesions and three more sessions in 25 lesions. Nodes were irradiated in 24 patients with a total dose of 27.5 Gy in 5 weekly fractions of 5.5 Gy. Hormone therapy was administered in 113 patients and 12 patients received neoadjuvant chemotherapy. At 5 years local progression-free rate was 78% with 19 patients (15%) that developed local recurrence. The OS was 38% and the disease specific survival was 71%. Acute dermatitis was developed as G1 for 24 patients and G2 in 10 patients. Fibrosis appeared in 46 patients. Despite being older patients with more advanced tumours, they recommend surgery when possible, followed by hypofractionated radiotherapy (15).

Martin *et al.* in 2008 reported a prospective singlearm, small series of 30 patients older than 50 years that underwent conserving surgery. Nodes were negative in all patients. They received a total dose of 30 Gy in 5 fractions of 6 Gy twice a week over 15 days. At 3 years, the local control was 100% with no develop recurrences. Acute dermatitis was developed in 20 patients as grade 1 and in 9 patients as grade 2 (16).

Kirova *et al.* in 2009 analyzed a single institution, nonrandomized retrospectively group of 50 patients. Median age was 80 years. All of them stage T1 or T2. Axillary dissection was realized in 33 patients with positive results in 2 patients. They underwent lumpectomy, followed by a total dose of 32.5 Gy administered in 5 weekly fractions of 6.5 Gy. Nodes were not irradiated. A range between 60 and 78% of patients received hormone therapy. At 5 years, cancer specific survival, LRR-free survival and metastases free survival were 95%, 94% and 95% respectively. Acute dermatitis was up to grade 2, but the percentage of patients who have developed it has not been reported. Fibrosis was developed in 17 patients (17).

The first randomized once weekly prospective trial is UK FAST Trial, published in 2011. There were 3 arms, the standard 50 Gy in 25 fractions of 2 Gy, compared to another 2 arms, consisting of 5 weekly fractions of 5.7 Gy or 6 Gy per fraction. In the hypofractionated arm, there were 613 patients, with a median age of 62.8 years. All patients were stage I or II and underwent lumpectomy. Hormone therapy was received for 542 patients. The primary endpoint was a 2-year change in photographic breast appearance. At 3 years, local control was 99.67%, only two patients developed local recurrence. The OS was 97.23%. Cancer specific survival, LRR-free survival and metastases free survival were 98.69%, 97.23 and 98.04% respectively. Acute dermatitis was developed in 120 patients as grade 1, 22 patients as grade 2 and 5 patients as grade 3. Cosmetic changes occurred in 146, and there were mild in 114 patients and marked in 32 patients. They conclude that moderate or marked changes were very similar between arms and a little bit greater in the group that received 6 Gy per fraction than in the group of 5.7 Gy (17.3% vs. 11.1% respectively) (18).

In 2015, Rovea et al. presented a retrospective nonrandomized analysis of a series of 291 cases with a total of 298 lesions. Median age was 80 years. Two hundred and eighty-one lesions were stages T1mic, T1 or T2, twelve lesions were stages T3 and T4 and five lesions were unknown stage. Nodes were negative in 66.1%, positive in 16.4% and unknown in 17.5%. The whole lesions were treated with conservative surgery. Nodes were not irradiated. The total dose administered was 32.5 Gy in 5 fractions of 6.5 Gy per fraction until the publication of FAST Trial. Since then, the schedule administered was 30 Gy in 5 fractions of 6 Gy. Hormone therapy was given to 232 patients, and adjuvant chemotherapy was given in 8 patients. At 5 years local control was 98%. The OS and cancer specific survival were 83.6% and 95.3% respectively. Acute dermatitis was developed as grade 2 or less for 294 patients. Three patients were grade 3 and one patient grade 4. Fibrosis was developed in 112 patients, telangiectasia in 7 patients, hyperpigmentation in 20 patients and edema was present in 36 patients (19).

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Dragun et al. published in 2017 the results of a prospective phase 2 trial. The number of patients was 158, with a median age of 59 years. They were stages Tis, T1 and T2. All of them underwent conserving surgery. Nodes were positive in a 10.1% but irradiation was not performed. Treatment schedule was a total of 30 Gy given in 5 weekly fractions of 6 Gy each one in 130 patients. Twenty-eight patients received a total dose of 28.5 Gy given in 5 weekly fractions. Boost was given in 22 patients as one more fraction of 5.7 or 6 Gy depending on their previous schedule, another 3 patients received a total of 8.1 Gy given in 3 fractions and another 3 patients received a total of 10 Gy given in 5 fractions. Hormone therapy was delivered to 42 patients and adjuvant chemotherapy was delivered in 45 patients. At 3 years, local recurrence was developed in only 2 patients and the OS was 96.2%. Acute skin reaction greater than grade 2 was developed in 36 patients. As late effects, cellulitis was developed in 3 patients (20).

Sanz et al. published in 2018 the results of an observational study, including 486 patients with a median age of 79 years. There were 380 stages 0, I or II, 85 stages III or IV, 10 recurrences and 11 were unknown. The percentage of patients with positive nodes or that received node irradiation, was not reported. Three hundred and eighty-two patients underwent lumpectomy, 97 mastectomies, 3 biopsies and none in 4 patients. Treatment schedule was firstly 6.25 Gy given in 6 weekly fractions in 441 patients and later with the aim to reduce secondary effects, they chose a 5 Gy schedule given in 6 weekly fractions in 45 patients. Boost was delivered in 35 patients as a one more fraction and in another 50 patients as two more fractions. Nodes were irradiated in 15% patients. Hormone therapy was delivered in 382 patients and neoadjuvant or adjuvant chemotherapy in 65 patients. At 5 years, local control was 96.5%. The OS and cancer specific survival were 74.2% and 90% respectively. Relapse free survival and metastasis free survival were 96.5% and 90% respectively. Acute dermatitis was developed as G2 or less in 394 patients and as grade 3 in 62 patients. Fibrosis was developed in 132 patients, hyperpigmentation or telangiectasia in 13 patients and edema or mastitis in 5 patients (21).

Discussion

Historically, the standard treatment was delivered in 25 fractions during 5 weeks. In the past few years, numerous publications have been developed about a moderate hypofractionated radiation therapy, delivered in 15–16 fractions during 3 weeks for early stage breast cancer with equivalent outcomes than

conventional treatment (6,7,10,22). Elderly patients receive fewer treatments than young women, whether surgery, radiotherapy or systemic treatments, sometimes due to the greater number of comorbidities, other times due to the lack of social support, difficulties to attend the treatment or distance to the treatment center may be some of the problems. Hypofractionated treatments, resulting in faster treatments and therefore in access to care and in a lower spending (23). This is a really important point, considering the vast volume of patients treated for breast cancer in a radiotherapy service.

The most collected by all studies and important late side effect was fibrosis, although some others such as hyperpigmentation, telangiectasia, edema or local pain may occur with some frequency. Although these side effects are not really important for life, sometimes, these can have a significant physical and psychological impact on patients (24). There are several factors that influence late side effects in normal tissue such as the age, smoking, post-surgical cosmesis, chemotherapy, breast volume, total radiation therapy dose, technique, fractionation and boost radiation (25). Other effects such as heart disease or symptomatic lung fibrosis are unlikely to be impacted with changes in fractionation. The studies reviewed collect data similar to historically standard schemes (6,7,10,22,26).

The only phase III study about extreme once weekly hypofractionated radiation therapy in breast cancer, is the UK FAST trial (18), designed with two arms related to extreme hypofractionation compared to standard treatment administered in 25 fractions. The two hypofractionation arms were designed based on the outcomes of the UK START trials, where it is suggest that the α/β ratio of breast cancer ranges from 3 to 5 Gy, and theoretically 5 fractions of 5.7 Gy are predicted to be equivalent to 50 Gy in 25 fractions in terms of tumour control assuming an α/β value of 3 Gy and 5 fractions of 6 Gy assuming an α/β of 4 Gy. The α/β from 3 to 5 Gy seems to imply a benefit with higher doses per fraction, according to linear quadratic model, but a dose greater than 3.2–3.3 Gy per fraction, seems to increase chronic toxicity. On the other hand, acute dermatitis grade 3 decreases with hypofractionation because a response to lower total dose which reduces late side effects (27-31). Based on radiobiology and the findings of FAST Trial, and the other studies that compared two different schedules of fractionation, late effects tend to be a little bit greater with doses of 6 or more Gy per fraction.

The studies included in the review have shown a good locoregional control rates with a small number of LRR and an acceptable chronic toxicity despite being increased. It is necessary to emphasize that the vast majority of patients were older, most of them with an early stage and therefore a better prognosis and most of them received hormone therapy influencing locoregional control. The worst results in terms of locoregional control are observed in the groups that have not undergone surgery, and followed by patient groups that have not received a boost.

Currently there is only one ongoing phase II nonrandomized clinical trial in Brazil, whose main endpoint is the number of patients with adverse events and is in the phase of completion (32).

Conclusions

Weekly hypofractionated radiation therapy in breast cancer could be a good option especially for elderly patients with biologically favorable early stage cancer and also for patients with advanced stages who are unfit to receive large daily treatments, or even in patients unfit for surgery despite increasing the risk of recurrence. Surgery is preferable if possible and it is advisable to administer a boost. Extreme weekly hypofractionation seems to be a safe treatment without significant side effects.

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References

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
- Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Available online: https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10year recurrence and 15-year breast cancer death: metaanalysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
- 4. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: metaanalysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127-35.
- Bastiaannet E, Liefers GJ, de Craen AJ, et al. Breast cancer in elderly compared to younger patients in the Netherland: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat 2010;124:801-7.
- START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of a radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331-41.
- START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of a radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331-41.
- 8. Harnett A. Fewer fractions of adjuvant external beam radiotherapy for early breast cancer are safe and effective and can now be the standard of care. Why the UK's NICE

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accepts fewer fractions as the standard of care for adjuvant radiotherapy in early breast cancer. Breast 2010;19:159-62.

- Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys 2011;81:59-68.
- Haviland JS, Owen JR, Dewar JA, et al. mSTART Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol 2013;14:1086-94.
- Rostom AY, Pradhan DG, White WF. Once weekly irradiation in breast cancer. Int J Radiat Oncol Biol Phys 1987;13:551-5.
- Baillet F, Housset M, Maylin C, et al. The use of a specific hypofractionated radiation therapy regimen versus classical fractionation in the treatment of breast cancer: a randomized study of 230 patients. Int J Radiat Oncol Biol Phys 1990;19:1131-3.
- Maher M, Campana F, Mosseri V, et al. Breast cancer in elderly women: a retrospective analysis of combined treatment with tamoxifen and once-weekly irradiation. Int J Radiat oncol Biol Phys 1995;31:783-9.
- Ortholan C, Hannoun-Lévi JM, Ferrero JM, et al. Longterm results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. Int J Radiat Oncol Biol Phys 2005;61:154-62.
- Courdi A, Ortholan C, Hannoun-Lévi JM, et al. Longterm results of hypofractionated radiotherapy and hormonal without surgery for breast cancer in elderly patients. Radiother Oncol 2006;79:156-61.
- Martin S, Mannino M, Rostom A, et al. Acude toxicity and 2-year adverse effects of 30 Gy in five fractions over 15 days to whole breast after local excision of early breast cancer. Clin Oncol (R Coll Radiol) 2008;20:502-5.
- Kirova YM, Campana F, Savignoni A, et al. Breastconserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionates radiotherapy. Int J Radiat Oncol Biol Phys 2009;75:76-81.
- FAST Trialists group, Agrawal RK, Alhasso A, et al. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol 2011;100:93-100.
- Rovea P, Fozza A, Franco P, et al. Once-Weekly Hypofractionated Whole-Breast Radiotherapy After Breast-Conserving Surgery in Older Patients: A Potential Alternative Treatment Schedule to Daily 3-Week

Hypofractionation. Clin Breast Cancer 2015;15:270-6.

- Dragun AE, Ajkav NJ, Riley EC, et al. First Results of a Phase 2 Trial of once-Weekly Hypofractionated Breast Irradiation (WHBI) for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys 2017;98:595-602.
- Sanz J, Zhao M, Rodríguez N, et al. Once-Weekly Hypofractionated Radiotherapy for Breast Cancer in Elderly Patients: Efficacy and Tolerance in 486 Patients. Biomed Res Int 2018;2018:8321871.
- 22. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513-20.
- 23. Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. JAMA 2014;312:2542-50.
- Al-Ghazal SK, Fallowfield L, Blamey RW. Does cosmetic outcome from treatment of primary breast cancer influence psychosocial morbidity? Eur J Surg Oncol 1999;25:571-3.
- Mukesh M, Harris E, Jena R, et al. Relationship between irradiated breast volume and late normal tissue complications: A systematic review. Radiother Oncol 2012;104:1-10.
- 26. Owen JR, Ashton A, Bliss JM, 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 randomized trial. Lancet Oncol 2006;7:467-71.
- 27. Jones B, Dale RG, Deehan C et al. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol (R Coll Radiol) 2001;13:71-81.
- Yarnold J, Bentzen SM, Coles C, et al. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. Int J Radiat Oncol Biol Phys 2011;79:1-9.
- Tutt A, Yarnold J. Radiobiology of breast cancer. Clin Oncol (R Coll Radiol) 2006;18:166-78.
- Qi XS, White H, Li SA. Is α/β for breast cancer really low? Radiother Oncol 2011;100:282-8.
- Dörr W, Hendry JH. Consequential late effects in normal tissues. Radiother Oncol 2001;61:223-31.
- 32. U.S. National Library of Medicine. Available online: http://ClinicalTrials.gov

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