REVIEW ARTICLE

Adjuvant Therapy for Women Over Age 65 With Breast Cancer

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SUMMARY

Background: Women over age 65 with breast cancer are often not treated in accordance with current guidelines as far as adjuvant therapy is concerned, because of the lack of adequate scientific evidence.

Methods: This article is based on a selective review of pertinent literature retrieved by a PubMed search, as well as on the German S3 guidelines for the diagnosis, treatment, and follow-up care of breast cancer, the treatment recommendations of the German Working Group on Gynecological Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO) and the German Society of Radiation Oncology (Deutsche Gesellschaft für Radioonkologie), US National Comprehensive Cancer Network, and the Cochrane database.

Results: Women over age 65 are underrepresented in randomized trials of treatments for breast cancer. Geriatric assessment is essential for therapeutic decision-making. Endocrine treatment is feasible for nearly all patients with hormone-sensitive tumors. In selected patients over age 65, chemotherapy significantly improves overall survival. The best evidence regarding toxicity is available for anthracycline monotherapy and for combined therapy with doxorubicin/cyclophosphamide or taxane/doxorubicin. Women without cardiac disease can be given trastuzumab, which may lead to reversible cardiotoxicity. Adjuvant radiotherapy significantly improves local tumor control and survival. Adjuvant radiotherapy that is carried out with modern treatment planning, as recommended by the current guidelines, is no more toxic to older patients than to younger ones; thus, it should always be given, unless there is a special reason not to.

Conclusion: Women with breast cancer over age 65 whose life expectancy is greater than 5 years, and who are not otherwise too ill, should be given chemotherapy, trastuzumab, and radiotherapy as standard adjuvant treatment. Adjuvant therapy can be reduced or omitted in frail patients. Patients over age 65 should be given the opportunity to enroll in clinical trials.

► Cite this as:

Sautter-Bihl ML, Souchon R, Gerber B: Adjuvant therapy for women over age 65 with breast cancer. *Dtsch Arztebl Int* 2011; 108(21): 365–71. DOI: 10.3238/arztebl.2011.0365

Each year, around 57 000 women in Germany are diagnosed with breast cancer. Almost half of them are over age 65, and about one third are over 70 (e1, e2). As is to be expected, older patients have higher rates of comorbidity affecting their tolerance of tumor treatment. However, improved medical care and increased awareness of the importance of a healthy lifestyle mean that many women of advanced age are in better general health than those of earlier generations (e3). Worldwide, however, only a certain proportion of older women with breast cancer are treated in accordance with guidelines (1, e4, e5). Germany is no exception in this regard, as shown by the recently published analysis of a large group of patients (2) (*Table 1*). This reluctance to treat older women in the same way as younger patients applies above all to chemotherapy, antibody treatment, and radiotherapy, but not to endocrine treatment (3, 4, e4, e6). We set out to establish under what circumstances and to what extent deviation from the current standard guidelines for treatment of breast cancer is justified in older women.

Method

We carried out a selective review of the literature in the PubMed database, using the search terms “breast cancer” and “elderly patient” and “adjuvant treatment” and “radiotherapy” or “chemotherapy” or “trastuzumab”. The search was limited to clinical studies, randomized clinical trials, and meta-analyses published between 2000 and January 2010. We also included published papers from relevant congresses in 2009. The current German S3 guidelines (5) and the treatment recommendations of the AGO Mamma (Breast Committee of the *Arbeitsgemeinschaft Gynäkologische Onkologie*, German Working Group on Gynecological Oncology) (6), the DEGRO (*Deutsche Gesellschaft für Radioonkologie*, German Society of Radiation Oncology) (7, 8), the NCCN (US National Comprehensive Cancer Network) (9), and the Cochrane database (e7) were considered. Evaluation – if not already carried out in the framework of the guidelines – was performed according to the Oxford criteria (e8) and the AGO recommendation level (*Table 2*).

Oncological treatment in old age

Age over 65 is often an exclusion criterion for clinical studies. All existing guidelines are based

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TABLE 1

Proportion of patients not treated according to the specifications of the guideline "Therapy of Breast Cancer 2004" (2)

Treatment not carried out	Age group (years), proportion (%)				
	50–64	65–69	70–74	75–79	> 80
Breast-sparing surgery	6	10	17	24	46
Mastectomy	50	50	48	42	39
Radiotherapy	9	9	14	27	60
Hormone therapy	13	12	14	9	7
Chemotherapy	33	36	54	77	98

predominantly on data from women under 65, and study data on women over 65 – even more so for those over 70 – are sparse. Given the high number of older women affected, this represents a significant gap in our knowledge. However, recent heightened awareness of this deficiency has led to age barriers being abandoned in the currently ongoing investigations, and studies specifically designed for older women have been initiated (*eTable 1*).

There is no generally accepted definition of the older female patient, but criteria exist for the assessment of biological age (10, 11, e9, e10) (*Table 3*). One practical instrument for assessing the feasibility of treatment in an individual case is expert geriatric evaluation, which includes not only the relevant comorbidities but also the patient's cognitive status and social environment (12) (*Table 4*). Standardized investigation of relevant parameters helps to differentiate irreversible age-related functional deficits from those which arise from the patient's current situation and are potentially reversible. Moreover, it permits a more objective assessment of the patient's individual situation and facilitates the decision whether, in light of her quality of life and life expectancy, adjuvant therapy is sensible and practicable (13, e11). Geriatric evaluation is therefore recommended when deciding whether and what treatment should be undertaken in older women (4) (level of evidence [LOE] 2b/B, AGO recommendation level ++).

The life expectancy of older female patients is often underestimated. Statistics show that a 70-year-old woman has a life expectancy of around 16 years, and an 80-year-old can expect to live for another 9 years (e1). There is also a widespread assumption that breast cancer is less aggressive in old age, among other reasons because of the higher proportion of hormone receptor-positive tumors, the lower frequency of HER2 overexpression, and other tumor biological characteristics (14). The data are contradictory, however: a study on the disease course of older breast cancer patients, most of whom had received no adjuvant systemic treatment, showed that their tumors were by no means more indolent (15).

Lower tolerance of treatment in older age also cannot automatically be assumed (e12). A number of studies on radiotherapy of thoracic tumors and breast cancer have yielded no pointers to reduced radiation tolerance in old age (16, e6, e13, e14). The tolerability of systemic treatment is also not always decreased in older patients (17). Given good initial cardiac condition, determination of the left ventricular ejection fraction (LVEF), and careful monitoring, even anthracycline-containing combinations and trastuzumab can be administered with adverse effects comparable to those in younger patients (18, 19). Older patients are more likely to be taking multiple medications, so one must be alert for interactions during chemotherapy (e15, e16) (*eTable 2*). There are no valid data on the quality of life in older women during and after adjuvant therapy.

TABLE 2

Recommendation levels (RL) of AGO Mamma (6)

RL	Definition
++	Treatment/intervention is highly beneficial, should be carried out
+	Treatment/intervention is of limited benefit, can be carried out
+/-	Treatment/intervention has shown no benefit, but can be carried out in individual cases
-	Treatment/intervention can be detrimental, should not be carried out
- -□	Treatment/intervention is clearly detrimental, should definitely not be carried out

TABLE 3

Risk groups and implications for the decision to treat or not treat patients over 65 (e10)

Group	CGA parameter ^{*1}	Two-year mortality	Implication for treatment
Group I: fit patients	Independent with no significant comorbidities	8–12%	Full dosage
Group II: vulnerable patients	Requires support in one or more activities of daily life One or two significant comorbidities	16–25%	Individually adapted precautions, initial dose reduction, special care
Group III: frail patients	Requires support in one or more activities of daily life Three or more significant comorbidities One or more geriatric syndromes Age over 85	>40%	Palliative and supportive treatment only

^{*1} CGA, Comprehensive geriatric assessment; ^{*2} activities of daily life and geriatric syndromes: see Table 4

Local control and survival

The quality of the surgery and the subsequent radiotherapy (RT) are decisive for local tumor control. Only in the past 10 years has high-level evidence (LOE 1a) been provided for the impact of this factor on the survival of breast cancer patients. For example, the latest meta-analysis from the Early Breast Cancer Trialists' Collaborative Group shows that, depending on tumor stage, RT achieves absolute local recurrence rates of no more than 30% after breast-sparing surgery (BSS) and 17% after mastectomy. This leads to improvement of overall survival. Independent of age, prevention of four local recurrences avoids one tumor-related death (LOE 1a) (20).

Because around three fourths of locoregional recurrences of breast cancer arise in the first 5 to 7 years after primary treatment, older patients too are likely to experience a local recurrence and the associated decrease in quality of life (e17).

Radiotherapy

Three randomized studies investigated the necessity of radiotherapy after BSS in older women with a favorable risk constellation (pT1–2, pN0, estrogen receptor [ER] positive and progesterone receptor [PR] positive). Surgery was followed by endocrine therapy with or without RT. In all three cases the local recurrence rate was significantly higher without RT [9% versus 2% (e18), 7.7% versus 0.6% (21), and 5.7% versus 0.5% (e19)].

In women of 70 and over—56% of them over 75—Hughes et al. (e18, e20) found no difference in 10-year survival (63% versus 61%), which led them to consider administration of tamoxifen alone as sufficient. The other two studies (21, e19), however, showed a significant reduction in disease-free survival without RT [84% versus 91% (21) and 93.9% versus 97.9% (e19)] (Table 5).

The authors of the most comprehensive retrospective cohort study on this topic to date concluded that

forgoing RT after BSS in older women leads to reduced likelihood of survival (22). Among a total of 4836 women between 50 and 85 years of age with prognostically favorable tumors (pT1–2, pN0–1), the greatest difference after forgoing RT was found in those over 75 (n = 773), where the tumor-specific survival rate was 88% in those who did not receive RT compared with 94% in those who did receive RT (p = 0.004). A National Cancer Institute analysis compared breast cancer mortality in women over 65 after mastectomy (n = 977) and after BSS with (n = 639) and without (n = 211) RT. The patients who received BSS alone showed a doubling of breast cancer mortality (hazard ratio [HR] = 2.19) relative to mastectomy (HR = 1.0). BSS with RT was almost equivalent to mastectomy (HR = 1.08) (e21).

A German cohort study (2) also showed significant (p<0.0001) reductions in tumor-specific survival (HR = 1.89) and overall survival (HR = 2.14) for patients aged 70 or older. This effect was even more pronounced in patients under 70 (HR = 3.29 to 3.45) (2). In the presence of risk factors, older women even profit after mastectomy. An analysis of the survival data of 2053 patients with pT3/4, pN2/3 tumors from the American database Surveillance Epidemiology End Results (SEER) showed 5-year survival of 50% without postoperative treatment, 56% with RT, and 59% with RT and chemotherapy (p = 0.002) (e22).

Hypofractionation and partial breast irradiation

German and international guidelines largely agree in recommending a total radiation dose of 50 Gy in fractions of 1.8 or 2 Gy five times per week as the standard for radiotherapy of breast cancer (7–9). This fractionation has proved effective over a period of decades and provides good cosmetic results without significant functional impairment of the risk organs heart and lungs (e23). In recent years hypofractionation—the administration of higher single doses but a lower total

TABLE 4

Parameters for geriatric evaluation (11, e9, e10)

	Instrument	Parameter and implication
Functional status	Activities of daily life	Ability to get out of bed, wash, dress, and go to the bathroom without assistance
	Instrumental activities of daily life	Preparation and eating of meals, moving around without assistance, cleaning, managing finances, shopping without assistance, taking medication → Evaluation of treatability
Comorbidities and geriatric syndromes	Comorbidity index	Cardiac, cerebrovascular, pulmonary diseases; hypertension; peripheral neuropathy; diabetes; kidney failure; impaired liver function; dementia; delirium; depression; history of falls; neglect; medication abuse; spontaneous fractures → Evaluation of treatment tolerance
Medication	Type and number of medications	→ Evaluation of interactions, e.g., with cytostatics
Cognitive functions	Mini mental status exam	Orientation, retentiveness, attention, memory, speech, reading, writing, copying → Evaluation of ability to cooperate
Emotional status	Geriatric depression scale	Contentment, interests, vitality, emptiness, boredom, energy, helplessness → Evaluation of compliance
Socioeconomic factors	Evaluation of social environment	→ Evaluation whether additional support interventions are required
Nutritional status	Mini nutritional assessment	Measurement of height and weight → Evaluation of weight loss

dose—has been tried out as a way of reducing the number of sessions. Higher individual fractions have a greater biological effect on tumor cells but also on normal tissue, with the risk of more frequent occurrence of dose-limiting late complications (e24). In a number of randomized studies doses of 2.6 to 3.3 Gy have been given three to five times weekly for 3 to 5 weeks, a total of 13 to 16 fractions. To date, hypofractionation with individual doses of up to 3 Gy has shown no increase in long-term adverse effects and no decrease in local tumor control (e25–e28). No definitive conclusions can yet be drawn as to whether and with what risk profile hypofractionated RT is equivalent to the standard treatment. Nevertheless, in the United Kingdom, in Canada, and in the new guidelines of the NCCN hypofractionation is already accepted as an alternative to conventional irradiation (9, e28).

In partial breast irradiation, instead of the whole breast, only the tumor region is irradiated, again with higher single doses and a reduced number of fractions. Various techniques such as brachytherapy and intraoperative or external three-dimensionally planned RT are employed to this end. Several studies have shown that in women with defined risk factors, partial breast irradiation yields tumor control rates comparable to those with conventional RT (reviews: e29, e30). Recently, however, unexpectedly high rates of complications have been reported (e31). The ongoing studies of partial breast irradiation are summarized in *eTable 3*. Because of the lack of sufficient long-term data, partial breast irradiation is not yet recommended for routine

use in German or international guidelines (*eTable 4*) (5–7, e32).

For selected older women, however, both options—hypofractionation and partial breast irradiation—may represent a way of shortening the total duration of treatment. Otherwise, patients in good general condition should receive standard RT following BSS and also after mastectomy in the presence of risk factors such as pT3/4 and extensive lymph node metastases.

Endocrine therapy

Systemic endocrine therapy as laid down in existing guidelines can usually be carried out even in frail older women with hormone-sensitive tumors (LOE 1a/A, AGO recommendation level ++) (2–4, e4), although the anticipated benefit must be weighed against the potential cardiovascular or musculoskeletal complications and the patient's life expectancy. This form of treatment is therefore not discussed further here.

In women with severe comorbidity endocrine therapy represents an alternative to breast surgery (LOE 2b/C, AGO recommendation level +).

Chemotherapy

For chemotherapy too, data for older women are sparse. Of a total of 41 390 women over 65 years of age in the SEER collective, 4500 who had received either polychemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or combination therapy including anthracycline were analyzed retrospectively. In patients with axillary lymph node metastases

TABLE 5

Randomized studies of postoperative radiotherapy after breast-sparing surgery in older women with favorable risk factors

Author	n	Fu	Stadium	Age	Treatment	DFS/BCSS		Overall survival		Local recurrence rate	
Fyles (21)	769	5 years	pT1pN0 ER + PR positive	50–59: 25% 60–69: 30% >70:44%	Breast-sparing surgery	DFS p = 0.004		n. s.		p<0.001	
					Tam Tam + RT	+ RT 91%	– RT 84%	+ RT 93%	– RT 93%	+ RT 0.6%	– RT 7.7%
Hughes (e18)	636	10 years	pT1pN0 ER+PR positive	70–74: 44% ≥ 75: 56%	Breast-sparing surgery	BCSS n. s.		n. s.		p = 0.015	
					Tam Tam + RT	+ RT 98%	– RT 96%	+ RT 63%	– RT 61%	+ RT 2%	– RT 9%
Pötter (e19)	869	4.5 years	pT1–2 pN0 ER+PR positive	50–59: 28% 60–69: 36% >79: 35%	Breast-sparing surgery	DFS p = 0.0021		n. s.		p = 0.0001	
					TAM/An AM/An + RT	+ RT 97.9%	– RT 93.9%	+ RT 97.7%	– RT 96.2%	+ RT 0.5%	– RT 5.1%

Fu, Duration of follow-up DFS, disease-free survival; BCSS, breast cancer-specific survival; n. s., non-significant; Tam, tamoxifen; RT, radiotherapy; An, anastrozole; ER, estrogen receptor; PR, progesterone receptor

and negative hormone receptor status, both tumor-specific survival (HR = 0.72, 95% confidence interval 0.54 to 0.96) and overall survival (HR = 0.65, 95% confidence interval 0.52 to 0.82) were significantly better after chemotherapy than in women who had not received such treatment. This was also true for the subgroup of patients over 70. In contrast, chemotherapy yielded no benefit in node-negative patients with hormone-positive tumors (23, e33).

A similar retrospective analysis by the Cancer and Leukemia Group B (CALGB) confirmed significant ($p < 0.001$) improvements in disease-free survival and overall survival for women receiving optimal chemotherapy, regardless of age. It should be pointed out, however, that only 8% of the patients were over 65 and only 2% over 70 years old. Importantly, toxicity worsened with increasing age (e34).

In a prospective randomized CALGB study, 633 patients—65% of them over 70—were treated with either standard polychemotherapy (CMF), a combination of doxorubicin and cyclophosphamide (AC), or capecitabine alone. While only 62% of patients could complete the planned six cycles of CMF, 80% received all six cycles of capecitabine and 92% received all four cycles of AC. After median follow-up of 2.4 years, the polychemotherapy group showed better tumor-specific survival (HR = 2.09, $p < 0.001$) and overall survival (HR = 1.85, $p = 0.02$). The benefit was greatest in the subgroup of hormone receptor-negative women (HR = 2.62, $p = 0.001$). As expected, monotherapy with capecitabine exhibited the best tolerability, and AC was tolerated better than CMF (17). Other studies also showed that capecitabine had a good and CMF a more unfavorable side effect profile in older women (grade 3 toxicity 17% in patients ≥ 65 versus 7% in patients < 65) (24, e35).

Two further randomized studies compared chemotherapy – epirubicin ($n = 338$) or CMF ($n = 76$) – plus

tamoxifen with tamoxifen alone in node-positive patients. The recurrence rate with tamoxifen alone was significantly higher than with epirubicin plus tamoxifen (relative risk 1.93; $p = 0.005$), although overall 6-year survival was the same (79.1% versus 79.8%) (18). In contrast, addition of CMF to tamoxifen yielded no improvement in disease-free survival (24). Treatment with tamoxifen and epirubicin showed an acceptable toxicity profile (18), while the addition of CMF to tamoxifen led significantly more often to discontinuation of therapy and increased toxicity in patients aged 65 or older (24).

Anthracycline-free treatment regimens may be of interest for older women because of their low cardiotoxicity. In a study carried out in the USA, docetaxel plus cyclophosphamide was significantly better than doxorubicin plus cyclophosphamide with regard to 5-year disease-free survival (81% versus 75%; $p = 0.033$) and overall survival (87% versus 82%; $p = 0.032$). The benefit was the same for patients under 65 ($n = 856$) and those over 65 ($n = 160$). The rate of febrile neutropenia in older patients was twice as high for docetaxel plus cyclophosphamide as for doxorubicin plus cyclophosphamide, and also twice as high as in younger patients (8% versus 4% in each case) (e36).

In a pooled meta-analysis of four randomized (neo-)adjuvant studies ($N > 4500$), regimens including taxanes showed age-dependent differences in treatment postponement (< 60 years 9%, 60–64 years 12.6%, ≥ 65 years 13.7%; $p = 0.001$), dose reduction (5.1%, 6.7%, 8.1%; $p = 0.019$), hospitalization (16.0%, 23.4%, 18.1%; $p < 0.001$), treatment discontinuation (11.8%, 17.2%, 18.7%; $p < 0.001$), and death (0.2%, 0.3%, 1.0%) (e37). Toxicity was lower in sequential administration than in combined administration.

With due consideration of the advantages and disadvantages of chemotherapy, women up to 70 in good general condition should receive the standard

recommended treatment (LOE 1a/A, AGO recommendation level +). While the NCCN guidelines do not advise chemotherapy for women over 70, the AGO recommends it, albeit preferably in studies (LOE 2a/C, AGO recommendation level +). Apart from the treatment regimens recommended in guidelines, the limited toxicity data that are available on older patients permit consideration of anthracycline monotherapy, or alternatively four cycles of either docetaxel/doxorubicin or doxorubicin/cyclophosphamide.

Trastuzumab

Since higher cardiotoxicity in older women cannot be ruled out, most studies on adjuvant therapy with trastuzumab have only included younger postmenopausal women with a normal LVEF (25, e38, e39); patient numbers are too low for analysis of efficacy. Among women under 60, grade 3/4 adverse effects were observed in 14.7% of trastuzumab patients versus 11% in the control group (e40). Age over 60, hypertension requiring treatment, and initial LVEF <55% have been described as risk factors for cardiotoxicity (e41). In the HERA study age over 60 was not a significant risk factor, but diabetes, high body mass index, and hypothyroidism were (e42).

A group of 45 women aged 70 or older with LVEF < 50% was analyzed retrospectively. At 18 months' follow-up there were four cases of symptomatic and eight of asymptomatic cardiotoxicity; all except one were reversible after cessation of treatment (e43). The AGO guidelines recommend that chemotherapy plus trastuzumab be offered to fit older women who have HER2 overexpression (LOE 2b/C, AGO recommendation level +).

Conflict of interest statement

Prof. Sautter-Bühl and Prof. Souchon declare that no conflict of interest exists. Prof. Gerber has received honoraria and reimbursement of travel costs from Roche, Amgen, Sanofi-Aventis, AstraZeneca, Novartis and GlaxoSmithKline.

KEY MESSAGES

- Calendar age alone is not an adequate criterion when deciding whether or not to perform adjuvant therapy. Biological age should be estimated by means of a defined score based on general condition, mental-cognitive status, and comorbidities.
- Frail older women should receive reduced standard treatment. If the risk-benefit analysis is negative, adjuvant therapy (irradiation, chemotherapy, trastuzumab) need not be given.
- Endocrine therapy can be administered in nearly all women with hormone-sensitive tumors.
- Treatment monitoring is obligatory in older women to ensure early detection of any adverse effects.
- All patients should be given the opportunity to enroll in a clinical study.

Manuscript received on 21 April 2010, revised version accepted on 6 September 2010.

Translated from the original German by David Roseveare.

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