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).

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
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, once-weekly 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 86.5%. Secondary effects were fibrosis in 14 patients, telangiectasia in 10 patients and brachial lymphoedema in 5 patients (13).

A prospective single-arm study was developed by Ortholan et al. in 2005. One hundred fifty patients with a
Table 1 Summary of outcomes of the studies related with elderly patients treated by extreme weekly hypofractionated radiotherapy

<table>
<thead>
<tr>
<th>Trial, year</th>
<th>Design</th>
<th>Eligibility criteria</th>
<th>Age, years</th>
<th>Number of patients/lesions</th>
<th>Surgery</th>
<th>HT/CHT (%)</th>
<th>Dose (Gy)</th>
<th>Fractions (Fx)/number of patients</th>
<th>Follow-up (years)</th>
<th>Local and regional recurrence</th>
<th>Dermatitis G1–2</th>
<th>Dermatitis G3–4</th>
<th>Late toxicity (fibrosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rostom et al. 1987</td>
<td>Retrospective</td>
<td>I–IV 69.2°</td>
<td>84/86</td>
<td>Lumpectomy 13; mastectomy 18; No surgery 53; 2</td>
<td>HT 4.8 ; CHT 0</td>
<td>39</td>
<td>6.5 Gy×6 Fx/84</td>
<td>NO</td>
<td>3</td>
<td>NR</td>
<td>45.3%</td>
<td>3.5%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Baillet et al. 1990</td>
<td>Prospective, randomized</td>
<td>T1–4, N −/+ 53°</td>
<td>125</td>
<td>Lumpectomy 45; mastectomy 52; no surgery 28</td>
<td>HT NR; CHT 22.4</td>
<td>23</td>
<td>5.75 Gy×4 Fx/125</td>
<td>NO</td>
<td>5</td>
<td>7%</td>
<td>NR</td>
<td>NR</td>
<td>11.2%</td>
</tr>
<tr>
<td>Maher et al. 1995</td>
<td>Retrospective</td>
<td>T1–4, N0-2 81</td>
<td>70</td>
<td>No surgery</td>
<td>HT 100; CHT 0</td>
<td>32.5</td>
<td>6.5 Gy×5 Fx/26 +6.5 Gy×1 Fx/44</td>
<td>3</td>
<td>16%</td>
<td>10%</td>
<td>3%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Ortholan et al. 2005</td>
<td>Prospective, single-arm</td>
<td>T1–4, N0–1 78</td>
<td>150/151</td>
<td>Lumpectomy 108; mastectomy 43</td>
<td>HT 91.3; CHT 2.7</td>
<td>32.5</td>
<td>6.5 Gy×5 Fx/100 +6.5 Gy×1 Fx/30; +6.5 Gy×2 Fx/16; +15 Gy×1 Fx (BQT)/4</td>
<td>5</td>
<td>2.3%</td>
<td>27.8%</td>
<td>0%</td>
<td>39.1%</td>
<td></td>
</tr>
<tr>
<td>Courdi et al. 2006</td>
<td>Retrospective</td>
<td>T1–4, N0–1 83</td>
<td>115/124</td>
<td>No surgery</td>
<td>HT 98.3; CHT 10.4</td>
<td>32.5</td>
<td>6.5 Gy×5 Fx/23 +6.5 Gy×1 Fx/7; +6.5 Gy×2 Fx/69; +6.5 Gy×3 Fx/25</td>
<td>5</td>
<td>15%</td>
<td>27.4%</td>
<td>0%</td>
<td>37.1%</td>
<td></td>
</tr>
<tr>
<td>Martin et al. 2008</td>
<td>Prospective, single-arm</td>
<td>&lt;3 cm, N0 &gt;50</td>
<td>30</td>
<td>Lumpectomy</td>
<td>HT NR; CHT 0</td>
<td>30</td>
<td>6 Gy×5 Fx/30</td>
<td>NO</td>
<td>3</td>
<td>0%</td>
<td>30%</td>
<td>13.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Kirova et al. 2009</td>
<td>Retrospective</td>
<td>T1–2, N0–1 80</td>
<td>50</td>
<td>Lumpectomy</td>
<td>HT 60–78; CHT 30</td>
<td>32.5</td>
<td>6.5 Gy×5 Fx/50</td>
<td>NO</td>
<td>5</td>
<td>6%</td>
<td>NR</td>
<td>0%</td>
<td>33%</td>
</tr>
<tr>
<td>FAST Trialist group, 2011</td>
<td>Prospective, randomized</td>
<td>&lt;3 cm, N0 62.8</td>
<td>613</td>
<td>Lumpectomy</td>
<td>HT 88.7; CHT NR</td>
<td>28.5/30</td>
<td>5.7 Gy x5 Fx/305; 6 Gy×5 Fx/308</td>
<td>3</td>
<td>0.33%</td>
<td>23.2%</td>
<td>0.8%</td>
<td>23.8%</td>
<td></td>
</tr>
<tr>
<td>Rovea et al. 2015</td>
<td>Retrospective</td>
<td>T1mic–4, N0–2 80</td>
<td>291/298°</td>
<td>Lumpectomy</td>
<td>HT 77.9; CHT 2.7</td>
<td>30/32.5</td>
<td>6 Gy×5 Fx/57; 6.5 Gy×5 Fx/241</td>
<td>NO</td>
<td>5</td>
<td>2%</td>
<td>27.4%</td>
<td>1.3%</td>
<td>39.2%</td>
</tr>
<tr>
<td>Dragan et al. 2017</td>
<td>Prospective, single-arm</td>
<td>0–II, N −/+ 59</td>
<td>158</td>
<td>Lumpectomy</td>
<td>HT 73.4; CHT 28.5</td>
<td>28.5/30</td>
<td>5.7 Gy×5 Fx/78; +6 Gy×1 Fx/22; +2.7 Gy×3 Fx/3; +2 Gy×5 Fx/3°</td>
<td>3</td>
<td>1.3%</td>
<td>NR</td>
<td>22.8°</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Sanz et al. 2018</td>
<td>Retrospective</td>
<td>In situ–IV, recurrence, N −/+ 79</td>
<td>486</td>
<td>Lumpectomy 382; mastectomy 13.4; no surgery 7</td>
<td>HT 78.6; CHT 13.4</td>
<td>30/37.5</td>
<td>5 Gy×6 Fx/45; +1–2 Fx/NR</td>
<td>5</td>
<td>3.3%</td>
<td>81.1%</td>
<td>12.8%</td>
<td>27.2%</td>
<td></td>
</tr>
</tbody>
</table>

°, age: median age except average age in studies. In the study published by Martin et al. patients were older than 50 years, but median or mean age is NR; °, twice-weekly schedules; °, the group to which the patients who have received boost belong has not been reported; °, acute effects have been reported as grade 2 or greater. NR, not reported; HT, hormone therapy; CHT, chemotherapy; Gy, Gray.
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 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 14 patients, with no grade 3 reactions. Fibrosis was developed 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 single-arm, 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).

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 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).

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 non-randomized 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.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

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