

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

Adjuvant Radiotherapy

Adjuvante Radiotherapie (RT)

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **Versions 2002 – 2017:**
**Blohmer / Budach / Friedrichs / Göhring / Janni / Kühn /
Möbus / Scharl / Seegenschmiedt / Souchon / Thomssen /
Untch / Wenz**

- **Version 2018:**
Budach / Huober / Kühn / Wenz

Preliminary Note

- **The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between experts of the AGO and DEGRO**
- **For technical details of radiotherapy we recommend to refer to the corresponding updated DEGRO practical guidelines 2014-2016**

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

Guidelines and Opinions

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:

Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. **Hypofractionated regimens involving 15 or 16 fractions are now widely accepted as standard of care.**

St. Gallen 2015: Gnant M, Breast Care 2015;10:124:

With respect to **hypofractionated** breast irradiation after breast conserving surgery, the panel felt that this is **appropriate for patients aged 50+** without chemotherapy or axillary involvement (89% Yes, 2% No, 9% Abstain), but **also for patients younger than 50 years** (71% Yes, 2% No, 27% Abstain), with uncertainty about patients with prior chemotherapy or axillary lymph node involvement (51% Yes, 18% No, 31% Abstain).

Statement J Harris, Dana Farber, Boston, SABCS 2015, PL1-01:

With regard to **hypofractionated whole breast irradiation**, cosmetic results are clearly better, patient satisfaction is improved, uncertainty about use in nodal RT. **We are using it just in about all (266 cGy x 15 with boost in about ½).**

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation



© AGO e. V.
in der DGGG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2018.1

- Radiotherapy of the affected breast
- Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)
- Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)
- In case of life expectancy <10 years and pT1, pN0, R0, ER/PR positive, HER2 negative, endocrine therapy (all criteria) radiotherapy can be omitted after individual counseling accepting an increased risk of in breast recurrence

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
1a	B	+
1a	B	+

Additional Information with Regard to Effects of Breast Radiotherapy (BCT)

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **Hypofractionation:**
 - „Some normal tissue effects were less common after the 15 fraction regimen than the control schedule (breast shrinkage, telangiectasia, and breast oedema).“
 - In 1 of 5 trials: “There were significantly fewer distant relapses up to 10 years in the 40 Gy group (HR 0.74, 95% CI 0.59–0.94), which contributed to the significantly higher rates of disease-free survival and overall survival in the 40 Gy group compared with the 50 Gy group.“ ($HR_{OS}=0.8$; $p=0.042$)
(*START B: Haviland JS et al. Lancet Oncol 2013; 14: 1086–94*)

- **Elderly patients should be advised about the following :**
 - In older patients with pT1-2 (≤ 3 cm) pN0 hormone receptor-positive breast cancer, breast irradiation for breast conserving therapy is able to reduce the risk of a local recurrence by about 8% over 10 years. A benefit with regard to metastasis-free survival and overall survival has not been found yet.

BCS $\geq 70y$ $< 4cm$ cN0 : Tamoxifen vs. Tamoxifen + RT

Time: 1994-1999, since 8/1996 only pT1cN0 ER/PR+ or unknown allowed

@10 yrs (95% C.I.)	Tamoxifen	Tamoxifen plus Radiotherapy	Hazard Ratio
Local recurrence-free ($\Delta=8\%$)	90% (85%-93%)	98% (96%-99%)	HR=0.18 (95% CI, 0.07 to 0.42; P < .001)
Mastectomy-free	96% (93% - 98%)	98% (96% - 99%)	HR=0.50 (95% CI, 0.17 to 1.48; n.s.)
Distant metastasis-free	95% (91% - 97%)	95% (92% - 97%)	HR=1.20 (95% CI, 0.63 to 2.32; n.s)
Overall survival	66% (61% - 71%)	67% (62% - 72%)	HR=0.95 (95% CI, 0.77 to 1.18; n.s.)

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1



Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **Boost-RT (improves local control, no survival benefit)**
 - Premenopausal
 - Postmenopausal, if >T1[#], G3, HER2-positive, triple negative, EIC (at least 1 factor)
- **Intraoperative irradiation (intraop. APBI)**
 - As boost-irradiation followed by WBI
 - As sole radiotherapy modality (IORT 50 kV, IOERT)**
 - >50 years**
 - >70 years**
- **Postoperative partial breast irradiation as sole radiotherapy modality (APBI)**
 - Interstitial brachytherapy
 - >70 years**
 - Intracavity balloon technique
 - IMRT***

Oxford		
LoE	GR	AGO
1b	B	++
2b	B	+
2a	B	+
1a	A	+/-*
1a	A	+
1b	B	+/-*
1b	B	+
2b	B	-*
2b	B	-*

* Study participation recommended;

** only for pT1 pN0 R0 G1-2, HR+, non-lobular, no extensive DCIS, IORT during first surgery;

*** no long term data

continuous parameter with regard to risk of relapse

EORTC 22881-10882: Boost vs no Boost (Endpoint: Ipsilateral Breast Recurrence)

@20 yrs (95% C.I.)	Boost (n=2.661)	No boost (n=2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ =-1.4%)	59.7% (56.3–63.0)	61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Ipsilateral Breast Tumour Recurrence			
All patients	12.0% (9.8–14.4)	16.4% (14.1–18.8)	HR=0.65 (0.52–0.81); p<0.0001
≤40 years (Δ =11.6%)	24.4% (14.9–33.8)	36.0% (25.8–46.2)	HR=0.56 (0.34–0.92); p=0.003
41–50 years (Δ =5.9%)	13.5% (9.5–17.5)	19.4% (14.7–24.1%)	HR=0.66 (0.45–0.98); p=0.007
51–60 years (Δ =2.96%)	10.3% (6.3–14.3)	13.2% (9.8–16.7)	HR=0.69 (0.46–1.04); p=0.020
>60 years (Δ =3.0%)	9.7% (5.0–14.4)	12.7% (7.4–18.0)	HR=0.66 (0.42–1.04); p=0.019

(Median F/U 17.2 y)

acc. to: Bartelink et al. Lancet Oncol 2015; 16: 47–56

EORTC 22881-10882: Boost vs no Boost (Endpoint: Any First Recurrence)

@15 yrs/20 yrs (95% C.I.)	Boost (n=2.661)		No boost (n=2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ = - 1.4%)	59.7% (56.3–63.0)		61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Any First Recurrence				
All patients (Δ ≥4%)	@15y @20y	28.1% 32,8%	32.1% 38.7%	HR=0.92 (0.81-1.04), n.s.
≤40 years (Δ >6%)	@15y @20y	41.5% 49.5%	48.1% 56.8%	HR=0.80 (0.56-1.15) , n.s.
41–50 years	@15y @20y	34.0% 38.6%	35.6% 44.2%	HR=0.91 (0.71-1.16), n.s.
51–60 years	@15y @20y	28.5% 34.7%	28.7% 36.2%	HR=0.96 (0.76-1.21), n.s.
>60 years	@15y @20y	27.4% 32.1%	29.1% 32.8%	HR=0.94 (0.74-1.19), n.s.

(Median F/U 17.2 y)

acc. Bartelink et al. Lancet Oncol 2015; 16: 47–56. Suppl.

Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **> 3 tumor infiltrated lymph nodes (Lnn.)**
- **1–3 tumor infiltrated Lnn. (high risk)**
- **1–3 tumor infiltrated Lnn. (low risk*)**
- **T3 / T4**
 - **pT3 pN0 R0 (and no additional risk factors)**
- **If R0 is impossible to reach (for invasive tumor)**
- **In young pts with high risk features**

The indications for PMRT and regional RT are independent of adjuvant systemic treatment

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	+
5	D	+/-
1a	A	++
2b	B	+/-
1a	A	++
2b	B	++
1a	A	



Radiotherapy of the Chest Wall After Mastectomy (PMRT) in Case of 1-3 Axillary Lymph Node Metastases

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

PMRT
can be omitted
LoE 3b B AGO +

PMRT
to be discussed
LoE 3b B AGO +/-

PMRT
recommended
LoE 3b B AGO +

ER pos, G1, HER2 neg, pT1
(at least 3 criteria present)

Kyndi et al. 2013

Applies for patients, who don't fulfill the mentioned criteria for high or low risk

≥45 y. AND >25% pos. ax. Lnn in case of axillary dissection OR
<45 y. AND (ER neg. OR >25% pos. ax. Lnn in case of axillary dissection OR medial tumor location)

Truong et al. 2005

<40 y. OR
HER2 pos. OR
lymphovascular invasion

Shen H et al. 2015

G3 OR
lymphovascular invasion OR
triple negative

Different publications

Comment: In case of an indication for radiotherapy of regional lymph nodes, radiotherapy of the chest wall should also be administered

Radiotherapy of the Axilla

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **Tumor residuals after axillary dissection**
- **Sentinel node negative**
- **Axillary dissection not indicated**
e.g. cN0, SLN pos. (see chapter surgery)
- **Extracapsular tumor spread (ECS)**
- **Axillary micrometastases or isolated cells found in regional lymph nodes**

Oxford		
LoE	GR	AGO
5	D	++
1b	B	--
2a	B	-
2b	B	-
1b	B	--

Axillary Interventions in Patients with Positive Sentinel Lymph Nodes

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

1-2 pos. SLN: Axillary dissection or RT of the axilla

- If BCT and ACOSOG Z011-criteria fulfilled
 - No axillary treatment
- If mastectomy, PMRT indicated and ACOSOG Z011-criteria fulfilled
 - No further axillary treatment
- If BCT and ACOSOG Z011-criteria not met
- If mastectomy: PMRT and ACOSOG Z011-criteria not met, or PMRT not planned

≥ 3 pos. SLN

- Axillary dissection
- Radiotherapy of the axilla

	Oxford		
	LoE	GR	AGO
■ If BCT and ACOSOG Z011-criteria fulfilled	1b	B	+/-*
■ No axillary treatment	1b	B	+/-
■ If mastectomy, PMRT indicated and ACOSOG Z011-criteria fulfilled	5	D	+/-*
■ No further axillary treatment	5	D	+/-
■ If BCT and ACOSOG Z011-criteria not met	1b	B	++*
■ If mastectomy: PMRT and ACOSOG Z011-criteria not met, or PMRT not planned	1b	B	++
■ Axillary dissection	1b	B	++
■ Radiotherapy of the axilla	1b	B	+

* Study participation recommended

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG)



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

RT to supra-/infraclavicular lymphatic regions

- **≥ pN2a or level III involved**
- **pN1a high risk***
 - *tumor central or medial and (G2-3 or ER/PgR-negative)
 - *tumor lateral and premenopausal and (G2-3 or ER/PgR-negative)
- **pN0 high risk** with central or medial tumors**
 - ** premenopausal and G2-3 and ER/PgR-negative

Oxford		
LoE	GR	AGO
1b	A	++
2a	B	+
2a	B	+/-

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

Internal mammary lymph node region (IMN)

- **pN0 high risk*** with central or medial tumor**

***premenopausal and G2-3 and ER/PgR-negative

- **pN1a high risk***

*tumor central or medial, and (G2-3 or ER/PgR-negative)

*tumor lateral and premenopausal and (G2-3 or ER/PgR-negative)

- **pN2a high risk****

**G2-3 or ER/PgR-negative

- **pN1b-c, pN2c, pN3b**

- **IMC-RT, if cardiac risk factors are present
or if trastuzumab is given**

	Oxford		
	LoE	GR	AGO
pN0 high risk*** with central or medial tumor	1b	B	+/-
pN1a high risk*	2a	B	+
pN2a high risk**	2a	B	+
pN1b-c, pN2c, pN3b	2a	B	+
IMC-RT, if cardiac risk factors are present or if trastuzumab is given	2b	A	--

Fractionation of Radiotherapy in Case of Radiotherapy of the Regional Lymph Nodes



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **Conventionally fractionated radiotherapy
(total dose about 50 Gy in approx. 25-28 fractions
in about 5-6 weeks)**
- **Hypofractionated radiotherapy
(total dose approximately 40 Gy in 15-16 fractions
within 3-5 weeks)**

Oxford		
LoE	GR	AGO
1a	A	++
2b	B	+/-

Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

(median follow-up 10.9 yrs)

Adjuvant treatment	n*	Hazard ratio (95%CI)
No adjuvant reported	625	0.91 (0.59 - 1.39)
Chemotherapy	954	1.05 (0.84 - 1.32)
Endocrine therapy	1185	0.82 (0.63 - 1.06)
Both (endocrine th. and chemotherapy)	1200	0.72 (0.55 - 0.94)
Total	4004	0.88 (0.76 - 1.01)

* missing data on 40 patients

www.ago-online.de

**FORSCHEN
LEHREN
HEILEN**

Poortmans et al. ECCO Amsterdam 2013

Radiotherapy following NACT

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

Pretreatment	Posttreatment	RT-BCS	PMRT	RT-RN
Locally advanced	pCR / no pCR	yes	yes	yes
cT1/2 cN1+	ypT1+ o. ypN1 + (no pCR)	yes	yes	yes
cT1/2 cN1+	ypT0/is ypN0	yes	Increased risk of relapse ¹	
cT1/2 cN0 (Sonogr.bligat)	ypT0/is ypN0	Ja	nein	nein

Oxford		
LoE	GR	AGO
1a/1a/1a	A/A/A	++/++/++
1a/2b/2b	A/B/B	++/+/+
2b/2b/2b	B/B/B	+/+/+
2b/2b/2b	A/B/B	+/-/-

Locally advanced: T3-4 or cN2-N3,

BCS: Breast conserving surgery, PMRT: Post mastectomy radiotherapy, RN: Regional nodes

¹ Criteria for increased risk of relapse:

- pN0 premenopausal high risk: central or medium tumor localization, and (G2-3 and ER/PgR-negative)
- pretreatment pN1a/ cN+* high risk: central or medium tumor localization and (G2-3 or ER/PgR-negative) or premenopausal, lateral tumor localization and (G2-3 or ER/PgR-negative)

* = confirmed by core biopsy

Concomitant Use of Systemic Therapy with Radiotherapy

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1

- **Trastuzumab* concurrent with radiotherapy**
- **Tamoxifen concurrent with radiotherapy**
- **AI (letrozole, anastrozole) concurrent with radiotherapy**

Oxford		
LoE	GR	AGO
2b	B	+
2b	B	+
2b	B	+

* In HER2 pos. tumors parasternal RT should generally be avoided; no concurrent trastuzumab should be avoided in parasternal RT

Interaction between Smoking and Risk of Irradiation-induced Side Effects

Oxford		
LoE	GR	AGO
1a	A	
		++
		++

- Enhanced risk of lung cancer secondary to breast cancer radiotherapy in smokers
- Inform patients about the risk
- Recommend to stop smoking

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2018.1