



Altered fractionation in radiation therapy for breast cancer in the elderly: are we moving forward?

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Abstract: Radiotherapy is a pivotal treatment for treating breast cancer. However, its role in the management of elderly patients is still under debate. Some authors suggest be avoided after surgery for early stage, some others advocate its adoption. For breast cancer treatment different schedules are used both for whole and partial breast irradiation, in adjuvant as well as definitive setting. Which one is better for elderly patients is a controversial topic. Numerous studies focused on both moderate or extreme hypofractionated irradiation have been published. However, only few addressed the topic on elderly patient population. The data on hypofractionated radiotherapy showed that for whole breast, locoregional and post-mastectomy treatment, this approach is a valid option reporting similar efficacy and toxicity to the standard fractionation. Also accelerated partial breast irradiation for patients with favourable early stage disease represents a viable option allowing for de-escalation by targeting radiation dose to the part of breast tissue at highest recurrence risk. Undoubtedly, for frail and elderly patients a short course of radiotherapy could increase their adherence and the quality of life. In the same manner, the preoperative approach has been applied for both whole and partial breast irradiation, allowing for more precise target delineation compared to the post-surgical one, eventually leading to a smaller treatment volume, to less geographical missing and possibly to a lower radiation-induced toxicity. Some more long-term results could make us more confident in prescribing adjuvant or preoperative partial breast irradiation. These approaches could be the most appropriate treatment for elderly patients, potentially preserving quality of life and increasing the tolerability to the irradiation.

Keywords: Breast cancer; elderly; radiotherapy; hypofractionated radiotherapy; altered fractionation; preoperative radiotherapy

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Introduction

The role of radiotherapy (RT) in increasing local control after breast-conserving surgery (BCS) is well established (1). However, for elderly patients this issue is still under debate. There is not agreement in the international community on how to treat elderly patients with breast cancer (2) with under-treatment of this population becoming more

common in the modern era (3).

On one hand, in elderly women with lesions less than 2 cm and clinically node-negative, estrogen receptor-positive (ER+) tumours undergoing BCS, the omission of adjuvant RT has been shown to be feasible in randomized trials (CALGB9343 and PRIME II) with long-term follow-up, given a decreased incidence of local recurrence and

a rate of metastasis or breast cancer mortality apparently not negatively affected (4-8). In fact, based on these trial results, the National Comprehensive Cancer Network (NCCN) guidelines (version 1.2016) recommend that adjuvant RT should be omitted for patients 70 years old and older with T1N0M0 ER+HER2- negative breast cancer (9). In fact, no risk factors predictive of local relapse were found (age, tumour diameter or grade, margin status, lympho-vascular invasion, ER status). On the other hand, the only variable predictive of local recurrence was the omission of RT (6).

Moreover, some observational studies and a large propensity-score study showed a decreased risk of death for elderly breast cancer patients treated with RT (10-12). Ali *et al.* analysed a total of 5,688 patients, 1,549 (27.23%) of whom treated with hormone therapy (HT) alone and 4,139 (72.77%) treated with RT plus HT after BCS (12). In the Propensity Score-matched sample, patients who had received RT plus HT revealed a 38% lower risk of death compared with patients who were treated with only HT (12). Additional data have been recently showed in a National Cancer Database study (13). The authors evaluated overall survival (OS) between patients with triple negative breast cancer after BCS who either received postoperative RT or not. A statistically significant decrease of OS was observed across a range of age groups, as well as pT stage and chemotherapy usage stratification. The authors warned about the study limitations, nevertheless they suggest caution in omitting adjuvant RT in this setting (13).

Some authors have argued that for elderly women with disease features similar to those of the CALGB9343 and PRIME II (5,6) studies RT should be avoided (14). Others have recommended for a more individualized approach based on tumour characteristics, comorbidities and patient preferences (6).

Conversely, RT by means of the hypofractionated approach has been shown as equivalent to the standard fractionation in terms of efficacy and toxicity (15-17) and the American Society for radiation oncology (ASTRO) published the guidelines for the use of hypofractionation for pT1-2 pN0 breast cancer patients 50 years old or more (18).

Few years later, the American Society of Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) have solicited clinical trials focused on elderly patients in order to optimize treatment in this patient group (19,20). However, de Glas and colleagues (1) highlighted that only 4% of the ongoing trials for breast cancer treatment are specifically including elderly patients.

Undoubtedly, age is a significant prognostic factor when estimating OS, and accordingly, for the clinical decision

making process. In fact, it may influence which treatment strategy is ultimately prescribed, above all because the majority of elderly patients die because of non-breast cancer-related reasons (21). As a matter of fact, more than one third of breast cancer patients are diagnosed at the age of 70 or more years. Furthermore, elderly women more likely have health issues that could influence the tolerability and benefit of treatments. Those patients could benefit from de-escalation and time reduction of RT achieving low risk of relapse with minimal adverse effects. From whole breast irradiation to no RT, hypofractionation and its extreme expression, the radiosurgery, could be a more appropriate choice, based on stage and risk factors. Whilst comorbidities increase dramatically with age standing for independent life-limiting conditions, breast cancer continues to be a significant cause of death in elderly women.

From this perspective, we conducted a literature review focused on radiotherapy de-escalation for elderly breast cancer patients. The aim of this study is to discuss the literature data highlighting potential opportunities for using altered fractionation in this group of patients.

Methods

A literature review was carried out based on PubMed search for English studies including 15 patients at least. The keywords used were “breast cancer” and “elderly breast cancer” combined with “radiotherapy”, “hypofractionated radiotherapy”, “adjuvant radiotherapy”, “partial breast irradiation”, “hypofractionation” and “altered fractionated radiotherapy”. The cut-off of 65 years was chosen to stake off the elderly patient group (22). A discussed literature review was undertaken in a setting of evolving views concerning the treatment paradigm for older women diagnosed with breast cancer.

Results

Hypofractionated RT delivers a higher dose per fraction compared to the standard fractionation (2 Gy daily) in fewer fractions over a shorter overall treatment time (accelerated hypofractionation).

For breast cancer treatment different schedules are used both for whole and partial breast irradiation, in adjuvant as well as definitive setting. Which one is better for elderly patients is under debate.

The radiobiological rationale stands on the knowledge that breast cancer cells have equal radiosensitivity to the

surrounding normal tissues (similar α/β ratio) (16,17). Therefore, an increase in daily dose involves an advantage instead that an increased risk of toxicity.

Hypofractionation

Four published randomized trials represent the powerful landscape from which the whole breast standard fractionation RT started to lose its supremacy. The first randomized controlled trial focused on the hypofractionation for breast cancer is the START-Pilot (16) published in 2006. Comparing 2 arms of hypofractionation (39 Gy and 42.9 Gy in 13 fractions and 5 weeks) and 1 arm of standard fractionation, the authors did not find any significant differences among the hypofractionation groups and the standard one in terms of local control. However, they found a statistically significant difference between the two groups of hypofractionation, being in favour of the one delivering 42.9 Gy (16). Moreover, the authors estimated that the alpha/beta ratio of breast cancer is almost 4.6 Gy, confirming that a hypofractionated schedule represents the best choice to deliver RT for this tumour (16). Then, the Canadian Group published the results about a randomized controlled trial (RCT) comparing the standard fractionation to a hypofractionated schedule delivering 42.5 Gy in 16 fractions during 22 days (15). No differences were found between the two arms in terms of local control and toxicity. Likewise, the START-A and START-B trials showed no differences between the analysed hypofractionated schedules and the standard one in terms of 10-year local control (LC), disease-free survival (DFS) and OS, as well as the reported toxicity (17). Last but not least, being the trials designed to provide direct estimate of α/β for local cancer control and normal tissue responses, avoiding differences in treatment time (5 weeks), we can infer that assuming $\alpha/\beta = 3$ Gy, when 2 Gy fractions are used, 0.65 Gy are wasted per day (23,24).

Also for locoregional irradiation the data about the hypofractionation are reassuring (17,25-27), to the point that the Royal College of Radiologists published in 2016 a Consensus statement on hypofractionation in breast cancer (28), stating that all adjuvant RT for local or locoregional treatments of breast cancer should be delivered in a hypofractionated regimen with no more than 15 fractions and 40 Gy of total dose.

These findings were corroborated by a recently published meta-analysis of randomized trials that included more than 8,000 patients (29).

At the same time, a higher dose per fraction than those

evaluated in the aforementioned studies could represent the most suitable scheme for breast RT in elderly patients. The literature data are very reassuring and the radiobiological rationale is solid. In fact, assuming that the alpha/beta ratio for breast cancer is between 3 and 4.6 Gy (27,30,31), a schedule delivering 5 fractions of 5.7 or 6 Gy should be equivalent to the 50 Gy delivered in 25 fractions (32). The long-term results of the UK FAST-Forward trial (N =4,000), evaluating two dose levels of a 5-fraction schedule delivered in 5 days *versus* the current UK standard of 40 Gy in 15 fractions (33), will clarify this scenario.

Lastly, also for post-mastectomy RT the hypofractionation is a valid option showing similar efficacy and toxicity to the standard fractionation (34,35). A prospective single arm phase II trial focused on delivering postmastectomy hypofractionation to the chest wall and regional lymphatics with a 3-week fractionation schedule showed acceptable toxicity and outcomes (34). These results have been confirmed by a recent randomised, non-inferiority, open-label, phase 3 trial. The authors found that OS and DFS were similar in the hypofractionated and conventional fractionated RT groups, reporting with the former approach less frequent grade 3 acute skin toxicity than the conventional one (36). Two phase III trials on post-mastectomy hypoRT are ongoing (ClinicalTrials.gov Identifier: NCT02384733 and NCT03127995) and based on these results we could overcome all uncertainties.

Among the “hypo” scenario, a once-weekly schedule has been evaluated by different authors. The first published clinical trial of once-weekly hypofractionated RT schedule was published by Rostom *et al.* (37). It was a phase II trial focused on a dose per session of 6.5 Gy/day, one session per week to elderly patients. The authors showed a good locoregional control and a sufficient cosmetic outcome. In 2006, Ortholan *et al.* published a similar study that included 150 patients undergoing either conservative or radical surgical treatment, delivering the same weekly hypofractionation regimen, in which a good clinical outcome was also reported (38). Other published studies have also shown comparable toxicity and locoregional control rates (31,39-41).

However, despite the strength of available data, recent studies suggest that hypofractionation remains significantly underutilized (42,43).

Partial breast irradiation

The expanding use of accelerated partial breast irradiation

(APBI) for patients with favourable early stage disease has allowed for de-escalation by targeting the dose to a limited volume of breast tissue that is at highest risk of relapse. In fact, the APBI approach treats only the surgical bed plus 1- to 2-cm margin, rather than the whole breast. The rationale is that the most frequent region of local tumour recurrence in case of early stage breast cancer is the surgical bed (44). Therefore, the main benefits of postoperative APBI are related to the treatment delivered around the tumour bed. In this scenario, APBI has becoming a viable option to replace the standard whole breast irradiation. Moreover, in a recently published study, a dosimetric comparison among different techniques for APBI delivery [VMAT, CyberKnife (CK) and 3D-CRT] provided equivalent dose conformity (45). However, the authors concluded that in CK treatment, despite the long treatment time, the delivery accuracy is expected to be better than 3D-CRT and VMAT due to the controlled organ motion.

The pros of APBI are the shorter period of treatment and the confined exposure of organs at risk with an assumed equivalent efficacy compared to standard fractionated whole-breast RT by means of increasing the radiation fraction dose and decreasing the target volume (46). As other altered fractionation, this approach is of special interest in elderly or frail patients. However, APBI is still a matter of debate. Numerous studies have been published and the results are not homogeneous. Some authors showed fair aesthetic outcome after external beam RT (47,48), by contrast, some others highlight the better toxicity outcomes (44,49,50). A meta-analysis of randomized phase III trials published in 2015 demonstrated that APBI is associated with a higher risk of local relapse, finding that two trials assessing 1,407 participants reported significant benefit in the whole breast irradiation versus APBI group in terms of 5-year local recurrence (51). However, there were no differences in nodal recurrence, systemic recurrence or OS and the rate of severe toxicity was very low (<3%) in both treatment arms and comparable within the studies (51). On the other hand, another meta-analysis did not found any difference in the 5- and 8-year OS, except for the 10-year OS that was better in the APBI approach in only one study (OR =0.56, 95% CI: 0.35–0.91) (52). No differences were reported in the 5-year local recurrence, cancer-specific survival, DFS, rate of contralateral breast cancer, and distant metastasis (52).

Recently, results of the UK IMPORT LOW trial (53) have been published. In this trial the patients were randomized to receive whole breast RT with a schedule of

40 Gy in 15 fractions, 36 Gy to whole breast and 40 Gy to the partial breast (reduced-dose group) or 40 Gy to the partial breast only. The results showed similar results between partial breast and reduced-dose RT groups compared with the standard whole breast hypofractionated irradiation (53). In the last few months, Korzets *et al.* (54) published their results on a meta-analysis of nine trials comparing adjuvant APBI to whole breast RT in early-stage invasive breast cancer comprising 14,514 patients. They found that APBI is correlated to higher odds for local recurrence and toxicity (54).

It is crucial in the decision making process whether APBI treatments could be as effective and safe as whole breast RT. There are at least five published consensus statement criteria for the delivery of APBI off protocol (ASTRO – American Society for Radiation Oncology, GEC-ESTRO – Groupe Européen de Curietherapie-European Society for Radiotherapy and Oncology, ABS – American Brachytherapy Society, ASBS – American Society of Breast Surgeons – ESTRO-ACROP GEC-ESTRO 2018) (55,56). In summary, the most important eligibility criteria are the age (>60 years for ASTRO; >45 years for ASBS), absence of BRCA 1/2 mutations, tumour diameter <3 cm, no multicentric or multifocal lesion, ER+, absence of lymphovascular invasion and lymph node involvement, negative surgical margins, no extensive intraductal component and no neo-adjuvant therapies.

At least 7 are the prospective (ongoing or with published only early results) trials focused on APBI versus whole breast RT (57–65). Their results will be added to the recently published ESTRO-ACROP guidelines (55), and may allow drawing more clear conclusion, maybe overcoming the difficulties due to the use of various technical approaches used to deliver APBI (external beam RT delivered by different techniques, high dose rate or pulsed dose rate interstitial brachytherapy multicatheter with ¹⁹²Ir, balloon-based intracavitary brachytherapy, single-dose intraoperative RT), and also due to the large variability in terms of dose prescription, dose fractionation, positioning and geometry (44,66–70).

Undoubtedly, for frail and elderly patients a short course of RT could increase the quality of life and the opportunity to be treated. Some more long-term results could make us more confident in prescribing APBI as post-surgery approach.

Definitive and preoperative radiation therapy

Almost half of women aged ≥75 years is diagnosed with

breast cancer, and current research reports decreasing standard-of-care treatment with BCS in this population (71). Previous data showed scarce local control with HT alone and unacceptable toxicity with standard fractionated definitive RT to the whole-breast (72,73).

The preoperative approach has been applied for both whole and partial breast irradiation. Numerous studies on preoperative RT are focused on standard fractionation with or without concomitant chemotherapy, being the most focused on treatment for locally advanced cases to debulk initially inoperable disease (74-76). However, neoadjuvant stereotactic RT and radiosurgery are becoming more and more in the limelight above all for early stage breast cancer. Several studies have been published and large cohorts of women with low-risk breast cancer received this treatment with acceptable clinical outcomes (66,77-82).

The delivery of preoperative RT to the intact tumour allows more precise target delineation compared to the post-surgical, eventually leading to a smaller treatment volumes, to less geographical missing and possibly to a lower RT-induced toxicity (79,83). Moreover, recently published studies have shown an antitumour immune responses activated by RT delivered at high doses to the bulk tumour (84-87). This immunomodulation effect of RT could represent a significant advantage possibly decreasing local and distant relapse or metastatic disease at long-term follow-up.

Arriagada *et al.* reported on 463 patients with advanced breast tumours treated with definitive RT showing an improved local control significantly associated with high radiation dose and small tumour size (88). Van Limbergen *et al.* reported on 221 patients with operable breast cancer treated with definitive RT after 15.5-year follow-up (89). They showed an excellent 10-year LC rate of 96% and 83% in tumours ≤ 1.0 cm and 1.1 to 3.0 cm, respectively (89). The authors highlighted that each 1 cm increase in tumour diameter led to an 8% decrease in LC. Lischalk *et al.* (3) conducted a dosimetric analysis supporting the feasibility of stereotactic ablative RT and APBI as definitive treatment for early stage breast cancer. They showed a significant normal tissue sparing, especially for the breast, lung, and heart.

Recently, a population-based analysis of the long-term effects of neoadjuvant RT has been published. The authors evaluated the outcomes of patients with early-stage breast cancer who received either adjuvant or neoadjuvant RT in terms of OS and cancer-free survival rates (74). They found that overall the hazard of developing second primary cancer

is significantly decreased when RT is delivered before than after surgery, especially for ER+ patients. For elderly patients, they found that in all stratified groups the risk of developing second primary tumours was slightly higher (HR ≥ 1.01 , P=0.0001). No decreased OS was found (74). Riet *et al.* recently published a large series of patients treated with preoperative slightly hypofractionated RT (90). The authors published their long-term results with a median follow-up of 32 years in 187 patients who had undergone preoperative RT followed by mastectomy and axillary dissection. With a median OS of 12 years and a toxicity rate of 19%, the only pathological factor negatively affecting the prognosis was the node involvement. The 10-, 20- and 30-year OS rates were 55%, 41% and 25%, respectively (90). It is noteworthy that triple-negative breast cancer had a higher response rate to RT, but at same time higher local relapse rates. We could assume that preoperative RT combined with chemotherapy may improve local control and survival in triple negative tumours. This study could be considered the pioneer of the current cutting-edge approach. Even if retrospective, its results are reassuring and promising about the neoadjuvant RT setting. There are at least 7 on going or with published early results trials focused on neoadjuvant RT (91-96). Their results will provide key information for definitive and preoperative hypofractionated RT. In fact, numerous factors should be considered when preoperative RT for breast cancer is applied: the timing between the end of RT and the surgery, the imaging for assessing treatment and follow-up, the use of preoperative and postoperative sample for biomarker and radiobiological research and obviously patient selection.

The (hypo)-boost

The use of RT boost has been confirmed to provide a statistically significant reduction in ipsilateral breast tumour recurrence risk (4% at 20 years) for all age patients diagnosed with invasive breast cancers (91). Two large randomized trials, while no effect on long-term OS was found (17,92), showed that localized dose escalation positively affected local control by means of a boost to the tumour bed.

Several authors have reported outcomes on a boost delivered simultaneously during conventionally fractionated whole breast irradiation localizing dose escalation in the tumour bed without prolonging the overall treatment duration (93,94). However, definitive results are not yet published. In fact, the patient accrual for RTOG-

1005 phase III trial is concluded. This study compared a sequential treatment (15×2.67 Gy to whole breast followed by 5×2-Gy as boost) to a concomitant boost schedule (15×2.67 Gy whole breast RT/15×3.2-Gy simultaneous boost) (95). Almost at the same time, in Germany, Austria, and Switzerland, the current HYPOSIB trial tests a hypofractionated RT schedule with concomitant boost (16×2.5 Gy whole breast RT/16×3-Gy boost) (93).

Apart from external beam RT, the dose escalation to the tumour bed can be delivered by other technical methods, such as brachytherapy and intraoperative radiation therapy (IORT/ intraoperative electron radiation therapy; IOERT) (96). The combination with hypofractionated RT is currently under evaluation in 2 multicentric prospective trials: the TARGIT-B(oost) study and the HIOB trial (IORT electron boost followed by 3 weeks hypofractionated whole breast irradiation).

Conclusions

RT is crucial arm for fighting breast cancer, also for elderly patients. Nevertheless, for this group of patients the treatment of breast cancer is not standardized and the different options are still under debate.

Shifting from the conventional 5–6 weeks of treatment to 3, 2 or even 1 week schedule, shorten RT may preserve or improve patient's quality of life and may also facilitate treatment for elderly patients who need more assistance and in general for frail patients.

Altered fractionation could be applied by means of hypofractionation (over 2 or 3 weeks), accelerated partial breast irradiation (over 1 week) or definitive single session radiosurgery. By now, the former represents a standard approach, while the latter are under evaluation. However, the early results seem to be promising. In addition, as the benefit of the boost decreases with increasing age—and accordingly the indication for a boost for elderly is not mandatory—the use of hypofractionation and APBI becomes strengthened.

Despite more data on tolerability, fractionation and dose administration are needed to better tailor the radiation treatment for breast cancer in the elderly population, the hypofractionated schedule should be seriously considered when RT is delivered. However, although the evidence supporting hypofractionated breast irradiation has subsequently grown substantially, its adoption among appropriate patients remains low, especially among elderly patients (42,97,98).

A recently published study based on 37 cancer registries and 9 countries analysed the influence of comorbidities on the decision to whether treat or not women with early breast cancer with standard approach (43). The authors found that at elderly women often were offered less prompt and non-standard treatments, irrespective of comorbidities, increasing the risk of recurrence and mortality. They conclude suggesting all women, particularly the elderly, should whenever possible receive standard treatment so as to maximise the benefits of modern evidence-based treatments (43).

What we should consider “standard” for elderly patients is still controversial. In general, a treatment omission should be avoided. Since the role of age in the decision-making process is negligible, there is evidence that chronological age should not be a boundary for adjuvant or definitive RT (99,100).

Further trials are advocated to obtain clear data on which subgroup of patients can avoid RT. In fact, when choosing if and how deliver RT, we should consider life expectancy and the benefits and risks potentially associated with treatment, above all the effects on quality of life (100,101). A cancer-specific survival score could be a most convenient key-factor on which to hinge on choice (101) to avoid under- or over-treatment and improve clinical decision-making. Also because, given the relative complexity of breast cancer presentations, a one-size fits all approaches should be avoided taking into account disease biology, comorbidities, performance status, and also patient preferences (102).

Lasting, when hypofractionated radiotherapy is delivered, strict dose volume constraints to the near at risk organs are mandatory. To this end, advanced imaging modalities are crucial to optimize the target volume and at risk organs definition as well as the correct patient positioning (103).

Despite being too early for comment on efficacy results, it is worth to mention that partial breast preoperative RT has been showing good cosmetic outcome and its clinical application is spreading, hoping to offer a chance of curative treatment also to elderly and frail patients. As a matter of fact, wanting to venture a hypothesis, a 1-week schedule as adjuvant treatment to the whole or partial breast RT and a single fraction RT as definitive treatment to the lesion or lump could represent the future clinical practice, with a special focus on an individualized risk-adapted treatment strategy.

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