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Omission of adjuvant radiotherapy for older adults with early-stage breast cancer particularly in the COVID era: A literature review (on the behalf of Italian Association of Radiotherapy and Clinical Oncology)

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ABSTRACT

This review is aimed at evaluating whether radiation therapy (RT) can be omitted in older adult early-stage low-risk breast cancer (BC) patients. The published data are particularly relevant at present, during the COVID-19 pandemic emergency, to define a treatment strategy and to prioritize essential therapy.
Cochrane Database of Systematic Reviews and PubMED were systematically researched from outset through April 2020 using Mesh terms. Only randomized controlled trials (RCT), with one arm without adjuvant whole-breast irradiation (WBI), were included in the analysis. Recent literature regarding the COVID pandemic and BC RT was assessed.
The reported RCTs identified a group of BC patients (pT1-2N0M0 R0, grade 1–2, estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative tumours) in which the absolute risk of local recurrence (LR) was considered low enough to omit RT. The most common risk factors were tumor diameter, nodal and receptor status. Adjuvant RT had a significant impact on LR but not on distant metastasis (DM) or death.
During the COVID 19 pandemic, results from RTCs were re-considered to define treatment recommendations for BC patients. International scientific societies and radiation oncology experts suggested RT omission, whenever possible, in older adult early-stage BC patients.
Adjuvant RT might be omitted in a highly selected group of older adult early-stage BC patients with favourable prognostic factors. Hypofractionated regimens should be the standard. RT omission, partial breast irradiation (PBI), and ultra- hypofractionated regimens could be considered in selected cases due to the pandemic.
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1. Introduction

Breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI) is the standard treatment for patients with early-stage breast cancer (BC), even though radiation therapy (RT) benefit varies when adjusted for age, estrogen receptor (ER) status, and grading [1].

As the International Society of Geriatric Oncology (SIOG) indicated, there is no universally accepted age cut-off in defining the "elderly" nevertheless 70 years is currently the most commonly used cut-off for defining patients as older-adult within the field of geriatric oncology [2].

At present, given the impending rise in the number of older adults with cancer, there is a specific need for additional research in the treatment of these patients. Moreover, since chronological age alone may be misleading with regard to individual tolerance to cancer treatments, a multidisciplinary and multidimensional geriatric framework to analyze how age-associated physiologic factors might influence health and oncologic disease is mandatory [3,4]. The management of

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older adults with BC is a pivotal issue. Unfortunately, although about half of BCs occur in women aged >65 years [5,6] and BC incidence increases with age, a limited number of randomized controlled trials (RCTs) were specifically designed for early-stage older adult BC patients.

The aim of the present review is to discuss the published data regarding adjuvant RT in early-stage older adults with BC, to better define the best treatment approach based on tumor and patient characteristics. This is particularly relevant at present, during the COVID-19 pandemic which was declared a public health emergency by the World Health Organization (WHO) [7].

2. Material and Methods

We systematically researched the Cochrane Database of Systematic Reviews and PubMED from outset through April 2020 for relevant studies written in English about the impact of postoperative RT in older patients with BC. The search strategies were: "breast AND radiotherapy AND elderly".

"BreastNeoplasms/radiotherapy"[Mesh]"(("breastneoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms])) AND (OLDER[All Fields] AND ("women"[MeSH Terms] OR "women"[All Fields])) "Aged"[MeSH Terms]) AND "Breast Neoplasms/radiotherapy"[MAJR] ("Mastectomy, Segmental"[Mesh] OR "Segmental Mastectomy"[all fields] OR "Breast-Conserving"[all fields] OR "Breast Conserving"[all fields] OR "Segmentectomy"[all fields] OR "Segmentectomies"[all fields] OR "Partial Mastectomy"[all fields] OR "Lumpectomy"[all fields] OR "Local Excision Mastectomy"[all fields] OR "Local Excision Mastectomies"[all fields]) AND ("Breast Neoplasms"[Mesh] OR ((breast*[tiab] OR mammary[tiab]) AND (neoplasm*[tiab] OR tumor[tiab] OR tumours[tiab] OR tumor*[tiab] OR cancer*[tiab] OR carcinoma*[tiab])) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms] OR irradiation [all fields] OR "radiation therapy"[all fields] OR "irradiation therapy"[all fields] OR "Radiotherapy, Adjuvant"[Mesh]) AND ("Aged"[Mesh] OR aged [all fields] OR old[all fields] OR older[all fields] OR "Aged 50 and over"[Mesh] OR elderly[all fields] OR geriatric[all fields] OR geriatrics[all fields] OR "Aged Factors"[Mesh] Four blinded investigators (IP, SB, FG and SF) independently reviewed the publications for the final selection.

Randomized controlled trials comparing adjuvant endocrine therapy (ET) alone, WBI alone, or WBI and ET in older women (aged at least ≥50 years, regardless of menopausal status) were included in the analysis. Studies were retained for inclusion only if one or more relevant outcomes (local recurrence-LR; overall survival- OS, mortality, cancer-specific survival- CSS, disease-free survival- DFS, distant metastasis-free survival- DMFS,) were reported (Table 1). Risk ratios (RR) or hazard ratios (HR) with 95% confidence intervals (CI) were registered, if available.

The PubMED database from outset through June 2020 was searched to identify publications about BC RT in older adults during COVID-19 pandemic, with the following research strategies: breast cancer AND radiotherapy AND elderly AND Covid-19 OR Coronavirus (((breast cancer [MeSH Terms]) AND (coronavirus[MeSH Terms])) AND (adjuvant radiotherapy[MeSH Terms])) AND (elderly[MeSH Terms]) ((breast neoplasm [MeSH Terms]) AND (aged[MeSH Terms])) AND (betacoronavirus [MeSH Terms]) (((breast neoplasm[MeSH Terms]) AND (covid 19 [MeSH Terms])) AND (elderly, frail[MeSH Terms])) AND (radiation therapy[MeSH Terms]) (((breast cancer[MeSH Terms]) AND (coronavirus [MeSH Terms])) AND (elderly[MeSH Terms]) Only studies reporting specific recommendations for adjuvant RT in elderly BC patients under the conditions of the pandemic were retained.

3. Results

3.1. RT Omission: Randomized Trials

Our research returned 32,245 publications: after removal of duplicates, and exclusion of studies due to the wrong population, study design, topic, outcome, publication type, intervention, absence of comparison group, only 9 trials were included in our analysis.

Studies selected for this review are reported in Table 1 and will be briefly discussed below.

In the first published study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21, [8] 1009 patients were randomized to receive tamoxifen (TAM), RT and placebo, or RT and TAM. Approximately 50% of the women were aged ≥60. Cumulative incidence of ipsilateral breast tumor recurrence (IBTR) through 8 years was 16.5% with TAM, 9.3% with RT and placebo, and 2.8% with RT and TAM. Distant treatment failure rate and OS were not significantly different among the three groups ($p = 0.28$ and $p = 0.93$ respectively).

Two RTCs analyzed patients assigned to receive TAM vs RT and TAM. Fyles et al. [9] enrolled 769 women; approximately 70% and 40% were aged ≥60 and ≥ 70, respectively. The 5 years rate of LR and axillary relapse were higher in the TAM group ($p < 0.001$ and $p = 0.049$ respectively), but no significant difference in the rates of DM were documented ($p = 0.69$). The 5-year DFS was higher in the RT plus TAM group ($p = 0.004$). No differences between the two groups were found in the number of deaths overall (31 in the TAM plus RT group and 29 in the TAM group) or the number of deaths related to BC (10 in each group). The study, from the Cancer and Leukemia Group B (CALGB) 9343 [10,11], enrolled 636 BC patients ≥70 years. As compared with the TAM group, the TAM plus RT group experienced a significantly longer time to LR recurrence (HR, 0.18; 95% CI, 0.07 to 0.42; $p < 0.001$). At 10 years, 91% of patients in the TAM group (95% CI, 87% to 94%) compared with 98% in the TAM plus RT group (95% CI, 96% to 99%) were free from IBTR. No significant differences were found between the two groups in time to mastectomy ($p = 0.17$) and time to DM ($p = 0.50$). Ten-year OS was 67% (95% CI, 62% to 72%) and 66% (95% CI, 61% to 71%) in the TAM plus RT and TAM group, respectively ($p = 0.64$).

Ford et al. [12] randomized 400 patients aged <70 years. WBI significantly reduced the risk of LR ($p = 0.0001$) but did not impact on the risk of DM ($p = 0.63$) and on OS ($p = 0.59$).

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) [13] randomized 869 patients treated with ET (TAM and/or anastrozole). The mean age was 66 years, 35% of patients were >70 years. In the no-RT group more LR ($p = 0.0001$) and overall relapses ($p = 0.002$) occurred, while no difference in DM incidence was observed (5 in each group). DFS was higher in the RT group ($p = 0.0021$) but no significant difference in OS ($p = 0.18$) was documented.

Tinterri et al. enrolled 749 patients, aged 55–75 years [14,15]. No significant differences in IBTR (3.4% vs 4.4%) and OS (81.4% vs 83.7%) were reported between the two treatment groups. The median time to progression was 43.1 months in the RT group and 41.9 months in the no-RT group ($p = 0.8451$) [15].

In the PRIME II study [16] which enrolled 1326 low-risk BC patients >65 years treated with ET, WBI significantly lowered the IBTR risk (probability, rate) ($p = 0.0002$). No differences in regional recurrence, DM, contralateral BCs, or new BCs were detected between the two groups and 5-year OS was 93.9% (95% CI 91.8–96-0) in both groups ($p = 0.34$).

The Swedish Breast Cancer Group 91 RT (Swe BCG 91 RT) study [17] enrolled 1187 patients under 76 years (median age 60 years). After 15 years of follow-up, a higher cumulative incidence of IBTR (23.9% vs 11.5%, $p < 0.001$) and a lower recurrence-free survival (RFS) (51.7% vs 60.4%, $p = 0.0013$) were observed in the no RT group, while OS was not significantly different (68.4% vs 71.1%, $p = 0.68$, respectively).

Table 1
Summary of randomized controlled trials of RT after BCS.

Author, year	N	Population characteristics						LR	OS	DFS	DMFS
		Age	T, N	Er/PgR pos	Her-2	Axillary staging	ET				
Fisher, 2002	1009	≥70 (100)	T1 N0 (<1 cm)	Any	NR	ALND	TAM (668)	16.5% TAM, 9.3% RT, 2.8%RT + TAM p = 0.01	NR	NR	3.2 TAM, 3.3 RT, 1.5 RT + TAM p = 0.28
Fyles, 2004	769	≥50	T1-2 N0	Any (81% pos)	NR	ALND or clinical	TAM	7.7 vs 0.6 (HR 8.3; 95 CI 3.3–21.2 p < 0.001	No diff	91vs 84 p = 0.004	No diff
Hughes, 2004–2013 (CALGB 9343)	636	≥70	T1 N0 (<2 cm)	pos	NR	Clinical ALND	TAM	10 vs 2 HR 0.18; 95% CI, 0.07 to 0.42 p < 0.001	67 vs 66 HR 0.95; 95% CI, 0.77–1.18 p = 0.64	NR	95 vs 95 HR 1.20; 95% CI, 0.63–2.32
Ford, 2006	400	≤70 (post menopausal: 205)	T1-2 N0	Er pos 70%	NR	ALND	TAM	28.6 vs 49.8 p < 0.001	60.5 vs 57.6 p= 0.59	NR	33.8 vs 32.2 HR 0.91 CI 0.64–1.33; p = 0.63
Potter, 2007	869	≥50	T1-2 N0 (<3 cm)	Any	NR	ALND	TAM switched to ANASTROZOLE	5.1 vs 0.4 HR 10.21 CI 3.38–43.85 p = 0.0001	96.2 vs 97.9 No diff	HR 3.48 (95%CI, 1.49–8.12) p= 0.0021	No diff
Tinterri, 2014	749	411/749 > 65	T1–2 N0–1 (<2.5 cm, (max 3 positive nodes)	Any	NR	SLNB/ALND	NR	3.4% vs 4.4%	81.4% [95% (CI) 77.4–85.6] vs 83.7% (95% CI 79.8–87.8)	88.2% vs86.97%	86.9% (95% CI 83.3–90.6) vs 85.5% (95% CI 81.9–89.3)
Kunkler, 2015 (PRIME 2)	1326	≥65	T1-2 N0 (<3 cm)	Er pos and/or PgR pos	NR	SLNB or ALND	TAM	HR 5·19 (95% CI 1·99–13·52; p = 0·0007)	93·9% (95% CI 91·8–96·0) in both groups (p = 0·34).	No difference	NR
Killander, 2016 (SweBCG 91 RT)	1187	≥60 (50%)	T1-2 N0	Any 57% Er pos, 13% Er neg, and 30% not evaluated.	NR	ALND	TAM	21.8 vs 11 p < 0.001	71.1 vs 68.4 p = 0.68	NR	NR
Blamey, 2013 BASO II	204	<70	T1 N0 (<2 cm)	<90% Er pos	NR	SLNB or ALND	TAM	LR after WLE 1.9% per annum, vs 0.7% with RT vs 0.8% with TAM alone. RT: HR 0.37, CI 0.22–0.61 p < 0.001); TAM: HR 0.33, CI 0.15–0.70 p < 0.004	96% in all groups	NR	NR

ALND: axillary lymph node dissection; BCS: breast conserving surgery; CI: confidence interval; DFS: disease-free survival; DMFS: distant metastasis-free survival; Er: estrogen receptor; ET: endocrine therapy; Her2: human epidermal growth factor receptor 2; HR: hazard ratio; LR: local recurrence; NR: not reported; OS: overall survival; PgR: progesterone receptor; RT: radiation therapy; SLNB: sentinel lymph node biopsy; TAM: tamoxifen; WLE: wide local excision.

Finally, the BASO (British Association of Surgical Oncology) II trial [18] randomized 1135 patients aged less than 70 years into a 2 × 2 clinical trial of factorial design with or without RT and with or without TAM. The LR rate was reduced in patients who received RT or TAM (HR 0.37, < 0.001 after RT; HR 0.33, p < 0.004 after TAM); no patient randomized to both adjuvant treatments developed LR.

3.2. Recommendations During COVID 19 Pandemic

During the COVID 19 pandemic international scientific societies and radiation oncology expert groups, based on results derived from the previously reported RTCs, recommended considering RT omission, whenever possible, particularly in older adults with early-stage BC.

Our online search displayed 51,727 studies: after exclusion of those not focusing on specific recommendations for RT during the COVID 19 pandemic, 10 publications were included and are discussed below.

The European Society for Medical Oncology (ESMO) pointed out that where the expected advantage from the addition of RT is very low, as in older adult patients with low-risk BC treated with adjuvant ET, RT deferral or omission could be considered [19].

Similarly, The COVID-19 Pandemic Breast Cancer Consortium suggested RT can be safely delayed or omitted until the COVID-19 pandemic is over in patients >65–70 years with early-stage, node-negative, ER-positive invasive cancer planned for adjuvant ET [20].

Braunstein et al. [21] suggested RT omission in women aged ≥70 with ER-positive pT1-2N0M0 tumours, negative resection margins, who were fit for adjuvant ET.

Vordermark et al. [22], stated that RT omission in older adults at low risk of recurrence is supported by its limited benefit compared to the increased risk of a severe course of COVID-19 disease.

Regarding age, Coles et al. [23] proposed, in international guidelines written by a panel of experts, RT omission for patients ≥65 years, planned for treatment with ET, with pT1-2N0M0 R0, grade 1–2, ER-positive, human epidermal growth factor receptor 2 (HER2) negative tumor, as well as for younger women with relevant co-morbidities.

Franco et al. suggested that RT could be safely omitted for low-risk BC. However, when, WBI is required, one of the 5 fraction schedules

(28–30 Gy in once weekly fractions, or 26 Gy in 5 daily fractions) can be chosen. Boost dose to the tumor bed should be omitted in patients >40 years and/or with low-risk factors for LR [24].

Curigliano et al. [25] recommended evaluating RT omission in the light of the local situation, but to reconsider this indication for the individual patient every four weeks.

Loap et al. [26] reminded that older adult BC patients with favourable prognostic factors who did not receive RT had a significantly increased risk of LR at 5 and 10 years of 4% (vs 1% with RT) and 10% (vs 2% with RT) respectively. Consequently, they suggested hypofractionated regimens (32.5 Gy in 5 weekly fractions, or 28.5 Gy in 5 daily fractions) instead of RT omission for the oldest patients (>80 years).

Finally, PBI can also be proposed for treating selected older adult patients during the COVID pandemic. The Italian Association of Radiotherapy and Clinical Oncology (AIRO) Interventional Radiotherapy Working Group suggested that even PBI as delivered with brachytherapy (BRT) or IORT can be omitted in selected BC cases (age 70 years, invasive Luminal A, <2 cm, cN0, planned for ET) during the COVID pandemic [27].

4. Discussion

RTCs and a metanalysis [8–18,28] showed that WBI omission in older adults with early-stage BC patients with favourable prognostic factors was safe. In fact, although a slightly better LC was reported in the RT group, no OS advantage occurred. According to these findings, RT omission could be proposed in patients aged >70 years with hormone-receptor-positive stage I BC, planned for ET. In 2019, during the 16th St Gallen International Breast Cancer Conference, [29] the panelists suggested RT after BCS in women aged 70 years in good health and with substantial life-expectancy while recommending the avoidance of adjuvant RT in patients aged ≥80 years with stage I disease. In the same year, the AIRO BC study group stated that adjuvant RT could be omitted in a subgroup of low-risk older adult BC patients treated with adjuvant ET, but a careful evaluation of patient's comorbidities, including a Comprehensive Geriatric Assessment (CGA), should be performed [30]. A CGA is considered mandatory for optimal treatment management of BC in older adults [31] and the geriatric-8 (G8) tool is the most widely used to identify frail patients [32]. Life expectancy and comorbidities assessment are crucial in the clinical management of older adults with BC. The Surveillance, Epidemiology, and End Results–Medicare (SEER) database retrospectively evaluated 64,034 cases showing women with comorbidities and stage I tumours had similar or worse OS than women without comorbidities and stage II disease [33]. Furthermore, in the balance between RT and ET, patients should be informed about risks and benefits of both. In particular, ET-related toxicity, which are not negligible and include increased risk of endometrial cancer and thromboembolic complications for TAM, osteo-articular pain and risk of bone-loss, for aromatase inhibitors, should be carefully considered. [34]. Consequently, the ET discontinuation rate among older patients, was reported to be up to 38.4% in patients aged 75 or more [35], while RT was better tolerated, with higher rates of completion of RT course, up to 87.3% [36].

Ongoing trials will validate biomarkers use for the proper selection of very low-risk BC patients, in whom RT omission could be proposed [37–43].

In older adult patients reducing discomfort while preserving oncological outcomes and functional status is highly important [44]. Two therapeutic strategies can be adopted to reduce treatment time: hypofractionated WBI or PBI. Although RCTs [45–48] of hypofractionated regimens vs conventional fractionation, showed equivalence in LC and OS, women aged >70 years were under-represented, ranging from 4.2% to 16.7%. Ultra-hypofractionated schedules were proposed in the treatment of older adult early-stage BC patients. In particular, in the non-inferiority FAST-Forward phase 3 trial [49], patients were randomized to receive 26 or 27 Gy in 5 fractions over 1 week vs 40 Gy in 15 fractions over 3 weeks; LC was 1.4% for 26 Gy, 1.7% for 27 Gy and 2.1% for 40 Gy. Compared with 27 Gy in 5 fractions, 26 Gy in 5 fractions had a significantly lower risk of any moderate or marked breast or chest wall normal tissue effects ($p = 0.0001$) and breast shrinkage ($p = 0.0018$) and therefore should be preferred. It is worth noting that in this trial, the median age was 61 years, while older adult patients (aged ≥70 years) account for approximately only 15–16% of the entire enrolled population (a protocol amendment on Feb 2013 excluded the lowest-risk patients including women aged ≥65 years, pT1, grade 1 or 2, ER-positive, HER2 negative, pN0, M0).

Several PBI techniques, characterized by different invasiveness, are at present available. BRT, intraoperative RT (IORT) with electrons or low energy photons, and external beam RT [50–53]. Randomized phase 3 trials [54–62] suggested PBI can be safely administered.

Coles et al. suggested the use of external beam PBI with a once-daily or even less frequent schedule as an attractive alternative to conventional WBI, and recommended also BRT PBI [63].

Meattini et al. [64] reported a subgroup analysis of the Florence trial [61,65] in which external beam PBI compared to WBRT was confirmed as a safe and effective approach in 117 older adult BC patients aged ≥70 years (IBTR rate of 1.9% in both groups).

At present, there are no trials that compared different PBI techniques. However, while IORT with electrons seemed feasible in luminal A subtype, IORT with low energy photons was not considered as a recommended de-escalation strategy in early BC for its dosimetric and target conformation features [66–68], according to a panel of international expert in the second Assisi Think Tank Meeting (ATTM) [38], and its use should be limited to patients in a clinical trial or with the lowest risk of IBTR [38,66–68].

According to the clinical recommendations widely shared in recent months, during the COVID-19 pandemic, the benefit of RT must be carefully weighed against infectious risk, as recently confirmed in the recommendations of the International Society of Geriatric Oncology (SIOG) COVID 19 Working Group for the treatment of older cancer patients [69]. Therefore, delay and/or reduction of the number of hospital and healthcare centers access is highly recommended, and it is a widely adopted strategy to reorganize therapeutic and outpatient activities of Radiation Oncology Departments during the crisis [70]. Since older adults are the population at higher mortality risk from COVID-19 and higher risk of severe consequences from COVID-19, they derive fewer benefits, in absolute terms, from postoperative RT [71].

Ultra-hypofractionated regimens, PBI or RT omission in patients with favourable prognostic factors must be carefully considered during the COVID-19 pandemic. All treatment options should be discussed in a multidisciplinary tumor board, which may take place virtually and patient preferences should be considered.

5. Conclusions

In conclusion, in older adults with early-stage BC with favourable prognostic factors, therapeutic strategies (i.e. RT omission, ultra-hypofractionated regimens, and PBI) should be tailored based on tumor and patient characteristics, and discussed in a multidisciplinary tumor board, especially during the COVID-19 or other pandemics. Furthermore a CGA is necessary to properly select older adult patients for adjuvant RT.

Author Contributions

Study concepts: Isabella Palumbo, Simona Borghesi, Antonella Ciabattoni, Cynthia Aristei.
Study design: Isabella Palumbo, Simona Borghesi, Antonella Ciabattoni, Cynthia Aristei.
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Data analysis and interpretation: Isabella Palumbo, Simona Borghesi, Fabiana Gregucci, Sara Falivene, Antonella Fontana.
Statistical analysis: not applicable.
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We confirm that all authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and agree to its submission to the Journal of Geriatric Oncology.

Declaration of Competing Interest

The authors declare no conflict of interest.

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