Current Breast Cancer Reports (2020) 12:344–350
https://doi.org/10.1007/s12609-020-00395-8

LOCAL-REGIONAL EVALUATION AND THERAPY (A KONG, SECTION EDITOR)

De-Escalation of Local-Regional Therapy for Older Breast Cancer Patients

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Accepted: 26 October 2020 / Published online: 9 November 2020

Abstract

Purpose of Review Over the past decade, prospective clinical trials and retrospective data have changed clinical guidelines for the treatment of older patients, most notably those patients with early, hormone receptor-positive, clinically node-negative breast cancer. Here is a comprehensive review of the literature supporting de-escalation of local-regional therapy in older patients with breast cancer.

Recent Findings The de-escalation of treatment in elderly patients includes minimizing surgical interventions and adjuvant radiation therapy. Current Choosing Wisely® guidelines recommend considering the omission of surgical staging of the axilla in patients ≥ 70 with early-stage, hormone receptor-positive breast cancer. Primary endocrine therapy may be a suitable option for older patients with hormone receptor-positive breast cancer and short life-expectancy. The long-term results of the CALGB 9343 clinical trial reveal that radiotherapy omission is not associated with a survival benefit in patients ≥ 70 with early-stage, hormone receptor-positive, node-negative breast cancer, who receive 5 years of adjuvant endocrine therapy. The results of the RAPID trial support that shorter courses of radiation therapy are non-inferior to standard therapy and may be of significant value to older patients who require radiation. In addition, intraoperative radiotherapy may be useful in older patients with mobility issues who have higher-risk tumors and the current TARGIT-E aims to assess IORT in patients ≥ 70 with hormone receptor-positive tumors.

Summary Select older patients with breast cancer may benefit from the omission of axillary staging, less aggressive breast surgery, and shorter courses or total omission of radiation therapy. Current studies aim to continue to define the appropriate criteria for which older patients can benefit from de-escalation of local-regional therapy.

Keywords Breast cancer · Elderly · Breast surgery · Radiotherapy

Introduction

The annual number of new cases of breast cancer is steadily increasing in women age 70 and older. Compared to all other age groups, women in their eighth decade of life have the highest age-specific incidence of breast cancer [1]. Currently, approximately 30% of new annual breast cancer cases in the USA are in women over the age of 70, and this percentage is anticipated to increase to 34% by 2030 [1, 2]. This patient population has unique intrinsic biological and social characteristics compared to their younger cohorts, such as higher rates of comorbid conditions, less social support, and transportation barriers.

Over the past two decades, clinical trials have aimed to optimize the risk-benefit ratio for treatment options for older patients with breast cancer including incorporating less invasive breast and axillary lymph node surgery, abbreviated radiation therapy regimens, and, in some instances, possible omission of radiation therapy and surgery. Through the national media, the general public has also become aware of the de-escalation of cancer care in older adults and has further emphasized the need to assess treatment benefits and risks [3]. In certain circumstances, the primary objective of omitting therapy is to optimize patient treatment while simultaneously minimizing adverse side-effects and unnecessary healthcare costs. This review aims to summarize the published literature that supports de-escalation of surgery and radiation in older women with breast cancer.

This article is part of the Topical Collection on *Local-Regional Evaluation and Therapy*

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Surgical Therapy

Repeat Segmental Mastectomy for Recurrence

Standard therapy for a breast cancer recurrence in a patient who has previously received breast conservation therapy (BCT) is completion mastectomy [4]. However, repeat segmental mastectomy (with or without radiation therapy) may be an appropriate treatment regimen for select older patients [5••]. Consideration for this treatment option is partially due to the increase in post-operative disability seen in elderly patients who undergo mastectomy compared to those who undergo BCT [6]. A single-institution retrospective analysis found that while increasing patient age was associated with a decrease in the conformation of NCCN guidelines, there was no difference in local-regional recurrence, development of distant-disease, or breast cancer-related death [7]. Repeat segmental mastectomy can be considered for those patients with early-stage hormone receptor-positive tumors, who are also appropriately selected patients for radiotherapy omission based on clinical trial evidence [8•, 9••, 10••].

Axillary Nodal Staging

The role of axillary staging with sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) in older breast cancer patients has been a topic of consideration in recent years. Both procedures incur a risk of lymphedema development, which can be especially debilitating in older patients, although the risk of lymphedema development has been shown to be independent of chronological age [11]. In the setting of a clinically negative axilla, the role of nodal staging should be discussed in collaboration with the patient and the multidisciplinary breast cancer team to determine how nodal staging may influence adjuvant systemic and radiation therapy. If therapy will not be dictated by pathologically positive nodal disease, an omission of SLNB should be considered [12••]. Additionally, predictive models exist to aid in determining the likelihood of axillary nodal positivity and can also be incorporated into the decision-making process for the role of SLNB in the older patient with breast cancer [13•, 14].

In 2016, the Society of Surgical Oncology along with American Board of Internal Medicine released the Choosing Wisely® guidelines which recommend clinicians to consider omitting routine SLNB in women age ≥ 70 with early-stage, hormone receptor-positive, Her2-negative breast cancer with a clinically negative axilla [15•]. This guideline was largely supported by clinical trial evidence demonstrating no significant difference in breast cancer mortality in older patients with clinically T1 N0 hormone receptor-positive disease who received tamoxifen, when randomized to undergo ALND or no ALND [16•]. Since the release of these guidelines, several studies have demonstrated a steady decline in the rate of SLNB in older patients over the past several years [17, 18••].

Patient selection for the omission of axillary staging plays a critical role in optimizing care in the elderly as there is some data to support that nodal staging may improve survival [19•, 20•]. A retrospective study of the National Cancer Database (NCDB) analyzed over 133,000 women age ≥ 70 with clinical T1-T3 tumors, node-negative breast cancers who were then subdivided by those who underwent nodal staging versus those who did not. The authors found that patients who underwent nodal staging were more likely to receive adjuvant systemic and radiation therapy and had a higher rate of overall-survival; however, this finding may be attributable to patient selection bias of those who underwent nodal staging [19•]. Similarly, an analysis of the Surveillance, Epidemiology, and End Results Program (SEER) database found that in older women with stage 1 disease, increasing age was associated with a decrease in the rate of SLNB and, when controlling for other factors, may actually have a negative impact on outcome [20•]. The most recent NCCN guidelines highlight the lack of definitive findings to definitively conclude improved survival with nodal staging in elderly patients or to formally recommend nodal staging for those patients when its findings are unlikely to alter adjuvant therapies [4].

Complete Surgical Omission

Perhaps the most controversial topic for surgical de-escalation in older patients is the total omission of surgery for operable breast cancer. Surgical omission has seen an increase over the past decade, especially in those patients age ≥ 80, and may be warranted in select patients, such as those who are more likely to succumb due to their comorbidities rather than their breast cancer [21]. Online tools such as the University of California San Francisco's ePrognosis are available to the public and provide patient estimated life expectancy based on comorbidities and have previously been validated for patients with early-stage breast cancer [22, 23]. Additional tools such as the comprehensive geriatric assessment (CGA) can also be used. The CGA incorporates an individual's functional and cognitive status, nutritional state, psychological well-being social support, and medical conditions to predict morbidity and mortality in older oncology patients [24]. Primary endocrine therapy may be an option for patients with hormone receptor-positive breast cancer who are unsuitable surgical candidates given their other health conditions or for those patients who refuse surgery [25, 26]. A previous Cochrane meta-nalysis demonstrated that there was an improved progression-free survival for those patients with hormone receptor-positive tumors who underwent surgery; however, additional clinical trials have not demonstrated a direct impact on improvement in survival [26, 27, 28••].

Radiation Therapy

Adjuvant radiation therapy (RT) is generally well-tolerated by most older women, with evidence showing a decrease in local-regional recurrence rates and improved survival [29•]. However, as with surgical decision-making, several factors influence the role of RT in elderly patients. These include, but are not limited to, patient frailty, overall prognosis, patient mobility and physical limitations, time and transportation constraints, and adverse side effects of RT [30, 31]. Short-term follow-up analysis has revealed that overall quality of life in older patients who receive RT is largely unchanged compared to those who do receive RT [32•]. Additionally, those patients who are most likely to benefit from de-escalation of adjuvant RT are those with early-stage, hormone receptor-positive, clinically node-negative breast cancers who are suitable candidates for breast-conserving surgery and adjuvant endocrine therapy [33••].

Hypofractionated/Accelerated, Whole Breast Radiation Therapy (WBRT)

To minimize the timeframe needed to receive adjuvant RT, conventionally fractioned WBRT has largely been replaced by hypofractionated (also known as "accelerated") WBRT for women with early-stage, node-negative breast cancer. Long-term results have demonstrated that a hypofractionated course of RT is non-inferior to conventional RT regimens and allows the conventional administration time of 5–7 weeks to be shortened to a 3–5-week course [34•]. This decrease in administration duration can aid in minimizing patient transportation issues that older breast cancer patients may face. Several prospective studies have demonstrated that hypofractionated WBRT in elderly breast cancer patients is non-inferior to conventional fractionation, well-tolerated by the majority of patients, and provides lower transportation and temporal constraints for patients [35–37, 38•, 39].

Accelerated Partial Breast Irradiation (APBI) and Intraoperative Radiotherapy (IORT)

Given the success of hypofractionated WBRT, radiotherapy administration protocols have been developed to assess the role of APBI after breast-conserving surgery. APBI further decreases the time needed for RT administration down to 1–2 weeks and spares radiation to healthy tissues. If the RT dose is targeted towards the lumpectomy site, then larger doses can be given over a shorter duration [40••]. APBI can be administered through either brachytherapy catheters or external beam RT. The current American Society for Therapeutic Radiation Oncology (ASTRO) guidelines dictate that outside of the clinical trial setting, only patients ≥ 50 years of age who undergo BCT with negative margins (defined as at least 2 mm) for DCIS or T1 lesions, with low to intermediate grade tumors, should currently be considered for APBI [40••]. Several clinical trials have demonstrated that although APBI is non-inferior compared to WBRT for local recurrence rates, long-term toxicity and adverse cosmesis do occur more frequently in those patients who undergo APBI [41••, 42]. APBI may be exceptionally warranted for those older patients who meet ASTRO guideline criteria and have challenging transportation and mobility issues, to allow the administration time frame to be substantially decreased.

Intraoperative radiotherapy (IORT) was designed to allow for a single dose of radiation to be given directly to the lumpectomy cavity during the patient's initial operation. Two large clinical trials demonstrated that when comparting IORT to WBRT, there was an increase in the rate of local recurrence in the IORT group; however, for select patients, this recurrence rate was acceptable at less than 2% at 5 years [43, 44]. A recent analysis demonstrated that performing a delayed dose of a single IORT, by reopening the lumpectomy cavity, had similar overall survival to standard WBRT, but again demonstrated a higher local-regional recurrence rate [45]. Those older patients with favorable tumors who undergo lumpectomy and have contraindications to conventional adjuvant RT, may undergo IORT instead of conventional RT. Recent data reveals that patient health-related quality of life is similar between those who receive APBI in either the external beam or intraoperative settings in patients ≥ 60 years of age, but that acute local radiation side effects may be higher in those who receive IORT [46, 47]. A multi-institutional retrospective registry revealed that when comparing those patients age < 70 and ≥ 70 who receive IORT, acute toxicity and 1-year local recurrence rates were similar between the two age groups [48]. Currently, the TARGET-E study, a prospective phase 2 study of IORT in elderly patients, aims to further investigate the efficacy of a single RT dose in patients ≥ 70 years of age with small, node-negative breast cancers by evaluating local recurrence rates, survival, toxicity, and quality of life after 10 years [49••].

RT Omission

The most data-rich topic for de-escalation in local-regional RT in the elderly is in omitting RT for select patients with early-stage, node-negative, hormone receptor-positive tumors. In 2004, Hughes and colleagues first published the 5-year results of the Cancer and Leukemia Group B (CALGB) 9343 randomized controlled clinical trial. CALGB 9343 randomized 636 women age ≥ 70 with cT1-T2, N0, hormone receptor-positive tumors who underwent BCT to receive tamoxifen alone or tamoxifen plus conventional WBRT [8•]. While there was a higher incidence in local-regional recurrence in patients who received tamoxifen alone (4% vs 1%), there was no difference in the rates of mastectomy for recurrence,

development of distant disease, or overall survival at 5 years [8•]. Subsequently, in 2013, long-term follow-up (mean of 12.6 years) demonstrated similar findings with a 10-year overall survival rate of 67% for the tamoxifen plus radiotherapy group versus 66% for the tamoxifen group alone ($p < 0.05$) [9••]. A similar study was performed during the same time period in Europe: the PRIME II clinical trial. PRIME II included women ≥ 65 with cT1-T2 (up to 3 cm), N0, hormone receptor-positive tumors who were undergoing BCT [10••]. Those patients with grade 3 tumors or those with lymphovascular invasion were included, but patients were not allowed to have both features. As in CALGB 9343, patients were randomized to receive endocrine therapy (ET) alone or RT and ET. Five-year survival rates were similar between the two groups, but they did observe a modest reduction in ipsilateral recurrence in those patients who received RT [10••]. These two clinical trials made a substantial impact on treatment guidelines and led to an overall decrease in the rates of RT and decrease in the rates of mastectomy in older patients with breast cancer [50–52]. However, adherence with adjuvant ET in the setting of RT omission remains a significant predictor in long-term outcomes and patient compliance with ET should be carefully followed over the subsequent years after initiating ET [53•, 54]. Detailed and supportive communication has demonstrated to be key factors for adherence within this patient demographic [55].

Additional studies have been performed to validate the findings of these two large clinical trials [55]. Two separate meta-analyses from 2017 pooled data from four randomized controlled trials and confirmed that while RT does reduce the risk of ipsilateral recurrence, it does not impact distant or overall survival in older patients with early-stage, hormone receptor-positive, node-negative breast cancer treated with BCT and ET alone [56, 57•]. More recent clinical trials have expanded inclusion criteria for RT omission to assess if the findings in women age ≥ 70 can be applied to additional age groups. A prospective randomized control trial in Tokyo included 203 women, age ≥ 60 with cT1-T2 (up to 3 cm), node-negative, hormone receptor-positive tumors without evidence of lymphovascular invasion, who underwent BCT and had a tumor-free margin of ≥ 5 mm and were randomized to receive ET alone or ET and WBRT [58]. The trial found no difference in ipsilateral recurrence or overall survival at 5 years. While some patients did receive systemic chemotherapy within this cohort, the authors found no difference between recurrence or overall survival when controlling for systemic chemotherapy between the two treatment arms [58].

In addition, RT omission may be considered in those patients with significant transportation issues, comorbidities that may alter the benefit of local-regional control with RT, or those with an absolute contraindication to RT, regardless of tumor stage or tumor biology [59]. While chronological age is associated with a lower likelihood of receiving RT, even in the setting of nodal involvement, RT omission should be guided by the multidisciplinary breast cancer team and overall assessment of the benefit of RT to the patient [60]. It should be noted that in older patients with hormone receptor-negative disease, it appears that radiotherapy does improve overall and disease-specific survival [61••, 62•, 63]. These findings highlight the significance of careful patient selection for RT omission and how treatment plans should be carefully evaluated and discussed by the multidisciplinary breast cancer treatment team.

Conclusion

Over the past two decades, substantial clinical evidence has arisen to demonstrate that de-escalation of local treatment for breast cancer can be safe and effective in select older patients. The older patient with breast cancer needs a carefully selected plan that is not only tailored to the patient's specific needs but made by the multidisciplinary breast cancer team in collaboration with both patients and their family members. Careful attention must be made by providers to design treatment plans that utilize clinical data to maximize patient benefit while simultaneously minimize the risks of surgery and radiation therapy.

Compliance with Ethical Standards

Conflict of Interest The author has no relevant disclosures to report. This article does not contain any studies with human or animal subjects performed by any of the authors. The Author ICJME COI is included separately.

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