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## When are breast cancer patients old enough for the quitclaim of local control?

Almost half of the 71,660 women diagnosed annually with breast cancer in Germany are older than 65 years, about one third is over 70 years [19, 27]. The life expectancy of a 70-year-old woman is around 16 years [19]. Many of those women are in a better general health condition than former generations owing to improved medical care and an increased awareness of a healthier lifestyle [21, 35].

Thus, it seems plausible that the updated recommendations of the European Society of Breast Cancer Specialists (EUSOMA) [4] and the latest German S3 guidelines [22] see no age limitation for postoperative radiotherapy (RT) for elderly patients in good health (■ Tab. 1). However, the benefit of adjuvant treatment may be smaller in advanced age and patients may be predisposed for comorbidity. This dichotomy has prompted reinforced efforts to provide evidence-based recommendations for the management of elderly individuals with breast cancer. Several international guidelines have been amended with statements specifically addressing treatment of elderly women and have come to antipodal recommendations (■ Tab. 1).

One example is the indication for whole-breast radiotherapy (WBRT) for women over 70 years with low-risk tumors, which has recently become an issue of debate. The poignancy of this dispute is illustrated by four articles in the *Journal of Clinical Oncology* published in 2012, all of which addressed the issue of whether or not postoperative RT after breast-conserving surgery (BCS) could be reasonably omitted in selected women over 70 with low-risk breast cancer [2, 13, 31, 36]. This is currently propagated in the treatment guidelines of the American National Comprehensive Cancer Network (NCCN) ([24], ■ Tab. 1).

Overall, in early breast cancer the 10-year recurrence rate (local or distant) is halved by postoperative RT after BCS. As the latest analysis of the EBCTCG in 2011 confirmed, this proportional risk reduction is observed in all age groups, although the absolute benefit is more pronounced in younger women. Even for node-negative patients over 70 years, the 10-year recurrence rate was reduced from 17.7 to 8.8% [8].

### Does evidence justify a change of practice?

Notwithstanding these data, the NCCN recommends omission of postoperative RT in patients older than 70 years after BCS and use of tamoxifen or aromatase inhibitors for 5 years instead, provided that patients have negative axillary nodes and estrogen receptor (ER)-positive T1 breast cancer. As a substantiation, two randomized studies are cited in the guidelines, the first by the Cancer and Leukemia Group (CALGB), published 2004 [17] and updated at the ASCO 2010 [18], which is so far the only one exclusively addressing the issue of postoperative radiation in women over 70 years. Altogether, 636 women (55% of whom were older than 75 years) with T1 tumors, negative axillary nodes, and ER-positive disease were randomized to receive either tamoxifen alone (5 years) or additional WBRT. Local recurrence was 9% in the group treated with tamoxifen alone, in contrast to only 2% in the irradiated patients ( $p < 0.001$ ); overall survival was not affected, 42% had died at the time of evaluation. The authors conclude “the study demonstrates that lumpectomy

**Tab. 1** International guidelines for the treatment of breast cancer

NCCN <sup>a</sup> [24]	WBRT as a component of breast-conserving therapy is not always necessary in selected women 70 years of age or older. NCCN guidelines allow for the use of BCS plus tamoxifen or an aromatase inhibitor without breast irradiation in women age 70 or older with clinically negative nodes and ER-positive T1 breast cancer
Eusoma/SIOG <sup>b</sup> [4]	WBRT after BCS, with a boost to the tumor bed, should be considered in all elderly patients since it decreases risk of local relapse. There is no subgroup of fit older patients in whom post-BCS WBRT can be systematically omitted
S3 German <sup>c</sup> [22]	No subgroup has yet been identified in whom patients did not profit from RT after BCS in terms of improved local tumor control. Therefore, omission of RT in patients of advanced age even with favorable prognostic factors (pN0, ER-positive, low grade) should only be considered in presence of comorbidities with a substantial reduction of life expectancy

<sup>a</sup>National Comprehensive Cancer Network <sup>b</sup>International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists <sup>c</sup>DKG, Deutsche Krebshilfe, AWMF WBRT whole-breast radiotherapy, RT radiotherapy, BCS breast-conserving surgery, ER estrogen receptor

and anti-estrogen therapy without radiation is an appropriate treatment for older women with node negative, hormone receptor positive disease..." and "that physicians should weigh cost, inconvenience and adverse effects of irradiation."

A second paper cited in the guidelines to justify omission of RT in women over 70 years is quoted as providing "similar results." The Canadian study of Fyles et al. [12] published in 2004 refers to 769 women over 50 years (325 of whom were older than 70 years), with node-negative T1–2 breast cancer, who also were randomly assigned to receive tamoxifen plus RT or tamoxifen alone. Overall, the rate of local relapse at 5 years was 0.6% in the irradiated group and 7.7% with tamoxifen alone ( $p < 0.001$ ), with corresponding 5-year disease-free survival (DFS) of 84% vs. 91% ( $p = 0.004$ ) in favor of the irradiated group. A subgroup analysis of 611 patients with T1 tumors showed a 5-year local recurrence rate (LRR) of 0.4% with and 5.8% without RT. Noteworthy, at 8 years, the rate of LRR increased to 3.6% and 15.2%, respectively. The authors state that "the observation of late relapses in this trial makes tamoxifen plus breast irradiation the preferred treatment for such patients, particularly given its minimal toxicity."

The third randomized trial analyzing the effect of WBRT in women over 65 years (not mentioned in the NCCN guidelines) was performed by the Austrian Breast and Colorectal Study Group (ABCSCG) and included 869 women predominantly with T1/G1–2 tumors, node-negative and ER-positive disease, who

received tamoxifen/anastrozole either with or without postoperative RT [26]. The 5-year LRR was 0.4% for irradiated patients vs. 5.1% for those with endocrine therapy alone ( $p = 0.0001$ ); the overall 5-year recurrence rate was 2.1% vs. 6.1% ( $p = 0.002$ ).

### Why did practice not change?

Interestingly, neither the publications of the CALGB trial with the authors' explicit recommendation nor the amendment in the NCCN guidelines had substantial impact on clinical practice of RT application in older women in the U.S. [31]. This was demonstrated by a population-based study using SEER-medicare data, which identified 12,925 breast cancer patients, treated between 2001 and 2007, who fulfilled the inclusion criteria of the CALGB study. The mean age was 77 years. The aim of the study was to determine the extent to which the CALGB results influenced RT prescription before and after publication of the CALGB data in 2004. Overall, 76.5% of medicare beneficiaries received RT, thereof 79% before publication compared to 75% thereafter. In patients with a life expectancy of 10 years or more, RT use decreased from 92 to 89%. "Why did practice not change?" was the headline of the accompanying editorial by Giordano commenting on these data [13]. She states that "offering RT to a woman with a good prognosis tumor and a life expectancy of less than five years does not seem indicated and that these women were at risk for unnecessary adverse

effects, inconvenience—and possibly increased personal cost."

The shift of paradigm in the NCCN prompted one more contemporaneous publication: Albert et al. [2] reassessed the effect of RT in older women by analyzing the outcome of a large breast cancer patient cohort from the SEER database. The outcome of 16,092 women, age 66–79 years, treated with BCS for early breast cancer from 1992 to 2002 was analyzed and data were used to generate a nomogram for predicting the 5- and 10-year mastectomy-free survival (MFS) with and without RT according to individual tumor characteristics. The majority (70%) was older than 70 years, and 89.4% had postoperative irradiation. Most patients (82.6%) had tumors smaller than 2 cm and negative axillary nodes (84%). The 5- and 10-year MFS rates were 98.4% and 95.4% with RT vs. only 95% and 89% when RT was omitted ( $p < 0.001$ ). These data confirm several previous international cohort studies with large numbers of older women, all of which revealed increased local control and mostly improved survival as well [16, 30, 34, 41, 39]. Whether the nomogram proposed by Albert et al. is a suitable tool for predicting local recurrence has, however, been questioned [36] as MFS is only a surrogate parameter for local recurrence.

### Treatment risks and adverse effects

Assuming an increased frailty of the aging organism, the attempt should be to minimize toxicity. One of the frequently used justifications for omission of RT is to spare patients the unnecessary adverse effects of RT [13, 17]. However, with modern treatment planning, RT has minimal side effects [10].

This was recently confirmed by the Scottish PRIME trial [38], which specifically addressed the impact of RT on quality of life. The trial comprised 255 low-risk breast cancer patients over 65 years of age after BCS, who received endocrine treatment with or without RT. The study aimed to assess whether the omission of RT would improve quality of life, reduce treatment-related morbidity, and be more cost effective. The 5-year results published

in 2011 revealed that the hypothesized improvement of quality of life for un-irradiated patients was not observed and that even the level of breast symptoms was similar at 5 years.

While *local* treatment affects only the treated part of the organism, *systemic* therapy pertains to the system. The NCCN propagates tamoxifen and/or aromatase inhibitors in all ER- or PR-positive patients for 5 years or more, regardless of age [24]. The suggestion to replace RT by endocrine treatment assumes that patients will adhere to an at least 5-year medication. However, in clinical practice neither tolerance nor compliance to medication for such a time span is safely predictable, and the rate of discontinuation of tamoxifen and aromatase inhibitors is 15–30% [9, 25, 42]. Some of the side effects are thromboembolism and induction of endometrial cancer for tamoxifen, while aromatase inhibitors may cause arthralgia and bone density loss [6]. Moreover, both drugs are reported to affect psychosocial and cognitive function and to promote sleeping disorders and depression [4, 9, 23, 42].

### Age of 70: obliging or optional border?

In 2011, another large SEER database study was published with the headline “Improvement of breast cancer outcome over time—are older women missing out?” While the breast cancer death rates in women aged 64 years and younger decreased by 15.3% over the last 20 years, patients over 75 years had only a 7.5% reduction [30]. This reflects the trend to under-treat older women [5, 16, 34].

There is no generally accepted definition of the “older patient,” but criteria exist for the assessment of biological age [3, 7]. The distinction between “fit patients,” “vulnerable patients,” and “frail patients” has been established. Geriatric evaluation is a practical tool for individually assessing the feasibility of treatment. Standardized investigation of relevant parameters such as comorbidities, cognitive status, and social environment may help to differentiate irreversible age-related functional deficits from potentially reversible stress reactions [11]. Moreover, it permits a more objective assessment to be made of the patient’s in-

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### When are breast cancer patients old enough for the quitclaim of local control?

#### Abstract

**Background.** Although postoperative radiotherapy (RT) after breast-conserving surgery (BCS) halves the 10-year recurrence rate in breast cancer patients through all age groups, the question of whether RT may be omitted and replaced by endocrine therapy for women aged 70 years and older with low-risk factors has recently become an issue of debate.

**Methods.** Survey of the relevant recent literature (Medline) and international guidelines. **Results.** Three randomized studies investigating the effect of RT in older women revealed significantly increased local recurrence rates when RT was omitted, and a negative impact on disease-free survival was observed in two of these trials. Despite these findings, in one of the studies omission of RT in women over 70 is recommended, leading to a respective amendment in the guidelines of the American National Comprehensive Cancer Network. Several large retrospective cohort studies analyzing the outcome of patients over 65 years with and without RT have

since been published and showed a significantly improved local control in all subgroups of advanced age and stage, which predominantly translated into improved disease-free and overall survival.

**Conclusion.** No subgroup of elderly patients has yet been identified that did not profit from RT in terms of local control. Therefore, chronological age alone is not an appropriate criterion for deciding against or in favor of adjuvant RT. The DEGRO breast cancer expert panel explicitly discourages determination of a certain age for the omission of postoperative RT in healthy elderly women with low-risk breast cancer. For frail elderly women, treatment decisions should be individually decided on the basis of standardized geriatric assessment.

#### Keywords

Breast cancer · Life expectancy · Older patients · European Society of Breast Cancer Specialists guidelines · Radiotherapy

### Stellungnahme der Deutschen Gesellschaft für Radioonkologie (DEGRO): Wird bei Brustkrebs im Alter das Lokalrezidiv zumutbar?

#### Zusammenfassung

**Hintergrund.** Nach brusterhaltender Operation wird die 10-Jahres-Rezidivrate bei Brustkrebspatientinnen sämtlicher Altersgruppen durch eine postoperative Radiotherapie (RT) halbiert. Dennoch ist neuerdings eine Kontroverse darüber entbrannt, ob bei Frauen über 70 Jahre mit niedrigem Risikoprofil auf die RT verzichtet und stattdessen eine endokrine Therapie erfolgen sollte.

**Methoden.** Literaturrecherche der kürzlich zu diesem Thema publizierten Studien (Medline) und internationaler Leitlinien.

**Resultate.** In drei randomisierten Studien wurde die Effektivität der RT bei älteren Frauen untersucht und zeigte eine signifikant höhere Lokalrezidivrate bei Nichtbestrahlten sowie in zwei dieser Studien einen negativen Einfluss auf das krankheitsfreie Überleben. Dennoch wurde in einer Publikation der Verzicht auf eine RT bei >70-Jährigen empfohlen, was als Ergänzung in die aktuellen amerikanischen National-Comprehensive-Cancer-Network-Leitlinie übernommen wurde. Seitdem wurde in mehreren umfangreichen Kohortenstudien der Verlauf von Pa-

tientinnen >65 Jahre mit und ohne RT ausgewertet, wobei sich in sämtlichen Alterssubgruppen und Tumorstadien der >65-Jährigen eine signifikant verbesserte lokale Tumorkontrolle nach RT zeigte, die überwiegend auch zu einem verlängerten rezidivfreien und Gesamtüberleben führte.

**Schlussfolgerung.** Bislang wurde keine Subgruppe älterer Patientinnen identifiziert, die nicht durch Senkung der Lokalrezidivrate von einer RT profitierten. Die DEGRO-Expertengruppe Mammakarzinom sieht deshalb das kalendarische Alter allein nicht als hinreichendes Entscheidungskriterium gegen eine RT, diese sollte deshalb älteren Patientinnen in gutem Allgemeinzustand nicht vorenthalten werden. Bei gebrechlichen Älteren ist eine individuelle Entscheidung anhand eines standardisierten geriatrischen Assessments zu treffen.

#### Schlüsselwörter

Brustkrebs · Lebenserwartung · Ältere Patienten · EUSOMA Leitlinien · Radiotherapie

dividual situation and life expectancy, and helps to decide whether adjuvant therapy is sensible and practicable [4]. Therefore, geriatric assessment is recommended prior to treatment decision. Careful weighing of the risk–benefit relation is mandatory; however, it is not appropriate to regard age per se or comorbidities alone as risk factors precluding RT [14, 29].

The patient's preference is another crucial issue and not necessarily correlated with age. To sustain a local recurrence is a devastating experience for breast cancer patients irrespective of age and it seriously compromises quality of life [20]. The PRIME study confirmed that even low-risk patients over 65 years expressed significant concerns about tumor recurrence. Moreover, by the end of follow-up, patients who had received RT expressed less anxiety about recurrence than those who had not [38]. Older patients generally prefer to be well informed about treatment options [4]. The recently presented “patients' decision aid for older women with stage I breast cancer considering radiotherapy after lumpectomy” [40] may provide a valuable tool for easing the process of decision-making between physician and patient.

### Time, costs, and inconvenience

Quantitative supply with RT facilities varies substantially between different countries and a shortage of institutions may lead to long transport distances. This may cause inconvenience for elderly patients, especially when conventional WBRT extends over several weeks. This is less of a problem in most central European countries having a closer supply with RT institutions. Moreover, treatment time can be reduced, as hypofractionation has recently become an accepted alternative to conventional schedules especially for older individuals [32, 33, 37]. Accelerated partial breast irradiation is not yet recommended as a routine treatment outside prospective clinical studies [1, 22, 28] but may provide an option for the future when follow-up of randomized studies will be long enough to provide mature results.

In her editorial, Giordano [13] states that “in this era of rising health costs, we

will have to decide as a society, what level of cost to benefit we can sustain.”

This may be comprehensible, regarding the fact that RT costs in the U.S. are about three- to fourfold higher [15] than, for instance, in Germany. Using aromatase inhibitors as an alternative to RT would also be doubtful in terms of saving costs in Europe, as the price per tablet is about € 6, accounting for € 2,100 annually.

Regardless of regional differences in expense of RT, costs do not seem a legitimate reason to impose a several-fold higher recurrence rate on patients for the sole reason that they have passed a certain calendar age.

### Conclusion

- Chronological age alone is not an appropriate criterion for decision against or in favor of adjuvant treatment.
- No subgroup of elderly patients has yet been identified that did not benefit from RT in terms of local control.
- The DEGRO breast cancer expert panel explicitly discourages determination of a certain age for the omission of postoperative RT in healthy elderly women with low-risk breast cancer.
- In frail elderly women, omission of postoperative RT should be individually decided on the basis of geriatric assessment.

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**Conflict of interest.** On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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