



Breast radiotherapy in elderly women: myths, controversies, and current techniques in the adjuvant setting

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Abstract: In developed countries, breast cancer (BC) is the most common type of cancer in women, mainly affecting patients over age 60. Due to the increasing life expectancy and population ageing, the incidence of BC is expected to increase significantly in the coming years. However, no standardized clinical guidelines are available to assist in decision-making in elderly patients. Moreover, there is a lack of quality scientific evidence to guide treatment selection in this patient population, who are underrepresented in clinical trials. Consequently, up to 50% of elderly women are treated suboptimally, which implies a worse prognosis and survival. Given that the current estimated life expectancy of a healthy 70-year-old woman is 15 years, any treatment capable of reducing the likelihood of disease recurrence and cancer-specific mortality in this patient population would be beneficial. Adjuvant radiotherapy (RT) is one of the pillars of treatment for BC and it plays a key role in improving local control (LC) and overall survival (OS). Adjuvant RT is clearly indicated in young patients who undergo breast-conserving surgery (BCS) as well as in high risk patients, regardless of age. However, the use of adjuvant RT in older patients with early-stage disease has decreased in recent years—even in patients who undergo BCS—due to outdated concerns about the possible side effects of RT and reports suggesting that RT can be omitted in low-risk patients. One of the greatest challenges currently facing radiation oncologists who specialise in the treatment of BC is the selection of elderly patients who are likely to benefit from adjuvant RT. There is also a clear need to critically evaluate the available evidence and to apply those findings to routine clinical practice. Given this context, the aim of the present review is to clarify the current role of adjuvant RT in the management of BC in older women—particularly those with early-stage disease—and to dispel the myths surrounding the use of RT to treat elderly women. This review primarily focuses on the indications, controversies, and irradiation techniques used in this patient subgroup.

Keywords: Radiotherapy (RT); cancer; breast; elderly

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Introduction

Breast cancer (BC) is the most common type of cancer in women in developed countries (1). The probability of developing BC increases with age. The majority of cases occur in women over age 60, with women over age 70 and 80,

respectively, accounting for 30% and 12% of diagnoses (2,3). BC-related deaths have decreased drastically since the 1990s, although the main beneficiaries of this reduction are women under age 75, with cancer-specific mortality decreasing by 2.5% per year in women <75 years since the 1990s, but only

by 1.1% per annum in older women (4). In Europe, the overall mortality rate decreased by 13% from the 1990–1994 period to the 2000–2004 period, with a significantly greater reduction in mortality among women under age 65 versus older women (17% *vs.* 6%, respectively) (5).

Adjuvant whole breast radiation therapy (WBRT) is one of the mainstays of treatment for BC, improving both local control (LC) and overall survival (OS) (6), as shown in the meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (7). The value of adjuvant WBRT in young women or women with high-risk disease (regardless of age) is unquestioned, and it is considered a standard treatment option in clinical practice (8). However, in recent years, the use of adjuvant WBRT in older patients with low-risk disease has declined, especially since clinical guidelines included the option to obviate adjuvant RT based on reported findings from several studies suggesting that RT does not appear to improve OS (8–10). However, as we discuss in this review, the evidence to support the omission of adjuvant RT in older women is based on studies with important limitations.

In this context, a critical evaluation of the available scientific evidence regarding the value of adjuvant RT in the treatment of older women with BC will improve treatment selection and increase our understanding of the various factors—epidemiological, biological, social, and economic—that could influence the management of these patients, and this is what we are going to try to clarify in this review.

What does the term “elderly” mean and how does it influence the management of patients with BC?

There is a noteworthy lack of consensus regarding the definition of the term “elderly”. As early as 1995, the United Nations Committee on Economic Social and Cultural Rights of Older Persons (11) rejected the use of this term due to its lack of specificity and because it was assumed to refer to frail patients with precarious health (12–14). Although this term is commonly used to refer to people over age 65, this cut-off point is not based on scientific evidence, but rather borrowed (in all likelihood) from the field of socioeconomics since this is the age at which people in industrialized countries generally stop working and begin to collect retirement benefits (15). However, it may be inappropriate to apply this term to all people over age 65 given the long mean life expectancy in Western countries

(>80 years) (16,17) and considering that the health status of women in this age group is highly variable (18).

Rather than using an arbitrary age to define “elderly”, it would be more reasonable to use objective criteria to classify patients according to their “biological” rather than their chronological age. However, the instruments most commonly used in routine clinical practice to assess health status (e.g., the Karnofsky index, ECOG, performance status) have important limitations with regard to their capacity to assess the main domains of interest in elderly patients. Moreover, those tools cannot identify changes that could potentially be reversed through early interventions. The International Society of Geriatric Oncology (SIOG), in conjunction with the European Society of Breast Cancer Specialists (EUSOMA), has published recommendations for the management of elderly patients with BC. According to those recommendations, age should not be considered an impediment to the use of RT, but an objective geriatric assessment—such as the comprehensive geriatric assessment (CGA)—should be performed prior to making the therapeutic decision (19). The CGA is important because it provides valuable data to help select the most appropriate therapeutic approach, after careful consideration of the risks and benefits of the intervention, based on the patient’s life expectancy and baseline health status (20,21).

Myth 1: older women with BC have a better prognosis

This is a myth, as studies show that women over age 75 diagnosed with BC actually have *worse* survival outcomes than younger patients (22). Although this finding appears to be inconsistent with the fact that a higher proportion of tumours in this patient population present biological characteristics that are, a priori, suggestive of good prognosis (i.e., higher expression of estrogen and progesterone receptors; less peritumoral vascular invasion; lower rates of HER2/Neu overexpression; a lower proliferation index; a higher proportion with normal p53 expression; and fewer deleterious mutations) (23–25). However, the higher mortality rate among older women whose disease is, at least theoretically, more benign can be explained by the factors discussed below.

Are these tumours as indolent as they appear?

At diagnosis, elderly women with BC are more likely to present with nodal and distant metastases, and/or to

present molecular subtypes that are more aggressive than expected (26,27). Jenkins *et al.* evaluated 2,150 patients diagnosed with BC. After using the PAM 50® platform to reclassify patients, they found that the prevalence of luminal B, triple negative, and HER2+ cancer (28%, 13% and 13%, respectively) was higher than expected among patients over age 70 (28). Furthermore, the condition of the host also plays a role, with some studies showing that age-related alterations of the immune system disrupts mutation detection and repair mechanism, thus making the elderly more susceptible to developing more aggressive cancers, even in subtypes with an ostensibly better prognosis (29,30).

Late diagnosis

Late diagnosis among elderly patients can primarily be attributed to two main factors. First, the interruption of routine screening mammography and preventive medicine in older patients. In most countries with publicly-funded screening and prevention programs, routine screening mammographies are usually phased out around age 70 (31,32). The use of this somewhat arbitrary cut-off point is partly related to clinical trials conducted to evaluate the effectiveness of screening programs, which generally exclude patients in this age group, even though the findings from observational studies and computer models have shown that there may be a survival benefit for screening older women who have a long life expectancy (33-35). Nevertheless, this topic is controversial and no international consensus has yet been reached (36-38). The second main factor to explain late diagnosis in this patient population is the delay between the time the patient notices a suspicious breast lesion and subsequent medical evaluation of the lesion (39). This delay is especially common in the most frail or dependent patients, and also influenced by sociodemographic and economic factors (40,41).

Undertreatment

The final—but not least important—factor that may explain the higher mortality rate in older women is undertreatment. Studies show that close to 50% of older patients diagnosed with BC—especially those over age 70—receive suboptimal treatment that deviates from the recommendations of clinical guidelines (40,42). As a result, both prognosis and survival are worse in these patients (43). While the main reasons for undertreatment are not entirely clear, it is likely multifactorial. One explanation may be the

presence of comorbidities, which can negatively impact the patient's capacity to tolerate the indicated treatment. It is also possible that the treating physician believes that the indicated treatment is unlikely to provide a clinical or survival benefit due to the patient's baseline health status. In other cases, the factors associated with undertreatment are social, such as difficulties in the patient's ability to travel autonomously to the treatment centre, care dependency, or due to the specific preferences of the patient and/or family members responsible for providing care. In other cases, medical paternalism may play a role in treatment selection. Some physicians may avoid prescribing morbidity-inducing treatments, underestimate life expectancy, and/or question the patient's ability to tolerate treatment. Advanced age is independently associated not only with less adherence to the recommendations of clinical guidelines, but also with a lower probability of receiving BCS, a greater use of hormonal therapy, less use of adjuvant chemotherapy, and a lower probability of receiving radiotherapy (RT), even in patients in good general condition (44,45).

Myth 2: there is sufficient evidence to guide treatment selection

Older women, especially those in their 70s, are underrepresented in clinical trials (46) due to strict inclusion criteria, a failure to inform them about this option, or due to a medical or family concern about possible side effects (47-49). For this reason, level 1 evidence in this population is limited, and the evidence that is available is subject to debate. An article published in 2011 by the EORTC recommended that clinical trials be carried out in older patients (50). That publication even provided specific recommendations about how such a study should be designed, emphasizing the need to include endpoints related to quality of life (QoL), functional status and independence (in addition to the usual measures of efficacy). They also suggested the use of age 70 as the cut-off point for “old age” for study design purposes, including only patients who meet this age criterium. To conduct such a study, it is essential to use geriatric assessment tools such as the CGA to adequately stratify patients into comparable, homogeneous subgroups (50).

Controversy: can adjuvant WBRT be safely omitted after breast-conserving surgery (BCS)?

Most of the clinical trials performed to evaluate the role of

adjuvant WBRT have excluded patients older than age 70. In a meta-analysis, Clarke *et al.* demonstrated that adjuvant WBRT decreased cancer-specific mortality at 15 years; however, only 9% of the patients included in that meta-analysis were over age 70 (51). The absolute benefit of adjuvant WBRT in patients with early-stage disease decreases with age, which explains why several recent prospective trials have examined the effect of omitting adjuvant RT after BCS in selected patients (Table 1). Those trials assessed a range of endpoints, including OS, local recurrence (LR), and progression-free survival (PFS). The CALGB 9343 (53) and PRIME II (56) trials also included QoL as an endpoint.

In the CALGB 9343 study (53), 636 women over age 70 with stage T1N0, hormone receptor-positive (RE+) BC were randomized to receive adjuvant WBRT with tamoxifen or adjuvant tamoxifen alone. At 10 years, LC rates were significantly better in the adjuvant WBRT group (98% *vs.* 90%). The PRIME II trial (56) included women over age 65 with tumours <3 cm, N0, and RE+ who were randomized to the same treatments as in the CALGB 9343 study. At 5 years, LC was better in the adjuvant WBRT group, with no significant between-group differences in QoL, leading the authors to conclude that the combined use of adjuvant WBRT and tamoxifen after BCS does not negatively impact functional competence. The BASO II trial (55) evaluated 1,135 patients over age 50 with grade 1, stage T1 BC. The study assessed adjuvant treatment using a 2×2 design (with or without adjuvant WBRT and with or without tamoxifen). At 10 years, LC was better in the group that received adjuvant WBRT + tamoxifen, with no local relapses in that group. The 60 month follow-up results of the ABCSG 8 trial (54) reported outcomes from 869 patients (mean age, 66 years) with tumours <3 cm, RE+, grade 1 or 2, and N0 who were randomized after BCS to tamoxifen/anastrozole with or without adjuvant WBRT. In that study, adjuvant WBRT had a significant positive impact on LC. Finally, Fyles *et al.* (52) evaluated 769 patients over age 50 with T1-T2 tumours who underwent BCS and were randomized to receive adjuvant WBRT or adjuvant tamoxifen; local relapse rates were significantly better in the adjuvant WBRT group at both 5 years (0.6% *vs.* 7.7%) and at 8 years (3.5% *vs.* 17.6%) of follow up.

In summary, all of these trials showed that adjuvant WBRT + tamoxifen was significantly superior to adjuvant tamoxifen alone in terms of LC, although this advantage did not translate into an improvement in OS. The finding that combined treatment did not increase OS seemed to imply

that adjuvant WBRT could be safely omitted in selected patients. As a result, this approach is now considered an alternative to standard treatment (adjuvant WBRT + tamoxifen) in selected patients, and it is even included in some clinical guidelines (8).

Should we systematically omit adjuvant WBRT in elderly women with a good prognosis?

The findings of the aforementioned studies suggest that adjuvant WBRT can be omitted because it does not—despite its positive influence on LC—appear to improve OS. However, these findings must be interpreted cautiously, in part because it remains unclear whether those results can be extrapolated to the general population—particularly older women (>70 years)—who were underrepresented in most of those trials (except for the PRIME II and CALGB-9343 trials).

The meta-analysis by Matuschek and colleagues published in 2017, which included all of the aforementioned trials, revealed some highly interesting findings (57). First, although the individual studies included in the meta-analysis failed to show a survival benefit in OS for combined treatment with adjuvant WBRT + tamoxifen, this treatment approach significantly lowered the risk of LR (hazard ratio, 6.8), corresponding to an absolute reduction in LR of 3–5% and 9–14% at 5 and 10 years, respectively. This decrease in LR implies an increase in OS at 5- and 10-years of 3% and 7%, respectively. In this regard, the results of the CALGB-9343 trial—the only randomized controlled trial with a 10-year follow-up—show no recognizable plateau on the survival curves, raising the possibility that these curves will continue to diverge after year 10 in that trial, and possibly in the other clinical trials (53).

The retrospective study published by Herskovic *et al.* in 2018 presented some very interesting findings. Those authors evaluated the impact of omitting adjuvant WBRT in a real-world sample (outside of the controlled conditions of clinical trials) of women over age 65 with low-risk BC. The study retrospectively evaluated 61,395 women from the National Cancer Database who were diagnosed with BC during the years 2006–2013. At 48.7 months of follow-up, the OS rate in patients who received adjuvant WBRT + tamoxifen was significantly higher than in the patients who received adjuvant tamoxifen alone (93% *vs.* 83.6%, $P < 0.001$), with survival curves that began to separate at month 24. Despite the limitations inherent to the retrospective study design, the findings of that study

Table 1 Randomized studies that explore the option of omitting radiotherapy after BCS

Variable	Fyles (52)	CALGB 9343 (53) (Hughes <i>et al.</i>)	ABCSG 8 (54) (Pötter <i>et al.</i>)	BASO II (55) (Blamey <i>et al.</i>)	PRIME II (56) (Klunkler <i>et al.</i>)
Patients, n	769	636	869	1,135 (2×2: 406) [†]	1,326
Study type	Multicentric randomized	Multicentric randomized	Multicentric randomized	Multicentric randomized and 2×2	Multicentric randomized
Age, y	≥50	≥70	≥50	≥50	≥65
Tumour size (all pN0) (cm)	<5	<2	<3	<2	<3
RE/RP	100%	100%	100%	100%	100%
Menopausal status	100%	100%	100%	100%	100%
Surgery	BCS	BCS	BCS	WLE	BCS
Randomization	Tam + WBRT/Tam	Tam + WBRT/Tam	Tam + WBRT/Tam	No WBRT, no Tam/WBRT alone/Tam alone/Tam + WBRT	Tam + WBRT/Tam
N	386/383	317/319	414/417	95/107/106/98	658/668
Follow up	5 and 8 years	12.6 years	5 years	10 years	5 years
LR	5 yrs: 0.6%/7.7%*; 8 yrs: 3.5%/17.5%	2%/10%**	0.4%/5.1%***	15%/6.5%/7.5%/0%****	1.3%/4.1%*****
DFS	91% vs. 84%, P=0.004	98% vs. 91%, HR 0.18, P<0.01	97.9% vs. 93.9%, HR 3.48, P=0.0021	83%, HR 1/93%, HR 0.37/93%, HR 0.40/0, HR 0	90% vs. 84%
OS	91% vs. 84%, P=0.004	76% vs. 66%	97.9 vs. 94.5, P=0.18	96%	93% vs. 93%

[†]1,135 randomized to intention-to-treat, 406 in the 2×2 evaluation; *HR 9.3, P<0.001; **P<0.001; ***HR 10.2, P=0.0001; ****P<0.001; *****HR 5.19, P<0.001. BCS, breast-conserving surgery; DFS, disease-free survival; OS, overall survival; LR, local relapse; Tam, tamoxifen; WBRT, whole breast radiation therapy; HR, hazard ratio; RE/RP, estrogen and progesterone status; WLE, wide local excision (specimen margins >0.5 cm, if less, reexcision required).

suggest that large-scale population studies are the only type of study capable of detecting significant differences in OS because prospective trials with short follow-ups do not have sufficient statistical power to detect such differences (58).

The clinical trials discussed above that have compared adjuvant WBRT plus tamoxifen to adjuvant tamoxifen alone conclude that the two treatments are essentially equivalent in terms of OS. However, it is difficult to translate these results to real world settings given that 20% to 50% of patients stop taking tamoxifen due to poor tolerance (59,60), which implies that a significant proportion of these patients (who may not have received adjuvant WBRT) will not receive the full prescribed treatment of tamoxifen. As a result, these patients are likely to have a higher rate of LR, with a greater risk of cancer-specific mortality. Indeed, the study carried out by Killander *et al.* in Sweden confirmed this effect. Those authors compared BCS + adjuvant WBRT to BCS alone, finding 15-year LR rates, respectively, of

11.5% vs. 23.9% (P<0.001), with a trend towards worse OS in the group that did not receive adjuvant WBRT (71.1% vs. 68.4%, P<0.68) (61).

Given the findings described above, it is clear that we must proceed with extreme caution when choosing to omit RT in postmenopausal patients, even those with low-risk disease. Although it may be reasonable to consider omitting RT in patients with a life expectancy less than 5 years, determined objectively according to a validated CGA. This cautious approach is important to avoid introducing selection bias and to ensure that patients with a long life expectancy are not exposed to the unnecessary risk of developing locally recurrent disease caused by suboptimal treatment, which could potentially have a negative impact on survival. Therefore, the decision to omit adjuvant RT should only be taken after careful consideration of the risks and benefits of doing so. In this assessment, it is crucial to consider the implications of early interruption of hormonal

treatment (due to poor tolerance), and to ensure that strict oncological controls will be followed.

Controversy: rethinking toxicity

Recent studies have shown that elderly patients generally tolerate RT as well as younger patients (62–64), even when interventional techniques such as brachytherapy are used (65,66). These findings can likely be extrapolated to the treatment of BC, although few prospective studies have specifically evaluated this question (67). Despite the evidence support the use of adjuvant RT described in the preceding paragraphs, one reason given for obviating RT in older women is the potential for heart and lung toxicity, which could negatively impact QoL (68–70). However, the findings from the CALGB-9343 trial, which used validated instruments to assess QoL, showed that there were no differences in QoL between patients who received adjuvant WBRT+ tamoxifen versus those who received tamoxifen alone (53). The PRIME II study did not find any significant differences in QoL at 60 months post-treatment, although there were differences between groups in logistical concerns (transportation or accommodations) during the RT treatment phase (56). In terms of lung toxicity, radiation pneumonitis has been associated with the several different variables, as follows: the size of the lung volume irradiated within the tangential fields; irradiation of the supraclavicular and internal mammary lymph nodes; prior exposure to chemotherapy or tamoxifen; and smoking habit. Nonetheless, the incidence of symptomatic pneumonitis in patients treated with RT for BC remains negligible (71,72).

How does RT affect the heart in left BC?

In 2013, Darby *et al.* published a high-impact case-control study that correlated the mean heart dose (MHD) with the probability of an ischemic cardiac event, concluding that for each 1 Gy increase in MHD, the relative risk increased by 7%, and no dose level was considered safe (73). Despite the methodological quality of that study, it had several important limitations, mainly attributable to its retrospective design. The patient cohort was obtained from historical records of patients treated from 1958 through the year 2001, thus most of these patients were treated prior to the development of three-dimensional radiotherapy (3D-RT). In addition, the groups were not balanced in terms of comorbidities, the baseline cardiac risk was unknown in many of the patients, and the MHDs were estimated from a random selection of

20 treatment plans because the actual dosimetric values were unavailable. However, this prediction model was subsequently evaluated by van den Bogaard *et al.* in a 910 patient cohort treated with 3D-RT, with a follow-up of 9 years. The results of that study validated the model, showing that the accumulated incidence of acute cardiac events increased by 16.5% per Gy of MHD and that the best predictor of risk was the volume of the left ventricle receiving 5 Gy (74). Despite the limitations of those studies and the uncertainties surrounding the specific mechanisms of cardiac damage (75), it is inexcusable not to do everything possible to minimize the MHD using advanced technology (76), especially in a patient population that often presents comorbidities that may increase the negative impact of RT on their overall cardiac risk (77).

Beyond cobalt and conventional fractionation

Until the 1990s, the main radiotherapeutic treatment in patients treated with BCS was adjuvant WBRT using conventional fractionation of 45–50 Gy (daily sessions of 1.8–2 Gy), with/without a boost to the tumour bed (78). However, since that time, numerous alternative RT schemes have been explored. Some schemes have sought to reduce the number of sessions by increasing the dose per session while others have sought to decrease the size of the target volume. The advantage of such approaches is that they limit the number of hospital visits needed for RT treatment and they also lower costs without decreasing treatment efficacy and without increasing treatment-related toxicity (79,80). It is worth noting that practically all of the trials conducted to evaluate these different RT regimens have involved patients over age 50, with older women making up a substantial proportion of the patients, and thus the results are applicable to “elderly” patients.

Hypofractionated whole breast radiotherapy (HF-WBRT)

HF-WBRT is similar to adjuvant WBRT but with higher doses per session and fewer sessions (81). The radiobiological basis for this hypofractionated approach is based on the hypothesis that the alpha/beta ratio of the tumour is similar to that of the surrounding healthy tissue, and thus larger fractions would be more effective without causing severe damage to healthy tissues (82). In the RMH/GOG trial, the alpha/beta for BC was calculated as 4 Gy. That study compared two different hypofractionated schemes (39 Gy/13 fraction *vs.* 42.9 Gy/

Table 2 Baseline characteristics of randomized trials of hypofractionated radiotherapy for breast cancer (HF-WBRT)

Variable	START trial A (85)	START trial B (87)	Canadian study (88)
Patients, n	2,236	2,215	1,234
Study type	Multicentric, randomized	Multicentric, randomized	Multicentric, randomized
Age, years			
≤60	1,358 (60.7%)	1,331 (60%)	646 (52.3%)
>60	878 (39.3%)	884 (40%)	588 (47.7%)
Histological type			
Invasive ductal	1,750 (78.3%)	1,708 (77.1%)	Invasive carcinoma
Invasive lobular	266 (11.9%)	254 (11.5%)	
Other	220 (9.9%)	453 (11.4%)	
Tumor size (cm)			
≤2	1,138 (50.9%)	1,412 (63.8%)	994 (80.6%)
>2	1,085 (48.6%)	795 (35.8 %)	240 (19.4%)
Not known	13 (0.5%)	8 (0.4%)	
Primary surgery			
Breast-conserving (BCS)	1,900 (85.0%)	2,038 (92.0%)	BCS alone
Mastectomy	336 (15.0%)	177 (8.0%)	
Randomization	50 Gy, 25 fx ¹ /41.6 Gy, 13 fx/39 Gy, 13 fx	50 Gy, 25 fx/40 Gy, 15 fx	50 Gy, 25 fx/42.5 Gy, 16 fx
N (randomization)	749/750/737	1,105/1,110	612/612
Follow up	5 and 10 years	5 and 10 years	10 years
Local relapse (estimated % with event by 10 yrs)	7.4%/6.3%*/8.8%**	5.5%/4.3%***	6.7%/6.2%****
Normal tissue effects (breast induration, telangiectasia, edema)	Significantly less common in the 39 Gy group vs. the 50 Gy group	Significantly less common in the 40 Gy group vs. the 50 Gy group	71.3%/69.8% [†]

¹Fractions; *HR 0.91, P=0.65; **HR 1.18, P=0.41; ***HR 0.77, P=0.21; ****absolute difference, 0.5 percentage points, 95% CI, -2.5 to 3.5;

[†]good or excellent cosmetic outcomes (absolute difference, 1.5 percentage points; 95% CI, -6.9 to 9.8).

13 fraction) to conventional fractionation, finding that both hypofractionated schemes were isoeffective (83,84). Several phase III randomized trials have compared the oncological and cosmetic outcomes of HF-WBRT to conventional schemes. The START A, START B and the Canadian study all found that these treatments were therapeutically equivalent in terms of LC and OS outcomes, with a trend towards better acute cosmesis for the hypofractionated regimens, without significant differences in chronic toxicity (85-88) (*Table 2*) or cardiac toxicity in left BC (89). The results of these studies were reanalyzed in several meta-analyses (90-92), which confirmed the findings. As a result,

this hypofractionation schedule is now considered standard and supported by level 1 evidence in patients in whom irradiation of the breast or mastectomy bed is indicated (93-96). Delivering a boost to the tumour bed lowers the LR rate in all patients, but it is not clear whether a boost should be routinely administered given the lack of evidence demonstrating that this would improve OS. Moreover, the use of a boost has been associated with a slight increase in the risk of chronic skin toxicity (97). However, when necessary, the boost can be performed with HF-WBRT techniques that offer integrated boost, without causing a substantial increase in toxicity (98).

Partial breast irradiation (PBI)

PBI consists of treating the lumpectomy/tumorectomy bed alone, based on the assumption that 95% of LRs occur in the involved quadrant (99,100). However, the reality is that the role of PBI remains undefined due to the short follow-up of the studies that have evaluated this technique. Nevertheless, the role of PBI has evolved in recent years. Whereas it was previously considered an intermediate RT scheme situated between adjuvant WBRT and no RT, it is now considered a therapeutic alternative to adjuvant WBRT in selected low-risk patients, an indication that has been recognized in clinical guidelines. Although PBI was first limited to brachytherapy modalities (101,102), publication of the IMPORT LOW and Barcelona trials has provided sufficient evidence to support the use of external RT for PBI (103,104). Intraoperative radiotherapy (IORT) (105,106), a technique that is administered in a single session (intra- or peri-operatively), merits special mention as an example of a cost-effective technique that provides maximum concentration of local treatment (107,108). The two main trials that have evaluated IORT are the ELIOTT and TARGIT-A trials, with 5 and 3.8 years of follow-up, respectively. Although IORT has not been found to negatively impact OS, both of those clinical trials found higher LR rates in the untreated breast areas compared to the areas that received adjuvant WBRT (4.4% *vs.* 0.4% and 3.3% *vs.* 1.3%, respectively). For this reason, IORT should only be indicated with caution outside of clinical trials (109).

Numerous randomized trials have evaluated the oncological and cosmetic results of PBI compared to adjuvant WBRT (104-108,110-113) (*Table 3*). Meta-analyses of those trials have shown that although LR and primary second tumours were more common in patients treated with PBI, this had no negative impact on OS (114-116). Moreover, the meta-analysis by Vaidya *et al.* even found a modest but significant benefit in OS for PBI versus adjuvant WBRT (a difference of 1.3%, 95% CI, -2.5% to 0.0%, $P=0.05$, by the random effects model and 1.0%, 95% CI, -2.3% to 0.3%, $P=0.13$, by the fixed effects model) (117).

Therefore, even though the probability of developing LR is slightly higher in patients who undergo PBI, this approach may be an interesting alternative to adjuvant WBRT in elderly patients with low-risk disease and a long life expectancy who present a high risk of early discontinuation of hormonotherapy. PBI could also be of value in patients who would benefit from fewer RT treatment sessions to minimize the need to travel to the hospital. Although no

randomized trials have been conducted to compare PBI to the omission of adjuvant WBRT, the published data suggest that LR rates are lower in patients who receive PBI, which would support the maxim that “some radiotherapy is better than none at all”.

What about the technology?

Administering a homogenous dose distribution to the target volume is crucial to avoid producing “hot spots” that may cause local toxicity. Likewise, it is essential to minimize the dose to the organs at risk (OAR) (118,119). To achieve these objectives, we must not only select the most appropriate technique for each case, but also develop strategies to minimize the risks present throughout the entire treatment process.

In recent years, several studies have compared the dosimetric results of different external RT techniques for both adjuvant WBRT and PBI, without identifying any clearly superior approach (*Figure 1*). Moreover, the studies that have compared 3D-WBRT, inverse IMRT, field-in-field-RT, tomotherapy and/or VMAT for WBRT and PBI have reported conflicting results (120,121). The contradictory results of these dosimetric comparisons are probably due to the limited number of patients in those studies and because the results cannot always be extrapolated to all real-life patients due to phenotypic differences between women. Therefore, we must select the most appropriate approach based on each patient's anatomy and functional status (122,123). Nevertheless, it seems clear that techniques such as inverse IMRT, VMAT, and tomotherapy are all capable of achieving adequate dose conformity with better cardiac protection in patients who require irradiation of the internal mammary or supraclavicular nodal areas, even though this requires the administration of lower doses over larger lung volumes or to the contralateral breast (124,125); even so, there is no evidence that these low doses increase the risk of second tumours (126,127). However, the positive impact of these treatment modalities is not as relevant to patients treated with PBI or those who receive WBRT without regional nodal irradiation, especially if the treatment is performed using specific positioning or other techniques to protect the OARs, as we discuss below.

In patients with pendulous breasts the prone position allows for good dosimetric homogeneity, with lower doses to the OARs, particularly the lung (128). Most dosimetric studies have found that prone positioning decreases the MHD compared to supine positioning, although not in

Table 3 Randomized trials of partial breast irradiation (PBI) after BCS for breast cancer

Variable	IMPORT LOW (103)	Barcelona (104)	GEC-ESTRO (112)	TARGIT-A (105)	ELIOT (106)	Hungary (109)	University of Florence (111)	RAPID (111)
Patients, n	2,016	102	1,184	3,451	1,305	258	520	2,135
Study type	Multicentric, randomized	Multicentric, randomized	Multicentric, randomized	Multicentric, randomized	Single center, randomized	Multicentric, randomized	Multicentric, randomized	Multicentric, randomized
Randomization	WBRT/HF-WBRT/PBI	PBI/WBRT	PBI/WBRT	IORT/WBRT	IORT/WBRT	PBI/WBRT	PBI/WBRT	PBI/WBRT
N	674/673/669	51/51	633/551	1,721/1,730	651/654	128/130	260/260	1,070/1,065
Dose-fractionation	40 Gy/15 fx	37.5 Gy/10 fx BID	32 Gy/8 fx, 30.3 Gy/7 fx (HDR) BID; 50 Gy (PDR)	20 Gy SD to the surface of the tumor bed	21 Gy SD prescribed to the 90% depth	36.4 Gy/7 fx (HDR); 50 Gy/25 fx (electron)	30 Gy/5 fx (QOD)	38.5 Gy/10 fx BID
PBI arm								
Technique	IMRT	3D-CRT	HDR	IORT	IORT (electron)	HDR/electron	IMRT	3D-CRT
Age distribution								
≤60	Mean age: WBRT: 63 y	Mean age: WBRT: 70.1 y; PBI: 67.1 y	536 Pt (45.3%)	1,347 Pt (39.1%)	640 Pt (49.1%)	152 Pt (58.9%)	223 Pt (42.8%)	≤50: 257 Pt (12%)
>60	Reduced WBRT: 63 y; PBI: 62 y		648 Pt (54.7%)	2,104 Pt (60.9%)	665 Pt (51%)	106 Pt (41.1%)	297 Pt (57.1%)	>50: 1,878 Pt (88%)
Histology	IDC	IDC	IC/DCIS	IDC	IDC/ILC	IDC	IC/DCIS	IDC/DCIS
Tumor size (cm)	≤3	≤3	≤3	≤3.5	≤2.5	≤2	≤2.5	≤3
Nodal status	Negative/pN1	Negative	Negative/pN1mi/pN1a (by ALND)	N0, N1	Negative. If positive: WBRT	N0, N1mi	Negative, pN1	Negative
Follow up	5-year cumulative incidence	5 years	5 years	5 years	5 years	5 years	5 years	5 and 8 year cumulative rates
LR (%)	1.1/0.2/0.8	0	1.44/0.92	3.3/1.3	4.4/0.4	4.7/3.4	1.5/1.9	5 y: 2.3, 8 y: 3.0/5 y: 1.7, 8 y: 2.8
OS (%)	No significant differences	No significant differences	97.3/95.5. No significant differences	No differences, but significantly fewer non-breast-cancer deaths with TARGIT	96.8/96.9. No significant differences	94.6/91.8. No significant differences	99.4/96.6. No significant differences	-

BCS, breast conserving surgery; ALND, axillary lymph node dissection; IDC, invasive ductal carcinoma; IC, invasive carcinoma (any type); DCIS, ductal carcinoma *in situ*; GEC-ESTRO, Groupe Européen de Curiothérapie and European Society for Radiotherapy and Oncology; ABS, American Society of Breast Surgeons; ASTRO, American Society for Therapeutic Radiology and Oncology; ABS, American Brachytherapy; BID, twice a day (bis in die); HDR, high dose rate interstitial brachytherapy; PDR, pulsed dose rate brachytherapy; SD, single-dose; QOD, every other day (quaque altera die); Pt, patients; WBRT, whole breast radiotherapy; HF-WBRT, hypofractionated whole breast radiotherapy.

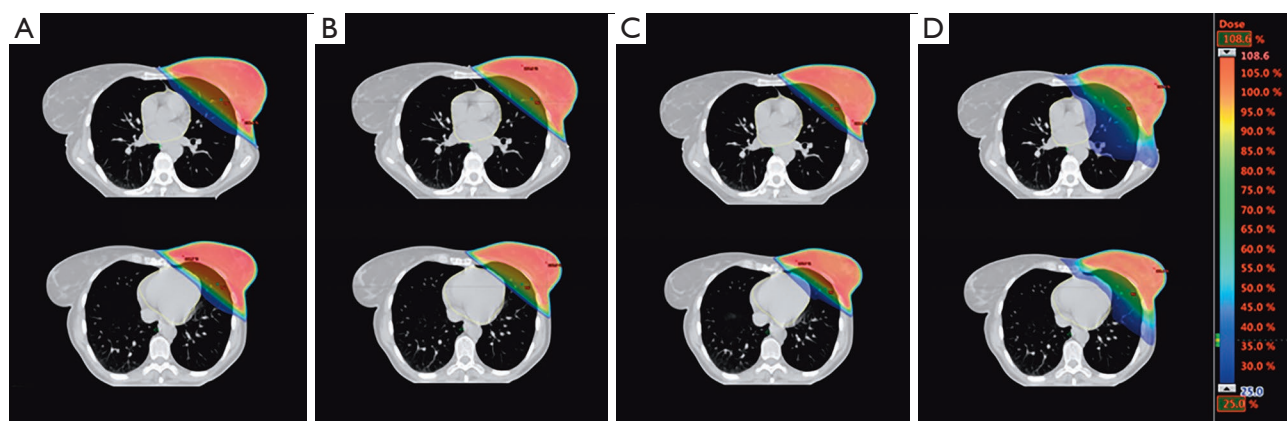


Figure 1 Images of the same patient in indication to receive Ad-WBRT. The upper row correspond to the same computed tomography slices at the level of the exit of the great cardiac vessels; the lower row were taken at the level of the left ventricle, showing the distribution of the isodoses with four different radiation techniques in free breathing: (A) three-dimensional treatment consisting of two lateral and opposite fields compensated with wedges; (B) multi-segment conformal 3-D radiotherapy; (C) multibeam inverse intensity-modulated radiotherapy (IMRT); (D) volumetric arc therapy (RapidArc®). All plans achieved a good conformation of the PTV, but in the case of C and D at the expense of increasing low doses on the heart and the ipsilateral lung, with a significant impact over the mean dose. However, these results cannot be extrapolated to all patients due to the significant anatomical heterogeneity between some women and others, which makes it essential to individualize and choose the most appropriate technique for each case.

all patients (129,130). In some women, the position of the heart is influenced by gravity and can “fall” towards the rib cage, thus increasing the MHD and the dose to the left ventricle (131). In addition, this position is not suitable for all patients since it can be uncomfortable and it is difficult to maintain in patients who have limited mobility (132).

Another approach to limiting the radiation dose to OARs is forced breathing or the deep inspiration breath-hold (DIBH) technique (*Figure 2*), which has been shown to provide the best cardiac protection of available methods (133-135). During inspiration, the lung expands and the diaphragm flattens, moving the heart away from the rib cage. The radiation is administered at this point, when the heart is at its most distant point from the target, thus reducing the MHD. The DIBH technique even may provide better dosimetric results with EBRT than with brachytherapy (136). There are several different modalities for this technique (137), including voluntary breath-hold in which the patient is instructed when to inspire and when to hold the breath during treatment. This implies a need for prior training and the active involvement of the patient during treatment. This technique may be difficult to perform in patients who have difficulties following complex visual or auditory commands (138). Another alternative breath-hold approach is the use of active breathing control

(ABC) devices, which are similar to the CPAP (continuous positive airway pressure) ventilator. ABC devices are used to monitor and control respiratory flow, interrupting breathing at the moment the radiation is administered (139). This technique provides better dosimetric results and greater reproducibility, but the device can be bothersome for elderly patients (140). Therefore, selection of the most appropriate procedures must be individualized and adapted to suit the functional characteristics and comorbidities of elderly patients.

A look ahead to the future

What is the next step?

New fractionation schedules and protocols for adjuvant RT are needed to further improve treatment tolerance and adherence and to reduce side effects (141,142). Cost-effectiveness is also an important consideration. The use of extreme hypofractionation schedules (>5 Gy per session) for both PBI and WBRT appears to be both feasible and efficacious with minimal toxicity in frail patients or those who find it difficult to travel to the clinic on a daily basis (143-145). Although some evidence to support this approach has already been published, we are still awaiting the long-term results of prospective randomized trials—including the

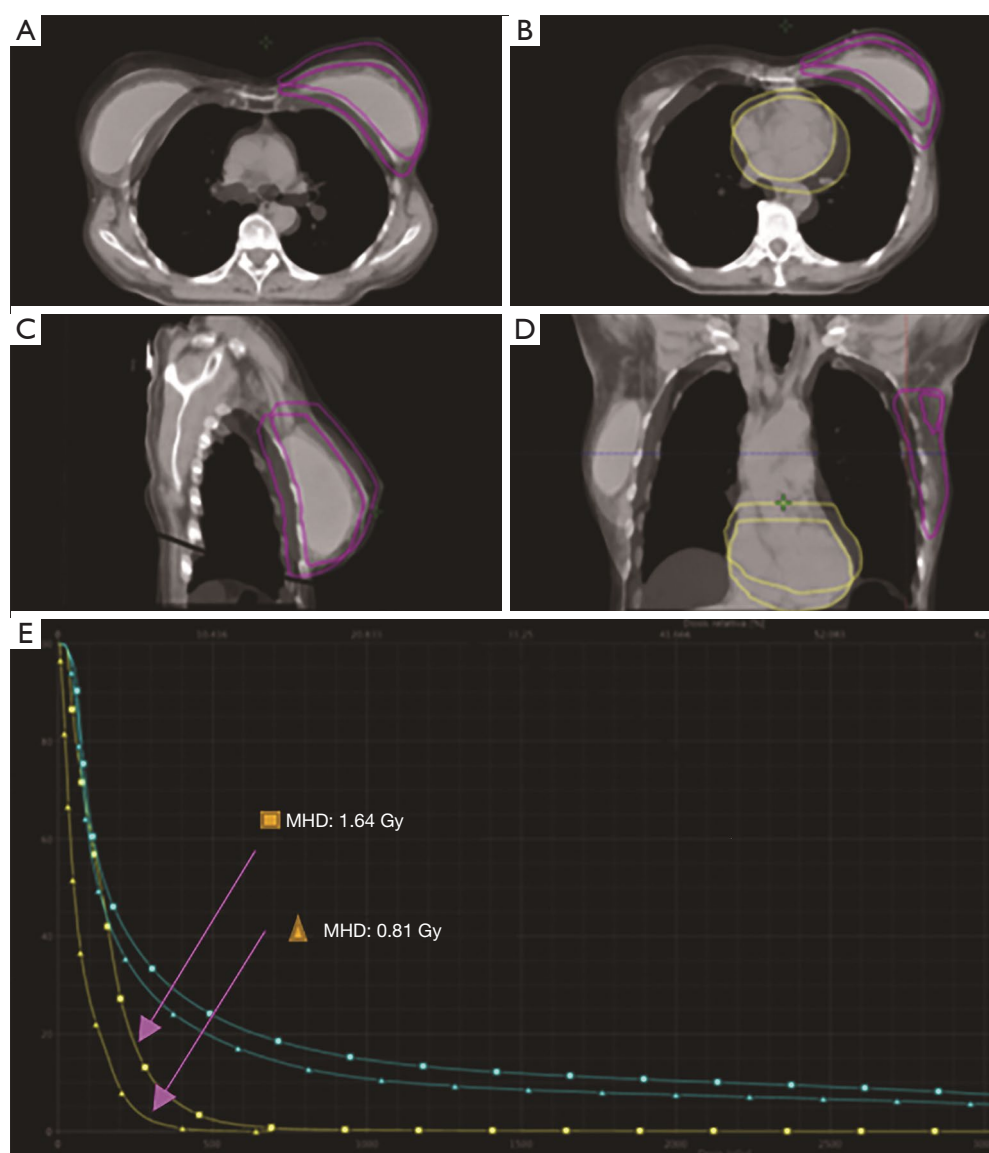


Figure 2 Fused images of the same computer slice in the same patient showing the anatomical differences and the changes in the dose-volume histogram (DVH) achieved using two different forward-planned-IMRT plans (deep inspiration breath hold and free-breathing techniques). (A-D) The axial, coronal and sagittal axes show how the PTV moves away from the heart due to deep-breathing lung filling. Magenta: breast PTV; yellow: heart. (E) DVH illustrating how the mean heart dose (MHD) decreases during deep inspiration as well as the dose received by the ipsilateral lung. Yellow: heart DVH curves; cyan: ipsilateral lung DVH curves. Square: free-breathing; triangle: breath-hold.

FAST trial (146) and NCT01803958 (147)—to confirm the safety and efficacy of extreme hypofractionated regimens.

The surgical resection of tumours in elderly patients with BC, even those with early-stage disease, is becoming increasingly less common. Consequently, there is an important need to develop non-invasive, low-toxicity treatments for patients with inoperable tumours or those

who refuse surgery. In fact, these are exactly the types of patients in whom radical RT may play a role given the poor results—in terms of both LC and OS—achieved with tamoxifen alone. The technical feasibility of radical treatment with SBRT or proton therapy has already been investigated in several studies (148-150), with prospective trials currently being planned (151).

Given the wide heterogeneity among elderly patients in terms of health status and life expectancy, the true challenge for the future is to match individual patients to the most appropriate RT protocol—which may even involve the omission of RT in highly selected cases—and to optimize health resources in an era of population ageing. In this regard, it is crucial to use objective measures to estimate life expectancy. Similarly, clinical trials are needed to determine the optimal treatment approach in the elderly. Despite the growing body of evidence, many unanswered questions remain. Although the numerous randomized and prospective clinical trials that have evaluated the omission of adjuvant WBRT appear to provide high quality evidence, these studies—as we have seen—have limited statistical power and relatively short follow-up periods. Studies with much longer follow-up times are needed to detect significant differences in OS, but it is worth underscoring that large scale retrospective population studies have already detected early differences in OS. Although such studies have important limitations and potential biases due to their retrospective design, the large number of patients in those studies may compensate for any design-related drawbacks; moreover, such studies provide real-world clinical evidence, outside of the highly controlled conditions of clinical trials. Indeed, for older women with a limited life expectancy, the findings of these population studies may be more relevant than those of clinical trials. Logically, the limited life expectancy of these patients further reduces the statistical power of the randomized trials, thus making it even more difficult to demonstrate the impact of any intervention on OS, even though the failure to treat these patients in real life could negatively impact both survival and QoL (152,153).

We believe that Big Data and Real World Data (RWD) could play an important role in overcoming the challenges described above. First, however, we must establish a precise definition of these terms, which remain unclear in the field of medicine (154). Ghani *et al.* (155) define big data as large datasets that were not limited in size and scope during the design phase, and which have not been collected to answer a specific hypothesis or question. The idea is that these data are collected without any initial hypothesis, but rather to create a large dataset for subsequent analysis to identify associations between the data, which may generate new models. For our purposes, it would perhaps be more interesting to analyse RWD to create “Real World Evidence” (156). Since such data are based on population registries and observational studies in which there is usually an initial hypothesis, the method used to analyse these data

is deductive, seeking to identify causal relationships (157).

As we have discussed, adjuvant WBRT is often omitted based on evidence suggesting that it does not improve OS. This treatment approach (i.e., the omission of WBRT) has been integrated into routine clinical practice based on results from conventional clinical trials with limited follow-up. However, when treatment approaches such as this are analysed using data from real-world populations obtained through population-based registries, it becomes possible to determine the true impact of the treatment—adjuvant WBRT plus tamoxifen may improve OS compared to adjuvant tamoxifen alone. Thus, the wider use of RWD would allow us to confirm—or refute—the efficacy of an intervention in non-ideal (i.e., real world) conditions. However, studies based on RWD should not be considered true substitutes for clinical trials. This is especially true considering that we still do not know how to accurately interpret the results obtained from such datasets given the heterogeneous sources of data and/or the variability in quality, complexity and integrity of the data included in those datasets. For this reason, any analysis of RWD must be done cautiously (158-161).

Conclusions

The optimal treatment of older women with BC is challenging. Moreover, there is no clear consensus regarding the definition of the term “elderly”. Clinical trials targeted specifically at this population are needed to clarify the many questions surrounding the optimal treatment of these patients. In the relatively near future, it seems likely that information technology and Big Data will help to improve treatment selection. However, based on the current evidence, there are no patient subgroups in which RT can be safely omitted. The available evidence shows that the risk of recurrence is higher in patients who do not receive RT, which could negatively impact OS. It is necessary to incorporate new techniques and further subclassify patients to facilitate treatment adherence, minimize toxicity, optimize costs, and preserve QoL.

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