



Controversies of radiation therapy omission in elderly women with early stage invasive breast cancer

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Contributions: (I) Conception and design: I Abu-Gheida; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: I Abu-Gheida, L Hammoudeh; (V) Data analysis and interpretation: I Abu-Gheida, L Hammoudeh; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Early stage invasive breast cancer is a disease that is prevalent in the elderly population. Data regarding radiation omission for elderly population is based on patients' age. Given the increased life expectancy, data on individualizing treatment decisions based on multiple tumor and patient related factors other than age only is emerging. This review aims to analyze published data to provide clinicians with a general oversight on approaching this question.

Keywords: Breast cancer; early-stage breast cancer elderly; radiation therapy; radiotherapy; hormonal therapy; endocrine therapy

Submitted Jun 08, 2019. Accepted for publication Jun 26, 2019.

doi: [10.21037/tcr.2019.06.47](https://doi.org/10.21037/tcr.2019.06.47)

View this article at: <http://dx.doi.org/10.21037/tcr.2019.06.47>

Introduction

Breast cancer remains the most commonly diagnosed non-cutaneous cancer in women (1). Increasing age remains one of the most important risk factors for develop breast cancer (2). Therefore, according to the American Cancer Society, 1 in 25 women of age 70 will likely developing invasive breast cancer compared to 1 in 43 for patients 50 years of age (3). The prevalence of breast cancer in elderly population is expected to increase as the average life expectancy of the population is tending to increase; reaching 81 years for women in the United States (4). Adjuvant radiation therapy after breast conserving surgery is currently considered the standard accepted treatment approach for patients with early stage invasive breast cancer (5). Elderly women population, on the other hand, remains under-represented in many trials. There have been several studies and trials attempting to address the radiation question, specifically in the elderly population. This review aims to analyze published data to provide clinicians

with a general oversight on how to approach this question in real life scenarios.

Prospective trials evidence

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 trial was one of the earliest trials that addressed this question of radiation benefit in early stage node negative invasive breast cancer (6). More than 1,000 patients with tumors \leq 1 cm treated with breast conserving surgery achieving negative margins were randomized to tamoxifen alone, radiation alone or radiation and tamoxifen treatment in a 1:1:1 ratio. Approximately 50% of patients enrolled in this trial were \geq 60 years old. Despite no disease-free survival or overall survival statistically significant difference between the treatment arms, radiation therapy did have a significant decrease of the 8-year ipsilateral breast tumor recurrence (IBTR)

Table 1 Prospective trial data of radiation omission trials in elderly women

Trial	Year published	Num.	Age	Tumor size	FU	Arms	IBTR	Remarks
NSABP B-21 (6)	2002	1,009	79% ≥50 years	≤1 cm	8	TAM	16.5%	59% ER+ 28% UNK
						RT + placebo	9.3%	
						RT + TAM	2.8%	
CALGB 9343 (7,8)	2004; 2013	636	≥70	≤2 cm	12	TAM	10%	99% ER+
						TAM + RT	2%	
ABCSG (9)	2007	869	≥50	≤3 cm	5	TAM/ANAS	4.1%	99% ER+; 33% G1; 62% GII
						TAM/ANAS + RT	1.3%	
PRIME II (10)	2017	1,326	≥65	≤3 cm	5	ET	5.1%	90% ER+; 40% GI; 55% GII
						ET + RT	0.4%	

ER, estrogen receptor; GI, Grade I; GII, Grade II; ANAS, Anastrozole; IBTR, ipsilateral tumor recurrence; ET, endocrine therapy; TAM, Tamoxifen; RT, radiation therapy; UNK, unknown; Num., number of patients; FU, follow-up.

compared to hormonal therapy alone. Of those patients who developed recurrence, 56% required mastectomy (6).

The Cancer and Leukemia Group (CALGB) 9343 was another trial that specifically addressed the omission of adjuvant radiation in elderly patients. In this trial, patients ≥70 years of age, diagnosed with early-stage node negative breast cancer, estrogen receptor positive (ER+) treated with breast-conserving surgery were randomized to 5 years hormonal therapy alone versus adjuvant radiation therapy and hormonal therapy (7). Twelve-year follow-up showed a remaining significant 8% locoregional recurrence benefit by the addition of radiation therapy (8). Despite the local benefit, there was no overall survival advantage from radiation. These results endorsed the national comprehensive cancer network (NCCN) to recommend observation in women >70 years of age diagnosed with T1N0 ER+ breast cancer treated with breast conserving surgery with negative margin, as long as adjuvant hormonal therapy is planned for 5 years at least.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) was another study that attempted to address the radiation question in women ≥50 years old diagnosed with early stage (< or = 3 cm) breast cancer (9). In this trial, 869 women were randomly assigned to receive 5 years hormonal therapy only versus hormonal therapy with radiation therapy after their surgery. Seventy-one percent of the trial patient population included patients ≥60-year-old. After a median follow-up of 54 months, it was noted that ipsilateral local relapse was significantly lower in the radiation arm compared to the non-radiated arm (0.4% vs. 5.1% respectively). As in the CALGB, there was no overall survival benefit noted despite that a trend favoring radiation therapy was found (9).

More recently, the PRIMEII larger randomized trial

attempted to address the question. In this trial, patients 65 years and older with early stage node negative, hormone receptor positive breast cancer (up to 3 cm in size) underwent breast conserving surgery with negative margins (≥1 mm). Patients were randomized to whole breast radiation versus no radiation. All patients were planned to receive hormonal therapy. The primary end point in this study was the IBTR rate. Again, this study showed a statistically significant difference in the 5-year IBTR (1.3% vs. 4.1%) favoring radiation therapy (10).

While all these trials continue to show a persistent ipsilateral tumor recurrence benefit by adding radiation therapy (Table 1), many physicians are omitting radiation therapy in elderly women with early stage breast cancer based only on their age, expecting that patients are going to be placed and tolerate hormonal therapy. However, multiple factors are to be considered prior to recommending radiation omission. First, the compliance rate of endocrine therapy varies amongst patients, while some patients could tolerate it more others might discontinue hormonal therapy due to its side effects (11). Therefore, placing patients who omit radiation therapy at a higher risk of disease recurrence. Second, as the definition of “elderly women” varied across trials, it is important to point out that not all patients aged 50, 65 or 70 years and older are the same. Many patients labeled as “elderly”, solely based on their age, are actually in an excellent health condition and are likely to live for more than 10 further years. In this group, the risk of IBTR continues to increase with time and therefore, adjuvant radiation therapy should be highly considered (8). Moreover, the Swedish Breast Cancer Group long-term follow-up showed that even for early stage Luminal A patients, omission of radiation therapy leads to an unacceptably

high rate of IBTR reaching 24% at 15 years (12). Reiterating the importance of avoiding overgeneralization and omitting radiation therapy for any patient labeled as “elderly” without taking into account their life expectancy. Finally, the current radiation therapy techniques offered are significantly less toxic than the previous methods utilized in older trials. A nomogram developed by Albert *et al.* could be used to address the potential value of adjuvant radiation therapy specifically in elderly patients assessing the mastectomy free survival (13). However, patients have their own unique comorbidities, tumor characteristics and risk factors, and therefore individualizing care rather than generalizing care based on age only.

HER2-neu negative and triple negative disease

Different breast cancer molecular subtypes have different rates of recurrence and survival (14). Other than the NSABP B-21 trial, all previously discussed trials mandated estrogen receptor positivity to evaluate radiation therapy omission in early stage invasive breast cancer (6,8-10). In an attempt to verify this difference amongst different breast cancer subtypes in elderly population; Haque *et al.* assessed the radiation impact in elderly breast cancer women with T1N0M0 who underwent BCS and assessed breast cancer specific survival (BCSS) in each distinct subtype (15). Molecular biomarkers were grouped into four categories: ER+/HER2+, ER+/HER2-, ER-/HER2+ and ER-/HER2-. Results showed that for any HER2-neu negative patient, radiation had a significant impact on BCSS. So patients with triple negative or even for ER positive/Her2-neu negative disease subtype, omission of radiation therapy and poor compliance to hormonal therapy might be detrimental even in elderly patients. On the other hand, Wu and colleagues showed that radiation omission in elderly women with tubular carcinoma could be considered given the low incidence of breast cancer related death (16). Finally, patients with metaplastic histology, frequently triple negative, have a high rate of loco-regional relapse and resistance to systemic therapy, and should therefore be considered for adjuvant radiation therapy regardless of age (17,18).

Cost effectiveness

Cost effective cancer treatment is paramount for all health care systems (19). Therefore, an argument for adjuvant radiation therapy omission in elderly women might be on the basis of cutting cost especially in the presence of salvage treatments. Han *et al.* showed that the omission of adjuvant

radiation therapy in women >60 years old with luminal A breast cancer had an overall estimate of 5.0 million dollar saving across Canada (20). It is important to note that the results were generalized from data originating from one tertiary care facility in Ontario, that utilizes intensity modulated radiation therapy (IMRT) for breast cancer treatment, translating into an inflated cost of radiation therapy. Therefore, other more cost-effective radiation therapy treatment approaches might appeal as an attractive alternative in reducing treatment cost and providing patients a safe option especially in those who could not tolerate endocrine therapy. Receiving the treatment over a shortened duration course is significantly associated with less treatment burden and cost on patients and health care systems. In the United Kingdom, whole breast radiation therapy delivered over a course of 1 week have been showed to be safe with acceptable toxicity rates (21). Therefore, FAST-FORWARD is currently and on-going trial in the UK randomizing patients to accelerated whole breast radiation therapy over 1 week (5 fractions) versus whole breast radiation therapy over 3 weeks (15-fractions). The other more detailed reported approach would be the accelerated partial breast irradiation (APBI). Now with 5- and 10-year phase III data reported, this could provide an attractive alternative to the standard 4–6 weeks costly radiation therapy (22). Sumodhee *et al.* addressed the value of APBI in elderly women as a compromise between whole breast radiation therapy and omission of radiation therapy (23). With a median follow-up of 8 years, the estimated 10-year mastectomy free survival rate was 97.4% which was comparable to patients receiving whole breast radiation therapy group (23).

Quality of life

All the previously discussed data showed the relatively good outcome of elderly women with early stage breast cancer. However, quality of life data, which is crucial for this population should be taken into account (24). To address this issue, recent study presented at the San Antonio annual breast cancer symposium in 2018 by Ward and colleagues specifically tackles this (25). The authors analyzed phase III and meta-analysis data comparing value of adjuvant hypofractionated 15 treatment radiation therapy in elderly women compared to 5 years of aromatase inhibitor (AI) therapy. They addressed the quality of life and cost of treatment in this patient group. It was suggested that the quality of life after radiation therapy only was nearly identical to patients treated with AI alone but with persistent

small increase in cost. However, for those patients who are noncompliant with endocrine therapy can be and probably should be treated safely with radiation therapy alone (25).

Ongoing trials

Finally, as the omission of radiation therapy remains unclear in elderly women with early stage invasive breast cancer, there are still ongoing trials addressing this question. The LUMINA trial (Risk of Local Recurrence Following Breast Conserving Surgery and Endocrine Therapy in Low Risk Luminal A Breast Cancer - NCT01791829) is an ongoing phase II trial evaluating the omission of radiation therapy for low-risk invasive breast cancer treated with BCS and endocrine therapy. patients >55 years with grade 1–2 unifocal ER+/PR+ Her2-negative invasive breast cancer are included in this trial with a 500-patient accrual target number.

Attempt to include genetic testing to aid in that decision is currently being evaluated in the Profiling Early Breast Cancer for Radiotherapy Omission (PRECISION) trial; NCT02653755. This currently opened phase II study evaluates the omission of radiation therapy in patients age 50–75 with unifocal, grade 1–2, ER+/PR+/Her2-negative T1 (≤ 2 cm) cancer. Patients with low Prosigna score (PAM-50) would be eligible for radiation omission. All patients must have a negative margins post lumpectomy, defined as no tumor on ink, and are planned 5 years of endocrine therapy. Another study evaluating the role of PAM-50 assay in omitting radiation therapy is the phase III non-inferiority EXPERT trial NCT02889874.

Oncotype DX score is another genetic marker that is also being evaluated to assess in the decision of radiation omission. The Individualized Decision of Endocrine Therapy Alone (IDEA) trial is an ongoing phase II study addressing the omission of radiation therapy for women with low risk invasive breast cancer post breast conserving surgery with an oncotype dx score of ≤ 18 NCT02400190. In this trial postmenopausal women between ages 50–69 with a unifocal, pathologically T1 N0 ER+/PR+ Her2-neu negative breast cancer removed with a negative margin ≥ 2 mm is being studied.

Conclusions

As the definition of elderly women age group remains poorly outlined, adjuvant radiation therapy in this population with early stage invasive breast cancer remains to show benefit in reducing local recurrence. Despite the no overall or cancer specific survival benefit in ER/PR+ patient population, data

supporting radiation omission in elderly patients should not be generalized to include all patients based on their age alone. Multiple patient and tumor related factors should be taken into account when counseling this population. Quality of life data in this patient population remains to be reported from ongoing and future trials. Finally, current ongoing trials individualizing treatment based on genetic recurrence scores might provide further insight on patients of whom radiation therapy benefit is marginal and could be omitted more safely.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Vincent Vinh-Hung and Nam P Nguyen) for the series “Radiotherapy for Breast Cancer in Advanced Age” published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.06.47>). The series “Radiotherapy for Breast Cancer in Advanced Age” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

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

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Cite this article as: Abu-Gheida I, Hammoudeh L, Abdel-Razeq H. Controversies of radiation therapy omission in elderly women with early stage invasive breast cancer. *Transl Cancer Res* 2020;9(Suppl 1):S126-S130. doi: 10.21037/tcr.2019.06.47