



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Adjuvant Radiotherapy

Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2018:**
**Blohmer / Budach / Friedrichs / Göhring / Huober/
Janni / Kühn / Möbus / Scharl / Seegenschmiedt /
Souchon / Thomssen / Untch / Wenz**
- **Version 2019:**
Budach / Rody / 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**

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HEILEN**

Guidelines and Opinions

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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

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- 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)

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- **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.)

Hughes KE et al J Clin Oncol 2013; 31:2382-2387

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

Oxford		
LoE	GR	AGO

- **Boost-RT (improves local control, no survival benefit)**

- Premenopausal
- Postmenopausal, if >T1[#], G3, HER2-positive, triple negative, EIC (at least 1 factor)

1b	B	++
2b	B	+

- **Intraoperative irradiation (intraop. APBI)**

- As boost-irradiation followed by WBI
- As sole radiotherapy modality (IORT 50 kV, IOERT)**
 - >50 years**
 - >70 years**

2a	B	+
1a	A	+/-*
1a	A	+

- **Postoperative partial breast irradiation as sole radiotherapy modality (APBI)**

- Interstitial brachytherapy
 - >70 years**
- Intracavity balloon technique
- IMRT***

* Study participation recommended;

1b	B	+/-*
1b	B	+
2b	B	-*
2b	B	-*

** 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 ($\Delta \geq 4\%$)	@15y @20y	28.1% 32,8%	32.1% 38.7%	HR=0.92 (0.81-1.04), n.s.
≤ 40 years ($\Delta > 6\%$)	@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

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- > 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	

* For definition of risk, go to next slide Radiotherapy of the Chest Wall After Mastectomy (PMRT)

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

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PMRT
can be omitted
LoE 3b B AGO +

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

Kyndi et al. 2013

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

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

PMRT
recommended
LoE 3b B AGO +

≥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

Boost in PMRT

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- **An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival¹**
- **An additional boost irradiation to a part of the chest wall should be given in case of of R1/R2-resection, if a secondary resection is not feasible²**
- **In case of extention of the tumor to the pectoral resection margin, but no clinical signs of extention beyond the fascia, the resection margin should be regarded as R0 (provided, that the pectoral fascia was resected). A boost radiotherapy is not required in this situation²**

Oxford		
LoE	GR	AGO
2a	B	
5	D	++
5	D	++

Radiotherapy of axillary lymph node dissection or negative sentinel node biopsy



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- Tumor residuals after axillary dissection
- Sentinel node negative
- Extracapsular tumor spread (ECS)
- Axillary micrometastases or isolated cells found in regional lymph nodes

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

Radiotherapy of axillary lymph nodes in patients with positive sentinel-lymph nodes**, who did not undergo axillary dissection

	Oxford		
	LoE	GR	AGO
BCS and ACOSOG Z0011-criteria⁺ met			
▪ Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)	2b	B	+*
BCS and ACOSOG Z0011-criteria⁺ <u>not</u> met			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	++*
ME and chest wall RT indicated and ACOSOG Z0011-criteria⁺ <u>not</u> met or ME and chest wall RT <u>not</u> planned			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	++
<u>>=3 pos. SLN</u>			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	+

* = Study participation recommended

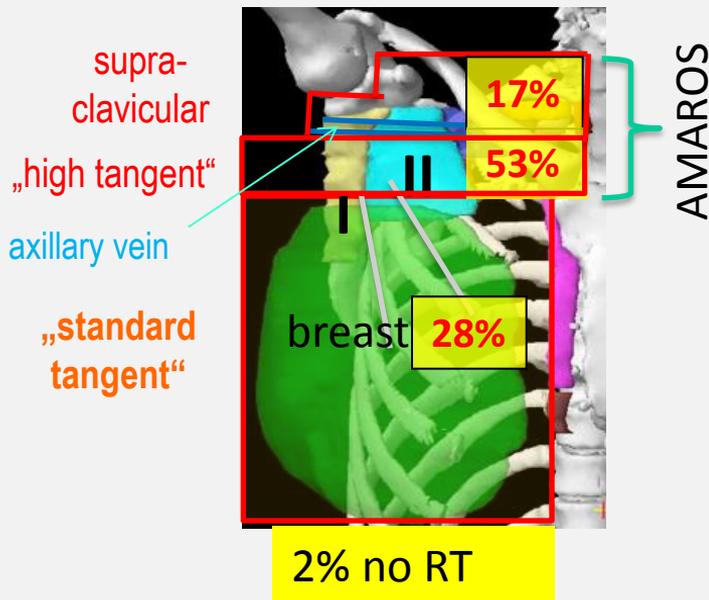
** = Macrometastases

⁺ = <T3, no palpable LN, R0, 1-2 positive SN, no extracapsular extension, no NACT

Dose in the axillary LN-levels I + II using different RT-techniques

ACOSOG Z0011 Trial
45% micrometast. in the exp. Arm

RT-volume
% of patientis



	mean dose*	encompassed volumen**
LN level 1		
AMAROS	>95%	>95%
high tangent	86%	79%
standard tangent	66%	51%
IMRT ⁺	29%	1%
LN-level 2		
AMAROS	>95%	>95%
high tangent	71%	51%
standard tangent	44%	26%
IMRT ⁺	7%	0%

* in relation to the prescribed dose in the breast

** % volume receiving the prescribed dose

+ Lee et al. Medicine 2016 (3)

Data from 228/856 pat.

Jagsi (2): “The results of Z0011 should not be extrapolated to patients who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included”

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



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RT to supra-/infraclavicular lymphatic regions

- **≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in the supra/infraclavicular LN**
- **1-3 positive axillary lymph nodes¹ in case of**
- central or medial tumor and G2-3 or ER/PgR-negative
- premenopausal patient and G2-3 or ER/PgR-negative
- **pN0 with central or medial tumors, if premenopausal and G2-3 and ER/PgR-negative**

	Oxford		
	LoE	GR	AGO
▪ ≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in the supra/infraclavicular LN	1b	A	++
▪ 1-3 positive axillary lymph nodes¹ in case of - central or medial tumor and G2-3 or ER/PgR-negative - premenopausal patient and G2-3 or ER/PgR-negative	2a	B	+
▪ pN0 with central or medial tumors, if premenopausal and G2-3 and ER/PgR-negative	2a	B	+/-

¹ not applicable for micrometastases

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



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Internal mammary lymph node region (IMN)

- **pN0 high risk with central or medial tumor and premenopausal and G2-3 and ER/PgR-negative**
- **1–3 positive axillary lymph nodes¹ in case of
- central or medial tumor and G2-3 or ER/PgR-negative
- premenopausal patient and G2-3 or ER/PgR-negative**
- **≥ 4 positive axillary lymph nodes**
- **involved internal mammary lymph nodes**
- **In case of cardiac risk factors or trastuzumab is given**

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

¹ not applicable for micrometastases

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

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- **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

(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

Poortmans et al. ECCO Amsterdam 2013

Radiotherapy following NACT

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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

Molecular prediction of radiotherapy

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- results of gene expression profiling (e.g. TAILOR RT, IDEA) should not used for indication of radiotherapy

Oxford		
LoE	GR	AGO
2b	A	++

Use of Systemic Therapy with concomitant locoregional Radiotherapy

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- **trastuzumab/pertuzumab* and concurrent radiotherapy**
- **T-DM1**
- **Tamoxifen and concurrent radiotherapy**
- **AI (letrozole) and concurrent radiotherapy**
- **Checkpointinhibitors**
- **Capecitabine**

	Oxford		
	LoE	GR	AGO
	1a	A	++
	1b	A	+
	2b	B	+
	2b	B	+
	3b	C	+
	2b	B	+

* concurrent trastuzumab and parasternal radiotherapy should be avoided

Interaction between Smoking and Risk of Irradiation-induced Side Effects

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

Oxford		
LoE	GR	AGO
1a	A	
		++
		++