

Controversial issues in radiotherapy after breast-conserving surgery for early breast cancer in older patients: a systematic review

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ABSTRACT

Breast cancer is the most common malignant disease among older women, and the number of new older patients per year is increasing year by year. Radiotherapy has been confirmed as an important treatment after breast conservation for the reduction of local recurrence and mortality for all patients, including node-positive cases. However, there are fewer clinical trials evaluating the toxicity and benefits of radiotherapy for older patients. Whether radiotherapy can provide substantial benefit for older patients after breast-conserving surgery is controversial. This systematic review will focus on the key aspects of this controversial issue.

Keywords: radiotherapy; older patients; early breast cancer

INTRODUCTION

Breast cancer is the most serious health issue and the leading cause of cancer death among females worldwide [1]. In 2017, 30% of new cancer patients in women were breast cancer patients, and the incidence increases significantly with age [1]. Radiotherapy (RT), as the mainstay of adjuvant treatment after breast-conserving surgery (BCS), halves the rate of recurrence and reduces the rate of death by approximately one-sixth [2]. However, there is not enough clinical trial evidence for evaluating the impact of RT after BCS in older patients, and the benefit has been questioned. The risk of recurrence and mortality are relative to age. It is complex to manage cases of early breast cancer (EBC) in older patients, because it is necessary to weigh up the treatment-related toxicity, complications and tolerability of treatment in view of increased age. With the increasing interest in geriatric oncology, several studies of older patients with EBC have been carried out worldwide, and controversies have emerged regarding whether RT should or could be omitted in this special group. Although some randomized trials have indicated an obvious decrease in local recurrence with RT, none have found significant differences in overall survival or other outcomes in older patients [3, 4]. On the other hand, observational studies have confirmed that some healthy older patients may obtain clinical benefit from RT [3–5]. The aim of this review was to

discuss the controversy about the use of RT in older patients with EBC as raised in previous studies.

THE DEFINITION OF OLDER PATIENTS IN EBC

Different studies have used different inclusion criteria for older age. As shown in Table 1 [3–12], the Cancer and Leukaemia Group (CALGB), the National Cancer Data Base (NCDB), Martelli *et al.*, Eaton *et al.* and Daugherty *et al.* recruited women over 70 years, while the PRIME II trials recruited women over 65 years. Fyles *et al.* recruited Canadian women over 50 years. Wickberg *et al.* recruited women over 55 years in Sweden. There is no widely recognized age cut-off for what composes an older patient. The WHO definition of advanced age is 65 years old, but it should not be defined uniformly for all countries and for all diseases. The effects of age differ between developed and developing countries, and when considering social or physiological age. There is heterogeneity in people of the same age, including physical, psychological, cognitive function, and financial and social status aspects. Assessment of biological age for treatment decision should take consideration into individual health status and comorbid disease. An system for effective assessment of ‘older age’ in patients with EBC is critically needed in clinical practice.

In order to address health status objectively, the International Society of Geriatric Oncology and the National Comprehensive Cancer Network recommend comprehensive geriatric assessment (CGA) before treatment decisions [13]. CGA is a systematic procedure to assess multiple comorbidities and functional status of older patients through which geriatric problems not detected by the routine oncology approach can be found. Several studies have reported that components of CGA, comorbid diseases, functional status, cognitive function, nutritional status, geriatric syndromes, and polypharmacy, are associated with survival and toxicity in older patients with malignancies.

THE ASSESSMENT OF LOW-RISK OF EBC

Even in older patients, BCS alone has higher rates of breast cancer death than those receiving BCS plus RT or mastectomy [14]. However, some trials have shown that RT after BCS compared with BCS alone reduces breast cancer recurrence among older women with early-stage disease but does not affect survival [15, 16].

The characteristics of low-risk patients in whom RT can be safely omitted have not been established yet. There are many risk factors for recurrence that have been used in past studies to assess the risk, including human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), estrogen receptor (ER), Ki67, the size of the tumor, grade, histology, margin status, and presence of lymphovascular invasion [17]. As shown in Table 1, the CALGB, Daugherty *et al.*, Holli *et al.* and Wickberg *et al.* studies recruited patients with tumor size up to 2 cm, while the PRIME II trials and Martelli *et al.* recruited patients with tumor size up to 3 cm, and Fyles *et al.*, the NCDB, and Eaton *et al.* recruited patients with tumor size up to 5 cm. Moreover, the various studies recruited patients who were hormone receptor status ER positive, ER negative, ER or PR positive, or unspecified. In addition, Ishida *et al.* [18] also performed a clinical study on the elimination of RT in patients with breast cancer after BCS, based on five-factor criteria, including:

advanced lymphatic invasion, lymphatic metastasis positivity, margin positivity, a high grade of intraductal carcinoma extension, and metachronous or synchronous bilateral breast cancer. Hughes *et al.* revealed that radiotherapy plus tamoxifen after BCS for older patients with ER-positive EBC achieved a slightly better locoregional control rate than tamoxifen alone after BCS; however, this did not translate into an advantage in overall survival, distant disease-free survival, or breast preservation [19]. In other words, 'low-risk' has a different meaning in different studies looking at whether the radiotherapy is required or not. It is desirable to use tumor characteristics and patient status to predict and classify reasonably the prognoses of older patients with breast cancer in order to risk stratify accurately, avoid unnecessary toxicity, and provide older patients with tailored recurrence risks.

Gene analysis and immunohistochemistry (IHC) techniques are currently used as the primary means to guide treatment. Xiao B *et al.* [20] identified *ESCO2*, *PACSN1*, *PTN*, *RGMA*, *CDCA2*, *PIGR*, *KLK4* and *CENPA* as valuable marker genes for luminal breast cancer in the clinic, and built a risk-scoring system that is available for diagnosis and treatment of luminal breast cancer in the clinic. This system has been validated as effective and reliable in predicting prognosis.

In the clinic, many patients with breast cancer who are ER-positive could be overtreated with chemotherapy according to clinicopathologic features. Recently, however, an assay for gene expression in breast cancer has become available for identifying the low recurrence risk patients, enabling them to avoid adjuvant chemotherapy. For instance, the Oncotype DX assay is a molecular assay that involves quantifying the expression of 21 genes, and can provide a recurrence score (RS) for ER-positive, node-negative breast cancer patients [21]. The Trial Assigning Individualized Options for Treatment (TAILORx) aimed to further verify and refine the clinical effectiveness of the 21-gene assay (Oncotype DX Recurrence Score, Genomic Health), and it has been demonstrated that tumor RS categorization is related to the risk of developing

Table 1. The main characteristics of past studies for older patients

Study	Year	Country	Period	Number	Age	Tumor size (cm)	ER/PR	Follow up (years)
CALGB (3)	2013	USA	1994–1999	636	≥70	2	ER+	12.6
Holli <i>et al.</i> (4)	2009	Finland	1990–1999	264	≥40	2	+	12.1
Daugherty EC (5)	2016	USA	1998–2011	5178	≥70	2	ER–	4.67
NCDB (6)	2018	USA	2004–2013	547	≥70	5	Unspecified	3.4
Eaton <i>et al.</i> (7)	2016	USA	1993–2007	3432	≥70	5	ER–	3.75
PRIME II (8)	2015	UK	2003–2009	1326	≥65	3	ER+	5
Fyles <i>et al.</i> (9)	2004	Canada	1992–2000	769	≥50	5	+	5.6
ABCSG (10)	2007	Austria	1996–2004	855	≥50	3	+	4.48
Martelli <i>et al.</i> (11)	2015	Italy	1987–1992	627	≥70	3	Unspecified	17.4
Wickberg <i>et al.</i> (12)	2014	Sweden	1981–1988	199	≥55	2	unspecified	20

ER = estrogen receptor; PR = progesterone receptor.

distant recurrences [22]. We can learn from this development and try to apply it to RT.

There have also been advances in IHC techniques, which are more economical than gene analysis. IHC4pClinical (IHC4pC) combines the expression of hormone receptor HER2 and of Ki-67 with clinicopathological parameters to identify patients with a low risk of recurrence [23], thus helping to avoid overtreatment with breast radiotherapy. IHC biomarkers have been confirmed as assessing the prognostic situation regarding local relapse following RT, and in order to further verify this, the PRIMETIME trial is studying the features of patients at 'very low' risk of recurrence by using the IHC4+C scoring system, and carrying out a prospective cohort study with 10 years or longer follow-up time [24].

THE TOXICITIES OF RT AFTER BCS IN OLDER PATIENTS

Despite advances in radiation techniques, the toxicities of RT in older patients with EBC still inevitably occur, including cardiac toxicities, second malignancies, and damage to the skin and the contralateral breast. When looking at the benefits of RT in the form of low relapse rate and reduced mortality, radiation-induced effects should be considered as well.

The heart is sensitive to radiation, and whatever techniques or dosages are used, side effects cannot be avoided. It has been reported that cumulative heart-specific mortality has a positive correlation with age at diagnosis and length of follow-up [25]. It is known that, compared with non-irradiated patients, patients who have been irradiated for breast cancer have a significantly increased risk of cardiac mortality. Numbers of patients with radiation-induced heart disease in breast cancer have increased, and most of them have ischemic heart disease [26]. RT for breast cancer results in variable cardiac radiation exposure and may increase the risk of ischemic heart disease occurring years after the treatment. Systemic treatments involving radiotherapy, anthracyclines, taxanes, and alkylating agents are commonly used to treat breast cancer. These anti-cancer agents also have cardio-toxicity and could contribute to ischemic cardiac disease [27]. Radiotherapy for left breast cancer does not increase the incidence of heart disease. A large study in women aged over 65 years suggested that heart disease incidence after RT had no significant difference between in right and left breast cancer following a maximum follow-up of 15 years [28]. In not a few reports, radiation pneumonitis was also related with age [29, 30].

Increased risk of second malignancies, specifically lung, esophagus and contralateral breast cancer, was thought to be closely connected with RT [31]. However, most of the previous studies that supported this view are found to have included patients treated with different RT techniques, or dosages that are no longer used. Also, the subjects were more concentrated on patients under the age of 60, so the studies lacked evidence in elderly patients. By meta-analysis, we have found that smoking and alcohol consumption are causes of lung cancer and squamous-cell carcinoma of the esophagus [32]. Therefore, when discussing second cancers of the lung or esophagus associated with RT in older patients, smoking and alcohol consumption in those patients should be considered. The addition of chemotherapy could increase the risk of second

cancers unless it was equally matched between the groups. For most non-smokers, the benefits of RT may far outweigh the absolute risks of radiation. It is just the reverse for long-term smokers [33]. Further research related to receipt of RT is needed.

Radiation dermatitis is the most common side effect of RT in breast cancer [34], clinical manifestations are mostly erythema, edema, ulcers, erosion and so on. This is due to the lack of tolerance of the chest wall skin after BCS and it is susceptible to radiation damage. However, the severity of the radiation dermatitis is not related to the patient's age.

Currently, there are lots of options for de-escalating the side effects of RT, such as hypofractionated radiation, the selective delivery of a boost dose to the lumpectomy cavity, and the introduction of accelerated partial breast irradiation, including brachytherapy [35]. Breast irradiation on the prone board with meticulous positioning and suitable photon energy can be used to prevent acute dermatitis and reduce the dose to organs at risk [36]. Regarding cardiac death, because population heart disease death rates are much lower than in the past, the estimated absolute cardiac risk due to RT has also decreased. Of all breast cancer survivors in one study, just 3% of second solid cancers in irradiated women resulted from radiation exposure [31]. A Danish study reflecting contemporary standards in radiation, suggested that older patients treated with RT have a small but significant increased risk of second cancers [37]. However, contralateral breast cancer incidence can be reduced by effective systemic therapy, and the absolute risk of contralateral breast cancer should be decreased to <1% by modern RT [33]. When assessing the benefits and risks of radiation therapy in older patients, in addition to considering tumor characteristics, other risk factors like lifestyle, environmental and genetic factors, rather than second cancers, should be given more attention.

PATIENT CHOICE

Factors influencing the patient's choice include the doctor's suggestions and the patient's cognition. The latter may be an important factor leading to omission of RT, and many suitable patients are ineligible for studies, which could affect the results.

One study found that 40% of surgeons and 20% of radiation oncologists thought it was unreasonable for older patients to neglect RT after BCS [38]. The omission of RT was closely related to estimates of survival benefits from RT and remaining life expectancy. In that study, 32% of surgeons and 19% of radiation oncologists overestimated the risk of locoregional recurrence [38]. Misestimating may lead to omission or overtreatment. We frequently observe psychological stress, anxiety, depression, sleep issues, fear of cancer recurrence, radiotherapy-induced fatigue, and pain in breast cancer patients treated by BCS, leading to effects on quality of life (QoL). Depression and its related symptomatology, is considered a risk factor for cancer incidence and progression [39]. Older patients are more prone to depression than younger patients due to frailty and functional impairments. Psychological treatments, through improving depressive symptomatology, can raise levels of QoL in oncologic contexts. Here, psychosocial care from medical staff can provide important support for reducing anxiety. The knowledge and attitudes of surgeons and radiation oncologists plays a key role in patient and prognosis.

Treatment in older patients with cancer is influenced by objective social factors such as retirement laws, the medical system, health-care policies, and cultural, religious and societal influences [39]. Compared with younger patients, in addition to experiencing more decline in their general physical and mental health, older patient groups may lack social support and financial resources. Patient care from the family and professional services can support older patients in continued treatment.

In addition to the above, there are some other points. Age is a risk factor for developing a postoperative complication after oncoplastic BCS [40]. Older patients have higher risks of comorbidity, because complications, tolerability of treatment and shorter life expectancy are affected by both aging and illness. The incidence rate of breast cancer recurrences increases with the follow-up time, so it may occur more than 10 years, even 15 years after diagnosis [41]. The incidence estimation may be unreliable in studies with a short follow-up time. In past literature, not considering comorbidities may have generated misleading conclusions. Furthermore, survival benefits are assessed by the statistical end points, including breast-cancer-specific survival, the disease-free survival rate, the local recurrence rate, the overall survival, and distant relapse. Different statistical end points can also lead to different conclusions.

CONCLUSION

There remains a challenge in the treatment of EBC in older patients. At present, the consensus is that for patients ≥ 70 years old with T1N0, ER-positive and node-negative EBC, omission of RT after BCS could be considered, especially when the risk of radiation-induced toxicities and complications exceeds the risk of cancer recurrence. 'Older breast cancer patients' have not yet been defined, and even if it had, treatment strategy should not be selected solely according to age. The choice of adjuvant treatment should also consider the patient's risk of recurrence and the QoL associated with different health outcomes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest associated with this manuscript. This manuscript is original, has not already been published, and is not currently under consideration by another journal. All the authors and the institutions where the work was carried out have approved submission of this manuscript.

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