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Adjuvant Radiotherapy

Adjuvant Radiotherapy (RT)

- **Versions 2002–2015:**
  Blohmer / Budach / Friedrichs / Göhring / Janni / Kühn / Möbus / Scharl / Seegenschmiedt / Souchon / Thomssen / Untch / Wenz

- **Version 2016:**
  Thomssen / Budach / Wenz

- **Version 2017:**
  Blohmer / Budach / Scharl / Wenz

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Further Information

References

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**
- **If agreement had not been reached in any statement, the corresponding DEGRO view is written in blue color**

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Guidelines and Opinions

St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:
Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. **Hypofractioned 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).

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Further Information

References

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

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	Oxford LoE	/ AGO GR	
➢ Radiotherapy of the affected breast	1a	A	++
➢ Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
➢ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)	1a	B	+
➢ 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	1a	B	+

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

- **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 >=70y <4 cm 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 (Δ=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

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	Oxford / AGO LoE	GR	
➢ **Boost-RT (improves local control, no survival benefit)**			
➢ Premenopausal	1b	B	++
➢ Postmenopausal, if >T1, G3, HER2-positive, triple negative, EIC (at least 1 factor)	2b	B	+
➢ **Intraoperative irradiation (intraop. APBI)**			
➢ As boost-irradiation followed by WBI	2a	B	+
➢ As sole radiotherapy modality (IORT 50 kV, IOERT)**			
➢ >50 years**	1a	A	+/-*
➢ >70 years**	1a	A	+
➢ **Postoperative partial breast irradiation as sole radiotherapy modality (APBI)**			
➢ Interstitial brachytherapy	1b	B	+/-*
➢ >70 years**	1b	B	+
➢ Intracavity balloon technique	2b	B	-*
➢ IMRT***	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

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

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@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 Tumor 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

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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.

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Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

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	Oxford / AGO LoE	GR	
➢ > 3 tumor infiltrated lymph nodes (Lnn.)	1a	A	++
➢ 1–3 tumor infiltrated Lnn. (high risk)	1a	A	+
➢ 1–3 tumor infiltrated Lnn. (low risk*)	5	D	+/-
➢ T3 / T4	1a	A	++
➢ pT3 pN0 R0 (and no additional risk factors)	2b	B	+/-
➢ If R0 is impossible to reach (for invasive tumor)	1a	A	++
➢ In young pts with high risk features	2b	B	++
➢ After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+ (CNB/FNA), cT3/4a-d)	2a	B	+
➢ Omission of RT if ypT0 ypN0 after NACT**	2b	B	+/-
The indications for PMRT and regional RT are independent of adjuvant systemic treatment	1a	A	

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*For definition of risk, go to Further information

**Study participation recommended

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	PMRT to be discussed	PMRT recommended
LoE 3b B AGO +	**LoE 3b B AGO +/-**	**LoE 3b B AGO +**
ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)	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)
Kyndi et al. 2013		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

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References

Radiotherapy of the Axilla

	Oxford / AGO LoE	GR	
➢ Tumor residuals after axillary dissection	5	D	++
➢ Sentinel node negative	1b	B	- -
➢ Axillary dissection not indicated e.g. cN0, SLN pos. (see chapter surgery)	2a	B	-
➢ Extracapsular tumor spread (ECS)	2b	B	-
➢ Axillary micrometastases or isolated cells found in regional lymph nodes	1b	B	- -

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Axillary Interventions in Patients with Positive Sentinel Lymph Nodes

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	Oxford / AGO LoE	GR	
1-2 pos. SLN: Axillary dissection or RT of the axilla			
➢ 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 Z0011-criteria not met, or PMRT not planned	1b	B	++
>=3 pos. SLN:			
➢ Axillary dissection	1b	B	++
➢ Radiotherapy of the axilla	1b	B	+

*Study participation recommended

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

RT to supra-/infraclavicular lymphatic regions	Oxford /AGO LoE	GR	
➢ ≥pN2a or level III involved	1b	A	++
➢ 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)	2a	B	+
➢ pN0 high risk** with central or medial tumors ** premenopausal and G2-3 and ER/PgR-negative	2a	B	+/-
➢ After NACT/NAT (indications as for PMRT) AGO[1]	2b	B	+/-
➢ After NACT/NAT if cN+ (CNB/FNA) (ind. as for PMRT) DEGRO[1]	2b	A	+

[1] Different interpretation of published data by AGO and DEGRO

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

Internal mammaria lymph node region (IMN)	Oxford LoE	/AGO GR	
➢ pN0 high risk*** with central or medial tumor	1b	B	+/-
***premenopausal and G2-3 and ER/PgR-negative			
➢ pN1a high risk*	2a	B	+
*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**	2a	B	+
**G2-3 or ER/PgR-negative			
➢ pN1b-c, pN2c, pN3b	2a	B	+
➢ IMC-RT, if cardiac risk factors are present or if trastuzumab is given	2b	A	--
➢ After NACT/NAT (indications as for PMRT) AGO[1]	2b	B	+/-
➢ After NACT/NAT if cN+ (CNB/FNA) (ind. acc. PMRT) DEGRO[1]	2b	A	+

[1] Different interpretation of published data by AGO and DEGRO

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

Guidelines Breast
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	Oxford / AGO LoE /GR	
➢ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)	1a A	++
➢ Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)	2b B	+/-

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

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(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

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Concomitant Use of Systemic Therapy with Radiotherapy

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	Oxford / AGO LoE / GR
➢ **Trastuzumab* concurrent with radiotherapy**	**2b B +**
➢ **Tamoxifen concurrent with radiotherapy**	**2b B +**
➢ **AI (letrozole, anastrozole) concurrent with radiotherapy**	**2b B +**

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

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Interaction between Smoking and Risk of Irradiation-induced Side Effects

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	Oxford / AGO LoE / GR	
➢ Enhanced risk of lung cancer secondary to breast cancer radiotherapy in smokers	1a	A
➢ Inform patients about the risk		++
➢ Recommend to stop smoking		++

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Further Information

References