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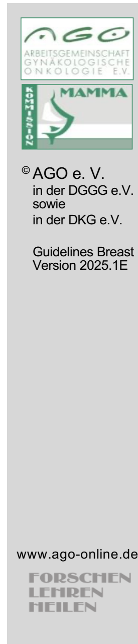
Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Adjuvant Radiotherapy



Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2024:**
  Blohmer / Budach / Friedrich / Friedrichs / Göhring / Huober / Janni / Krug / Kühn / Möbus / Rody / Scharl / Schmidt / Seegenschmiedt / Solbach / Souchon / Thomssen / Untch / Wenz

- **Version 2025:**
  Budach / Krug / Thomssen

Search Strategy
Search Terms: Radiotherapy Breast Cancer
Source: Pubmed 1/2010 – 1/2024

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials.

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Lancet. 2023 Nov 25;402(10416):1991-2003.

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

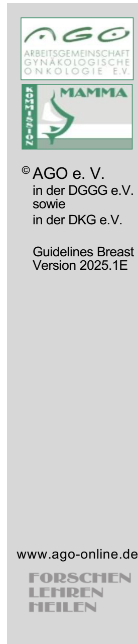
1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Lancet. 2014 Jun 21;383(9935):2127-35.

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, et al. Lancet. 2011 Nov 12;378(9804):1707-16.

Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, et al. Natl Cancer Inst Monogr. 2010;2010(41):162-77.



Preliminary Note

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

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10. Krug D, Baumann R, Combs SE, et al (2021) Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. Strahlenther Onkol 197:269–280.
11. Strnad V, Krug D, Sedlmayer F, et al (2020) DEGRO practical guideline for partial-breast irradiation. Strahlenther Onkol 196:749–763.
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Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation

	Oxford LoE	Oxford GR	AGO
Radiotherapy of the affected breast	1a	A	++
Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week)	1b	B	+/-
Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 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, resulting in an increased risk for in-breast recurrence without imparing survival.	1a	B	+

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Moderate Hypofractionation

1. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
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12. Meattini I, Becherini C, Boersma L et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 2022;23(1):e21-e31.

Ultra-Hypofractionation

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Elderly patients with low-risk features

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Randomized controlled trials of radiotherapy omission after breast-conserving surgery in early breast cancer

Trial	N	Time-frame	Inclusion criteria	Follow up	Local recurrence (no RT)	Local recurrence (RT)	Hazard ratio
Toronto-British Columbia	769	1992-2000	≥ 50 years, T1/2 N0 R0 (ink) 80% HR+	5 y 8 y	7.7% 17.6%	0.6% 3.5%	8.3
BASO-II	204	1992-2000	< 70 J., T1, G1 L0	5 y	0.8% p.a.	0.2% p.a.	7.34
CALGB 9343	636	1994-1999	≥ 70 years, T1 (98%) cN0 ER+ (97%), R0 (ink)	5 y 10 y	4% 8%	1% 2%	5.55
ABCSG-8A	831	1996-2004	Postmenopausal T ≤ 3 cm N0, G1/2, ER+ and/or PR+	5 y 10 y	5.1% 7.5%	0.4% 2.5%	10.2
PRIME II	1326	2003-2009	≥ 65 years, T ≤ 3 cm N0, ER+ and/or PR+, R0 (≥1 mm)	5 y 10 y	4.3% 9.8%	1.3% 0.9%	10.4

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Prospective observational studies of radiotherapy omission incorporating tumor biology and MRI

Trial	N	Time-frame	Inclusion criteria	Follow up	Local recurrence (95%-CI)
LUMINA	500	2013-2017	≥ 55 years, pT1 pN0 R0 (≥1 mm) **ER ≥1% PR ≥20% HER2 neg. Ki67 ≤ 13.25% (central lab)**	5 y	2.3% (1.2-4.1%)
IDEA	200	2015-2018	50-69 years, pT1 pN0 R0 (≥2 mm) **ER/PR pos. HER2 neg., Oncotype Dx RS ≤ 18**	5 y	50-59 y. 3.3% 60-69 y. 3.6%
PROSPECT	201	2011-2019	≥50 years, unifocal cT1 cN0, no LVI, no EIC, R0 (≥2 mm), ER/PR pos. and/or HER2-pos., **preoperative breast MRI**	5 y	1.0% (-5.4%)

- Discussion:
  - Confidence intervals of local recurrence (LR) rates overlap with control arms of previous trials.
  - Uncontrolled trials with limited follow up.
  - CALGB 9343 and PRIME II showed a doubling LR rates after 10 years vs. 5 years in the control arms and an increasing benefit of radiotherapy with longer follow-up.
  - In PRIME II, low ER expression was associated with an increased LR rate in the control arm.
  - Compliance for endocrine therapy was higher than expected in clinical routine.

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

	Oxford LoE	Oxford GR	AGO
▪ **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	+
▪ **Techniques**			
▪ Percutaneous boost (photons, electrons) as sequential boost	1a	A	++
▪ Multicatheter brachytherapy-boost	1a	A	++
▪ Percutaneous boost as simultaneous integrated boost (with conventionally fractionated whole-breast irradiation)	1b	B	+
▪ Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation)	1b	B	++
▪ Intraoperative boost irradiation (followed by whole-breast irradiation)	2b	B	+
▪ Intraoperative clip placement at the tumor bed if boost irradiation is indicated	2b	B	+

* continuous parameter with regard to risk of relapse

Boost in general (EBRT/Brachytherapy, sequential)

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Boost-RT in premenopausal p.
Boost-RT in postmenopausal p.

1. Bartelink H, Maingon P, Poortmans P et al; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):47-56. Including Supplementary appendix.
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Simultaneous-integrated boost (conventionally fractionated RT)

1. Hörner-Rieber J, Forster T, Hommertgen A et al. Intensity-modulated radiotherapy (IMRT) with simultaneously integrated boost shortens treatment time and is non-inferior to conventional radiotherapy followed by sequential boost in adjuvant breast cancer treatment: results of a large randomized phase III trial (IMRT-MC2 trial). Int J Radiat Oncol Biol Phys. 2020 Dec 12:S0360-3016(20)34651-4.
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5. Bantema-Joppe EJ, Schilstra C, de Bock GH, et al (2012) Simultaneous integrated boost irradiation after breast-conserving surgery: physician-rated toxicity and cosmetic outcome at 30 months' follow-up. Int J Radiat Oncol Biol Phys 83:e471–7.

Simultaneous-integrated boost (hypofractionated RT)

1. Paelinck L, Gulyban A, Lakosi F, et al (2017) Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation? A randomized controlled trial. Radiother Oncol 122:30–36.
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cancer, early toxicities of a randomized clinical trial. Radiat Oncol 7:80–10.

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Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI

1. Ciabattoni A, Gregucci F, Fastner G et al. IOERT versus external beam electrons for boost radiotherapy in stage I/II breast cancer: 10-year results of a phase III randomized study. Breast Cancer Res. 2021;23(1):46.
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IOERT in early stage breast cancer (HIOB): First results of a prospective multicenter trial (NCT01343459). Radiother Oncol. 2020 May;146:136-142.

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Clip placement

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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

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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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Moderate hypofractionation with simultaneous-integrated boost

	RTOG 1005 (ASTRO 2022)	IMPORT-HIGH (Lancet 2023)	HYPOSIB (ASTRO 2024)
Patient number	2262	2617	2179
Schedule Breast	40 Gy in 15 fx	36 Gy in 15 fx 40 Gy in 15 fx	40 Gy in 16 fx
Schedule Boost	48 Gy in 15 fx	48 Gy in 15 fx	48 Gy in 16 fx
Primary endpoint	Ipsilateral in-breast recurrence HR 1.32 (0.8-2.1) → Non-inferiority for SIB	Ipsilateral in-breast recurrence HR 1.04 (0.56-1.92) → Non-inferiority for SIB	Disease-free survival HR 1.10 (0.78-1.54) → Non-inferiority for SIB
Toxicity	Toxicity grade ≥3 (ROTG) p = 0.79	Any moderate / marked breast AE p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB)	No significant difference for grade ≥2 skin toxicity, fibrosis, teleangiectasia, nausea, hot flashes, pain

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Partial Breast Irradiation (PBI) after Breast Conserving Surgery (Invasive Cancer)*

	Oxford LoE	GR	AGO
▪ Eligible patients: Age ≥50 years, Tumor < 3 cm, pN0, ER/PgR pos.**, HER2 neg., G1-2**, L0 R0, non-lobular histology, no BRCA-mutation known			
▪ Postoperative partial breast irradiation			
▪ Interstitial Multicatheter-Brachytherapy	1b	A	+
▪ Intracavitary balloon-technique	2b	B	-
▪ Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 1.5 weeks)	1b	A	+
▪ 3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks)	1b	A	++
▪ 3D-conformal radiotherapy (10 x 3.85 Gy in 1 week)	1b	A	-
▪ Intraoperative Radiotherapy (IORT 50 kV, IOERT)			
▪ As sole radiotherapy, during first breast surgery	1b	A	+/-
▪ Intraoperative clip placement at the tumor bed if partial breasst irradiation is indicated	2b	B	+

*Definition of the target volume and practical procedures see the related DEGRO practical guidelines.
**Individual decision for PBI is possible, if one of the criteria is not met.

General guidelines

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Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)

Interstitial brachytherapy

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Intracavity balloon technique

1. Benitez PR, Keisch ME, Vicini F, et al:. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. Am J Surg. 2007 Oct;194(4):456-62.

IMRT (5x6 Gy)

1. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer. 2015 Jan 17. pii: S0959-8049(15)00002-7.
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3D-conformal RT (15x2.67 Gy over two weeks)

1. Coles CE, Griffin CL, Kirby AM et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet. 2017 Sep 9;390(10099):1048-1060.
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3D-conformal RT (10x3.85 Gy over one week)

1. Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol. 2013 Nov 10;31(32):4038-45.

2. Whelan TJ, Julian JA, Berrang TS et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet. 2019 Dec 14;394(10215):2165-2172.
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Intraoperative irradiation (IORT/IOERT)

1. Vaidya JS, Bulsara M, Baum M et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ. 2020 Aug 19;370:m2836.
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6. Halima A, Fane L, Parker S, et al (2024) Intraoperative Radiation Therapy for Early-Stage Breast Cancer: Updated Outcomes from a Single-Institution Experience. Ann Surg Oncol 31:931–935.
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Conserving Therapy: A Large Mature Single Institution Matched-Pair Evaluation of True Local Relapse, Progression Free Survival, and Overall Survival. Int J Radiat OncolBiolPhys 116:757–769.

Clip placement

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Meta-analyses on partial-breast irradiation

Meta-analysis of 13 studies with 15,561 patients comparing partial breast irradiation (PBI) and whole-breast irradiation (WBI), median follow-up 8.6 years; Odds Ratio (95%-confidence interval)

	Overall	**EBRT**	**EBRT/BT**	**BT**	**IORT**	**Absolute diff.**
Local recurrence (primary site)	1.01 (0.65-1.59)	0.85 (0.52-1.39)	0.84 (0.56-1.27)	0.87 (0.25-3.02)	**3.51 (1.36-9.11)**	+0.02%
Local recurrence (elswhere)	**2.21 (1.53-3.20)**	**2.26 (1.12-4.55)**	**2.07 (1.31-3.27)**	7.88 (0.42-146)	3.06 (0.1-91.59)	+0.64%

Meta-analysis of 11 studies with 15,438 patients comparing partial breast irradiation (PBI) and whole-breast irradiation (WBI); Hazard Ratio (95%-confidence interval)

	Overall	**EBRT**	**EBRT/BT**	**BT**	**IORT**
Overall survival	1.02 (0.89-1.16)	1.06 (0.83-.37)	1.10 (0.90-1.35)	0.64 (0.36-.12)	0.95 (0.72-1.24)

EBRT = external beam RT; BT = brachytherapy, IORT = intraoperative RT; EBRT/BT = both techniques were allowed on trial

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Comparison of different techniques for partial breast irradiation

	Intraoperative radiotherapy	Multicatheter interstitial brachytherapy	External-beam radiotherapy
Advantages	• Shortest possible treatment time • Direct visualization of the tumor bed	• High conformality • Longest available follow-up	• Broad availability • Reproducibility
Disadvantages	• Lack of complete knowledge of risk factors (e.g. margin status, lympho-vascular invasion) • Potentially increased risk of fibrosis with additional whole-breast irradiation • Availability limited to specialized centers • Prolongation of anesthesia	• Availability limited to specialized centers with high expertise • Additional invasive procedure • Additional hospital stay • Risk of target miss due visualization of the tumor bed	• Risk of target miss due visualization of the tumor bed • Larger irradiated volume due to intra- and interfractional motion

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Postmastectomy Radiotherapy (PMRT)* to the Chest Wall – Indication

	Oxford LoE	Oxford GR	AGO
▪ ≥4 tumor infiltrated lymph nodes (LN)	1a	A	++
▪ 1–3 tumor infiltrated LN (high-risk)	1a	A	+
▪ 1–3 tumor infiltrated LN (low-risk*, with ALND)	1b	B	-
▪ 1–3 tumor infiltrated LN (low-risk*, no ALND)	2b	B	+/-
▪ 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	++
The indications for PMRT and regional RT are independent of adjuvant systemic treatment	1a	A	
Inflammatory breast cancer: PMRT and regional nodal irradiation	2c	B	++

*See slide Radiotherapy of the Chest Wall After Mastectomy (PMRT). Low risk: pT1-2, involved 1-2 LN, ER/PR pos., HER2 neg.

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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al.: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) high risk

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
2. Wenz F, Sperk E, Budach W, et al: Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer. Strahlenther Onkol. 2014 Aug;190(8):705-14.
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5. Truong PT, Olivotto IA, Kader HA, et al: Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys. 2005 Apr 1;61(5):1337-47.
6. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
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9. Kunkler et al. GS2-03: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC SUPREMO randomised trial: on behalf of the SUPREMO trial investigators. San Antonio Breast Cancer

Symposium 2024.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) low risk

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with T3 / T4 breast cancer

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
2. Valli MC; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Controversies in loco-regional treatment: post-mastectomy radiation for pT2-pT3N0 breast cancer arguments in favour. Crit Rev Oncol Hematol. 2012 Dec;84 Suppl 1:e70-4.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with pT3 pN0 R0 breast cancer (and no additional risk factors)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after

mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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4. Kunkler et al. GS2-03: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC SUPREMO randomised trial: on behalf of the SUPREMO trial investigators. San Antonio Breast Cancer Symposium 2024.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
2. Freedman GM, Fowble BL, Hanlon AL, et al. A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. Int J Radiat Oncol Biol Phys. 1998 Jun 1;41(3):599-605.
3. Truong PT, Olivotto IA, Speers CH, et al: A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys. 2004 Mar 1;58(3):797-804.
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6. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother Oncol. 2009 Apr;91(1):23-32.

Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al:Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

Post-mastectomy radiotherapy (PMRT) and regional nodal irradiation for patients with inflammatory breast cancer

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649.
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SUPREMO: Post-mastectomy radiotherapy in intermediate risk breast cancer patients

Kunkler et al. SABCS 2024

- Prospective randomized controlled trial, n = 1607
- Inclusion criteria:
  - T1-2 N1, T3 N0, T2 N0 if G3 and/or L1
  - Simple mastectomy, reconstruction allowed. If N1, ALND with ≥8 removed nodes was required. NACT was allowed (26 patients).
- Randomization to Post-Mastectomy Radiotherapy or no RT.
- Primary endpoint: overall survival (powered to demonstrate improvement by 7%, 609 events)
- Patient characteristics:
  - Median 55 years, 24% T2N0, 29% T1N1, 45% T2N1, <1% T3N0, 63% 1-2 LK, 21% HER2 pos., 11% TNBC
  - No data on systemic therapy and type of surgery.
- Results:
  - No improvement in OS (HR 1.04, 95%-CI 0.82-1.30, 295 events)
  - Significant reduction in Chest wall recurrence (HR 0.45, 95%-CI 0.2-0.99; 2.5 vs. 1.1%)
  - Trend towards reduced regional recurrence (HR 0.61, 95%-CI 0.36-1.03, 4.5 vs. 2.7%)
  - No improvement in metastasis-free survival or disease-free survival
- Limitations:
  - No subgroup analyses were presented.
  - Regional nodal irradiation was not prespecified.

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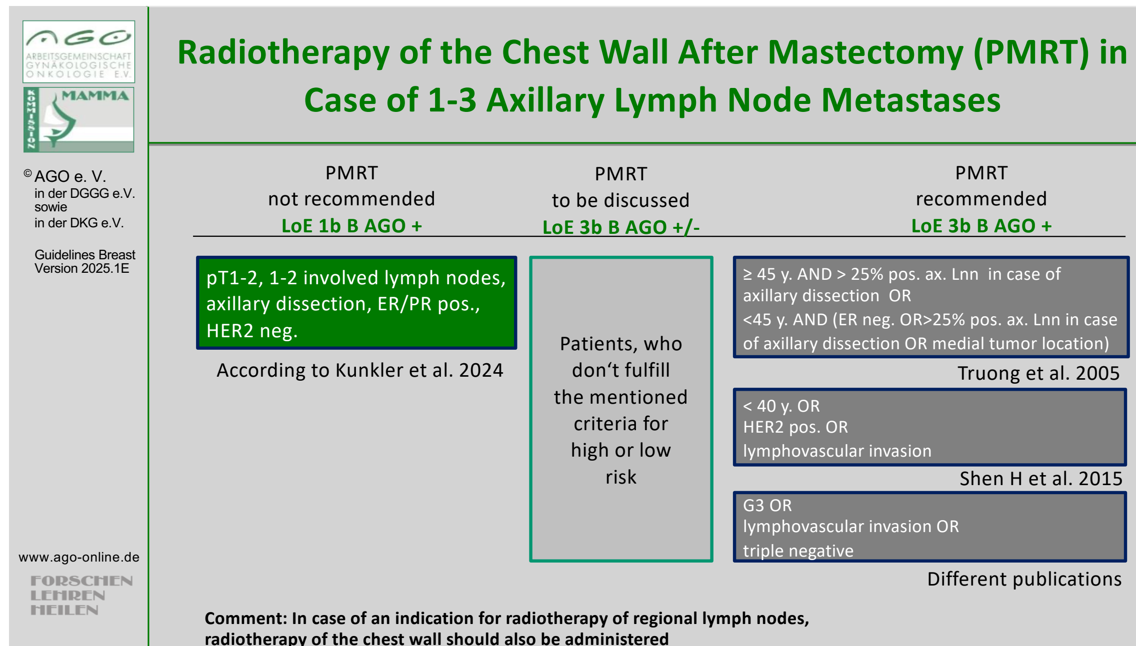
Kunkler et al. GS2-03: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC SUPREMO randomised trial: on behalf of the SUPREMO trial investigators. San Antonio Breast Cancer Symposium 2024.



1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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8. Shen H, Zhao L, Wang L, et al: Postmastectomy radiotherapy benefit in Chinese breast cancer patients with T1-T2 tumor and 1-3 positive axillary lymph nodes by molecular subtypes: an analysis of 1369 cases. Tumour Biol. 2015 Dec 2. [Epub ahead of print]

9. Kunkler et al. GS2-03: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC SUPREMO randomised trial: on behalf of the SUPREMO trial investigators. San Antonio Breast Cancer Symposium 2024

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) high risk

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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8. NCCN Guidelines for Treatment of Cancer by Site "http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf" download 2016
9. Shen H, Zhao L, Wang L et al: Postmastectomy radiotherapy benefit in Chinese breast cancer patients with T1-T2 tumor and 1-3 positive axillary lymph nodes by molecular subtypes: an analysis of 1369 cases. Tumour Biol. 2015 Dec 2. [Epub ahead of print]

10. Kunkler et al. GS2-03: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC SUPREMO randomised trial: on behalf of the SUPREMO trial investigators. San Antonio Breast Cancer Symposium 2024.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) low risk

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with T3 / T4 breast cancer

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
2. Valli MC; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Controversies in loco-regional treatment: post-mastectomy radiation for pT2-pT3N0 breast cancer arguments in favour. Crit Rev Oncol Hematol. 2012 Dec;84 Suppl 1:e70-4.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with pT3 pN0 R0 breast cancer (and no additional risk factors)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features

1. Garg AK, Oh JL, Oswald MJ, et al. Eff ect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 2007; 69: 1478–83.

2. Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77.
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Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.

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DEGRO practical guidelines for radiotherapy of breast cancer: radiotherapy following mastectomy.

1. Wenz F, Sperk E, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Strahlenther Onkol. 2014 Aug;190(8):705-14.
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Postmastectomy Radiotherapy (PMRT)* to the Chest Wall* – Fractionation

	Oxford LoE	Oxford GR	AGO
▪ Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
▪ After breast reconstruction	1b	B	++
▪ Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week)	1b	B	+/-
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 5-6 weeks)	1a	B	+

* Regarding fractionation for regional nodal irradiation, refer to slide „Fractionation of Radiotherapy in Case of Regional Nodal Irradiation“.

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Moderate Hypofractionation

1. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
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   Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol. 2019 Mar;20(3):352-360.
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6. Poppe et al. A Randomized Trial of Hypofractionated Post-Mastectomy Radiation Therapy (PMRT) in Women with Breast

Reconstruction (RT CHARM, Alliance A221505). ASTRO Annual Meeting 2024. 10.1016/j.ijrobp.2024.07.002

Moderate hypofractionation and breast reconstruction

1. Kim D-Y, Park E, Heo CY, et al (2022) Influence of Hypofractionated Versus Conventional Fractionated Postmastectomy Radiation Therapy in Breast Cancer Patients With Reconstruction. Int J Radiat Oncol Biology Phys 112:445–456.
2. Kim D-Y, Park E, Heo CY, et al (2021) Hypofractionated versus conventional fractionated radiotherapy for breast cancer in patients with reconstructed breast: Toxicity analysis. Breast 55:37–44.
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4. Wong JS, Uno H, Tramontano A et al. Patient-Reported and Toxicity Results from the FABREC Study: A Multicenter Randomized Trial of Hypofractionated vs. Conventionally-Fractionated Postmastectomy Radiation Therapy after Implant-Based Reconstruction. Presented at ASTRO Annual Meeting 2023 (LBA 5) https://doi.org/10.1016/j.ijrobp.2023.08.029
5. Ryu H, Shin KH, Chang JH et al. (2024) A nationwide study of breast reconstruction after mastectomy in patients with breast cancer receiving postmastectomy radiotherapy: comparison of complications according to radiotherapy fractionation and reconstruction procedures. Br J Cancer 131:290–298.
6. Poppe et al. A Randomized Trial of Hypofractionated Post-Mastectomy Radiation Therapy (PMRT) in Women with Breast Reconstruction (RT CHARM, Alliance A221505). ASTRO Annual Meeting 2024. 10.1016/j.ijrobp.2024.07.002

Ultra-Hypofractionation

1. Brunt AM, Haviland JS, Wheatley DA et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020 May 23;395(10237):1613-1626.
2. Meattini I, Becherini C, Boersma L et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 2022;23(1):e21-e31.

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RT-CHARM: Moderate hypofractionation in patients with breast reconstruction

Poppe et al. RT CHARM-trial (Alliance A221505), ASTRO 2024

- Prospective randomized controlled non-inferiority trial, n = 825
- Inclusion criteria: T1-3 N1-2, T3 N0, planned reconstruction within 18 months of radiotherapy
- Randomization to 25x2 Gy or 16x2.66 Gy.
- Primary endpoint: Reconstruction-associated complications at 2 years - non-inferiority was shown.
- Type of reconstruction was the most important predictor of complications (autologous vs. implant: OR 0.49; expander vs. immediate reconstruction OR 2.06)
- Locoregional recurrence 1.9 vs. 1.5% at 3 years.

Reconstruction-associated complications at 2 years

	25x2 Gy	16x2.66 Gy	Absolute difference
All patients	12.2%	14.2%	+2.1%
Immediate	11.9%	10.3%	-1.6%
Delayed	12.3%	15.6%	+3.3%
Autologous	8.9%	8.5%	-0.4%
Implant	13.8%	17.1%	+3.3%

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Poppe et al. A Randomized Trial of Hypofractionated Post-Mastectomy Radiation Therapy (PMRT) in Women with Breast Reconstruction (RT CHARM, Alliance A221505). ASTRO Annual Meeting 2024. 10.1016/j.ijrobp.2024.07.002

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Boost in PMRT

	Oxford LoE	Oxford GR	AGO
An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival	2a	B	
An additional boost irradiation to a part of the chest wall should be given in case of of R1 / R2-resection, if secondary resection is not feasible	5	D	++
In case of tumor extention 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 situation	5	D	++

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Thoracic wall boost irradiation

1. Mayadev J, Fish K, Valicenti R et al. Utilization and impact of a postmastectomy radiation boost for invasive breast cancer, Pract Radiat Oncol. 2014 Nov-Dec;4(6):e269-78

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

	Oxford LoE	Oxford GR	AGO
BCS or mastectomy and SENOMAC-criteria met**			
▪ Radiotherapy to the breast/chest wall and axilla (Level I-IV)	1b	B	+
▪ Radiotherapy to the breast/chest wall including LN level I+II to 5 mm below the axillary vein (PTV)***	2b	B	+
BCS or mastectomy and SENOMAC-Kriterien not met** ▪ Radiotherapy to the breast/chest wall and axilla (Level I-IV)	5	D	++
Mastectomy and SENOMAC-criteria met, radiotherapy to the chest wall not planned			
▪ Exclusive radiotherapy to the axilla	5	D	+/-
≥ 3 pos. SLN			
▪ Radiotherapy to the axilla (Level I-IV analog AMAROS)	1b	B	+

*Macrometastases ** T1-T3, no suspicious nodes on ultrasound (or FNP/CNB neg.), 1-2 involved SLN, no NACT
***only if there is otherwise no indication for regional nodal irradiation (see slide „Regional nodal irradiation")

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1-2 pos SLN: BCT:

1. Giuliano AE, Ballman KV, McCall L, et al (2017) Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 318:918–926.
2. Jagsi R, Manjoet C, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;Nov 10;32(32): 3600-6
3. Sávolt Á, Péley G, Polgár C, et al (2017) Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer A randomized, single centre, phase III, non-inferiority trial. European J Surg Oncol Ejso 43:672–679.
4. Tinterri C, Gentile D, Gatzemeier W, et al (2022) Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1–2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol 1–13
5. Algara M, Rodríguez E, Martínez-Arcelus FJ, et al (2022) OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized clinical trial. Radiother Oncol 176:76–82.
6. de Boniface J, Filtenborg Tvedskov T et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med. 2024 Apr 4;390(13):1163-1175.

1-2 pos SLN: Mastectomy:

1. Donker M, Tienhoven G, Straver ME et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10.
2. Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https://doi.org/10.1200/jco.22.01565
3. Sávolt Á, Péley G, Polgár C, et al (2017) Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer A randomized, single centre, phase III, non-inferiority trial. European J Surg Oncol Ejso 43:672–679.
4. de Boniface J, Filtenborg Tvedskov T et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med. 2024 Apr 4;390(13):1163-1175

>=3 positive SLN: Radiotherapy of the axilla

1. Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https://doi.org/10.1200/jco.22.01565
2. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

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Radiotherapy target volumes in the SENOMAC-trial

- Collection of radiotherapy target volumes for patients in the ITT population (n = 2624 patients)
- Collection of dosimetric data for patients receiving radiotherapy in Denmark and Sweden (n = 1229, data available for 96% of those patients)

ITT population (N = 2624)	SLNB (n = 1371)	ALND (n = 1253)
No RT	3.8%	5.3%
Breast/CW only	6.2%	5.8%
Breast/CW + RNI	88.8%	87.4%
RNI only	1.1%	0.9%
Missing	0.1%	0.4%

RTQA population (N = 1176)	SLNB (n = 611)	ALND (n = 565)
Breast/CW	100%	100%
Level I (complete)	55%	31%
Level II-IV	97%	97%

CW = chest wall, RNI = regional nodal irradiation, RTQA = radiotherapy quality assurance

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1. Alkner S, Wieslander E, Lundstedt D et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiother Oncol. 2024 Aug;197:110372.
2. de Boniface J, Filtenborg Tvedskov T et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med. 2024 Apr 4;390(13):1163-1175.

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Additional radiotherapy of the axilla after primary surgery

(in case of an indication for RT of the breast/chest wall[1] +/- supra-/infraclavicular and internal mammary node RT[2])

pN-Status		Oxford LoE	GR	AGO
cN0 / pNx analog SOUND/INSEMA	No intentional Rt to the axilla[1]	1b	B	-
pN0(sn) / pN1mic(sn)	No intentional Rt to the axilla[1]	1b	B	--
pN0/+ after ALND	No intentional Rt to the axilla[1]	1a	A	--
pN+(sn) analog SENOMAC/AMAROS[3] (no ALND)	Level I-IV	1b	B	+
pN+(sn) analog SENOMAC/AMAROS[3] (no ALND)	Level I-II[4]	2b	B	+
pN+(sn) not analog SENOMAC/AMAROS[3] (no ALND)	Level I-IV	5	D	++
Extensive perinodal soft tissue involvement in the axilla	Level I-IV	2b	B	+
Residual tumor in the axilla after ALND	Level I-IV	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately [3]T1-T3, no suspicious nodes on ultrasound (or FNP/CNB neg.), 1-2 involved SLN, no NACT [4]Cranial border 5 mm below the axillary vein. Only if there is otherwise no indication for regional nodal irradiation, see slide „Regional nodal irradiation"

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Clinically node negative without sentinel lymph node biopsy

1. Gentilini OD, Botteri E, Sangalli C et al. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes. JAMA Oncol 2023. 9: 1557-1564.
2. Reimer T, Stachs A, Veselinovic K, et al (2024) Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial. N Engl J Med. 2024 https://doi.org/10.1056/nejmoa2412063

Sentinel node negative or micrometastases in case of primary surgery

1. Krag DN, Anderson SJ, Julian TB, et al: Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival fi ndings from the NSABPB-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927–33.
2. Galimberti V, Manika A, Maisonneuve P, et al. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. Eur J Surg Oncol. 2014 Oct;40(10):1203-8.
3. Galimberti V, Cole BF, Viale G, et al (2018) Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. The Lancet Oncology 19:1385–1393.

Radiotherapy to the axilla instead of completion axillary lymph node dissection in case of sentinel lymph node involvement

1. Galimberti V, Cole BF, Zurrida S, et al. International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305.
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3. Jagsi R, Manjoet C, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;Nov 10;32(32): 3600-6
4. Alkner S, Wieslander E, Lundstedt D et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiother Oncol. 2024 Aug;197:110372.
5. de Boniface J, Filtenborg Tvedskov T et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med. 2024 Apr 4;390(13):1163-1175.
6. Donker M, Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10
7. Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https://doi.org/10.1200/jco.22.01565

Axillary soft tissue involvement

1. Naoum GE, Oladeru O, Ababneh H, et al (2024) Pathologic Exploration of the Axillary Soft Tissue Microenvironment and Its Impact on Axillary Management and Breast Cancer Outcomes. J Clin Oncol 42:157–169.

Tumor residuals after axillary dissection

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Aktualisierung 2017 Version 4.2. Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.

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Additional RT of the Axilla after Neoadjuvant Therapy

(in case of an indication for RT of the breast/chest wall[1] +/- supra- / infraclavicular and internal mammary node RT[2])

Expansion of the PTV (planning target volume) to level I-II[3]

N-status pre/post NACT	pN-status	Oxford LoE	GR	AGO
cN0 / ycN0	ypN0(sn)	5	D	-
cN0 / ycN0	ypN1mi(sn) / ypN+(sn) (no ALND)	5	D	+[4]
cN+$_{CNB}$ / ycN0	ypN0 / ypN0(i+) (sn/TAD)	5	D	+/-[4]
cN+$_{CNB}$/ ycN0	ypN1mi(sn/TAD) / ypN+(sn/TAD) (no ALND)	5	D	+[4]
cN0/cN+	ypN0/+ after ALND	2b	B	-
cN0/cN+	Extensive perinodal soft tissue involvement in the axilla	2b	B	+
cN0/cN+	Residual tumor in the axilla after ALND	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. [3]Cranial border 5 mm below the axillary vein. [4]Study participation recommended.

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Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy

1. Ryu JM, Lee SK, Kim JY, et al. Predictive Factors for Nonsentinel Lymph Node Metastasis in Patients With Positive Sentinel Lymph Nodes After Neoadjuvant Chemotherapy: Nomogram for Predicting Nonsentinel Lymph Node Metastasis. Clin Breast Cancer. 2017 Nov;17(7):550-55
2. Galimberti V, Ribeiro Fontana SK, Maisonneuve P. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol 2016;42(3) 361-8
3. Martelli G, Miceli R, Folli S, et al. Sentinel node biopsy after primary chemotherapy in cT2 N0/1 breast cancer patients: Long-term results of a retrospective study. Eur J Surg Oncol. 2017 Nov;43(11):2012-2020.
4. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, et al.: Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up, Eur J Surg Oncol. 2020 Oct 15;S0748-7983(20)30846-5.
5. Tee SR, Devane LA, Evoy D et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg. 2018 Nov;105(12):1541-1552.
6. Balic M, Thomssen C, Würstlein R, Gnant M, Harbeck N. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.
7. Classe JM, Loaec C, Gimbergues P et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019 Jan;173(2):343-352.

8. Moo TA, Edelweiss M, Hajiyeva S, et al. Is Low-Volume Disease in the Sentinel Node After Neoadjuvant Chemotherapy an Indication for Axillary Dissection? [published correction appears in Ann Surg Oncol. 2020 Feb 21;:]. *Ann Surg Oncol*. 2018;25(6):1488–1494.
9. Wong SM , Almana N , Choi J et al: Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer, Ann Surg Oncol. 2019 Oct;26(11):3502-3509.
10. Montagna G, Mrdutt MM, Sun SX, et al (2024) Omission of Axillary Dissection Following Nodal Downstaging With Neoadjuvant Chemotherapy. JAMA Oncol 10:793–798.
11. Cabıoğlu N, Koçer HB, Karanlık H, et al (2025) De-Escalation of Nodal Surgery in Clinically Node-Positive Breast Cancer. JAMA Surg 160:. https://doi.org/10.1001/jamasurg.2024.5913

Axillary soft tissue involvement

1. Naoum GE, Oladeru O, Ababneh H et al. Pathological Exploration of the Axillary Soft Tissue Microenvironment and Its Impact on Axillary Management and Breast Cancer Outcomes. J Clin Oncol 2023 Nov 15:JCO2301009. doi: 10.1200/JCO.23.01009.

Tumor residuals after axillary dissection

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Aktualisierung 2017 Version 4.2. Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.

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Impact of axillary soft tissue involvement on regional recurrence

Naoum et al. J Clin Oncol 2023 Nov 15:JCO2301009. doi: 10.1200/JCO.23.01009.

- Retrospective single center analysis, 2162 pat. with node-positive breast cancer treated 2000-2020.
- Analysis according to extracapsular extension (ECE) and axillary soft tissue involvement (AXT).
    - No ECE or AXT in 57.7%
    - ECE only in 24.9%
    - AXT only in 2.6%
    - ECE and AXT in 13.9%
- On multivariate analysis, AXT was significantly associated with distant failure (HR 1.61, p < 0.001), locoregional failure (HR 2.31, p < 0.001) and axillary failure (HR 3.33, p = 0.003).
- Regional nodal irradiation improved locoregional control in patients with ECT and/or AXT (HR 0.5, p = 0.03). Delivering a dose of < 50 Gy with conventional fractionation was associated with a higher risk of axillary failure.
- AXT was also associated with distant failure, locoregional failure and axillary failure in patients that underwent neoadjuvant chemotherapy.

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Naoum GE, Oladeru O, Ababneh H et al. Pathological Exploration of the Axillary Soft Tissue Microenvironment and Its Impact on Axillary Management and Breast Cancer Outcomes. J Clin Oncol 2023 Nov 15:JCO2301009. doi: 10.1200/JCO.23.01009.

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Regional nodal irradiation

	Oxford LoE	Oxford GR	AGO
RT to the supra-/ infraclavicular and internal mammary region			
≥ 4 involved axillary lymph nodes[1]	1a	A	++
1–3 involved axillary lymph nodes[1] • Central or medial tumor or • HR-negative	1a	A	+
pN0 and premenopausal with central or medial tumor and G3 and HR-negative	1a	B	+
Clinical involvement of the above mentioned regions	2b	B	+
In case of left-sided breast cancer with elevated cardiac risk or if simultaneous HER2-targeted therapy is given	2b	A	-

[1] not applicable for micrometastases

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet. 2023 Nov 25;402(10416):1991-2003.
2. Poortmans PM, Collette S, Kirkove C et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.
3. Poortmans PM, Weltens C, Fortpied C, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol. 2020 Dec;21(12):1602-1610.
4. Poortmans PM, Struikmans H, De Brouwer P et al., Side Effects 15 Years After Lymph Node Irradiation in Breast Cancer: Randomized EORTC Trial 22922/10925. J Nat Cancer Inst. 2021;113:1360-1368.
5. Whelan TJ, Olivotto IA, Parulekar WR et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
6. Kim YB, Byun HK, Kim DY et al. Effect of Elective Internal Mammary Node Irradiation on Disease-Free Survival in Women With Node-Positive Breast Cancer: A Randomized Phase 3 Clinical Trial. JAMA Oncol. 2021;e216036. doi: 10.1001/jamaoncol.2021.6036.
7. Thorsen LBJ, Overgaard J, Matthiessen LW, et al (2022) Internal Mammary Node Irradiation in Patients With Node-Positive Early Breast Cancer: Fifteen-Year Results From the Danish Breast Cancer Group Internal Mammary Node Study. J Clin Oncol JCO2200044. https://doi.org/10.1200/jco.22.00044

8. Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. Int J Radiation Oncol Biol Phys 2013; 86 (5): 860-866.

RT plus concurrent Trastuzumab +/- Pertuzumab

1. Bachir B, Anouti S, Jaoude JA et al. Evaluation of Cardiotoxicity in HER-2 Positive Breast Cancer Patients Treated with Radiation Therapy and Trastuzumab. Int J Radiat Oncol Biol Phys. 2022;S0360-3016(21)03432-5.
2. Belkacemi and J. Gligorov, Concurrent trastuzumab — internal mammary irradiation for HER2 positive breast cancer: “It hurts to be on the cutting edge”. Radiother Oncol 2010;94:119-20 (Letter to the editor).
3. Belkacémi Y, Gligorov J, Ozsahin M, et al. Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study. Ann Oncol 2008;19:1110-6.
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6. Kirova YM, Caussa L, Granger B, et al. [Monocentric evaluation of the skin and cardiac toxicities of the concomitant administration of trastuzumab and radiotherapy]. Cancer Radiother 2009;13:276-80.
7. Shaffer R, Tyldesley S, Rolles M, et al. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: A retrospective single-institution study. Radiother Oncol 2009;90:122-126
8. Aboudaram A, Loap P, Loirat D, et al (2021) Pertuzumab and Trastuzumab Combination with Concomitant Locoregional Radiotherapy for the Treatment of Breast Cancers with HER2 Receptor Overexpression. Cancers 13:4790.

RT to Supra-/infraclavicular lymphatic regions after NACT/NAT (indications as for PMRT)

1. Please check slide on radiotherapy after NACT

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Regional nodal irradiation: EBCTCG-metaanalysis 2023

	EBCTCG-metaanalysis („newer trials“, recruitment 1989 onwards)	
Patient number	12,167	
Median FU	13.7 years	
Design	7 randomized controlled trials and 1 national prospective cohort study	
Target volume	92% in the experimental arm had internal mammary irradiation	
Results	Absolute reduction at 15 years	Relative reduction
Any recurrence pN0 pN1-3 pN4+	2.6% 2.3% 2.9% 4.3%	RR 0.88 (95%-CI 0.81-0.95)
Breast-cancer mortality pN0 pN1-3 pN4+	3.0% 1.6% 2.7% 4.5%	RR 0.87 (95%-CI 0.80-0.94)
Mortality w/o recurrence	-3.0%	RR 0.90 (95%-CI 0.84-0.96)
Any death	-3.0%	RR 0.90 (95%-CI 0.84-0.96)

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet. 2023 Nov 25;402(10416):1991-2003.

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Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

	Oxford LoE	Oxford GR	AGO
▪ **Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)**	1b	B	++
▪ **Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)**	1a	A	+
▪ **Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)**	2b	B	-

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1. Poortmans PM, Collette S, Kirkove C et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.
2. Whelan TJ, Olivotto IA, Parulekar WR et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
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Hypofractionated regional nodal irradiation

	START-P/A/B subgroups	Wang et al.	DBCG Skagen 1 (Abstract)	HypoG-01 (Abstract)
Patient number	864	820	2963	1265
Fractionation	39-42.9 Gy in 13-15 fx	43.5 Gy in 15 Fx	40 Gy in 15 Fx	40 Gy in 15 Fx
Median FU	10 years	58.5 months	3 years	5 years
Primary endpoint	Late normal tissue effects	Locoregional recurrence	Lymphedema at 3 years	Lymphedema at 3 years
Statistical design	Retrospective analysis	Non-inferiority	Non-inferiority	Non-inferiority
Results	No statistically significant differences for LRR or late normal tissue effects	Non-inferiority for LRR (primary analysis)	No increased risk of lymphedema or LRR (primary analysis)	Non-inferiority for lymphedema Superiority for LRR, DDFS, OS

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Radiotherapy after NACT

Pretherapeutic	Posttherapeutic	RT-BCS	PMRT	RNI*	Oxford	
		AGO	AGO	AGO	LoE	GR
Locally advanced	pCR / no pCR	++	++	++	1a/1a/1a	A/A/A
cT1-3 cN1**	ypT+ ypN0	++	+	+/-[1]	1a/1b/1b	A/B/B
cT1-3 cN1**	ypT0/is ypN0	++	+/-[1]	+/-[1]	1a/1b/1b	A/B/B
cT1-3 cN0 / cN1** (Sonogr. obligatory)	ypN+/ypN1mi o. ypT3/4	++	+	+	1a/2b/2b	A/B/B
cT1-3 cN0 (Sonogr. obligatory)	ypT0/is ypN0	++	-	-	1a/2b/2b	A/B/B
cT1-3 cN0 (Sonogr. obligatory)	ypT1-2 ypN0	++	-	-	1a/2b/2b	A/B/B

Locally adcanced: T4 or cN2-N3

[1] Criteria for increased risk of relapse / benefit of locoregional radiotherapy:
- Central/medial tumor, HR-negative, premenopausal, non-pCR in the breast, residual micrometastases in the axillary nodes, cT3

* Regarding coverage of axilla level I/II please also see slides „Additional RT of the axilla after primary surgery" and „Additional RT of the axilla after neoadjuvant therapy". ** = confirmed by core biopsy

• In the case of residual isolated tumor cells, an individual decision is made as there are no data on RT

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Role of locoregional radiotherapy after neoadjuvant chemotherapy

Mamounas et al. SABCS 2023 – GS02-07 (NSABP B-51/RTOG 1304)

- Prospective randomized controlled trial, 1641 pts., 2013-2020, median follow-up 59.5 months
- cT1-3 cN1 (FNA/CNB) → ypN0 (SLNB/ALND) after standard neoadjuvant chemotherapy
- Randomization:
  - BCS: RT breast vs. RT breast + regional nodal irradiation
  - Mastectomy: No RT vs. Post-mastectomy RT + regional nodal irradiation
- Primary endpoint: Invasive breast cancer recurrence-free interval
  - 80% power to detect 4.6% absolute reduction (HR 0.65) – superiority trial, 172 events
- Patient characteristics: 80% cT1-2, 58% BCS, 55% SLNB, 78% pCR in breast, 20% TNBC, 20% Lum
- Results:
  - No improvement in BCRFI (HR 0.88), isolated locoregional recurrence-free interval (HR 0.37), distant recurrence-free interval (HR 1.00), DFS (1.06) and OS (HR 1.12)
- Discussion:
  - Short follow-up (benefit of RNI appeared in EBCTCG-metaanalysis after 10-15 years)
  - Underpowered for primary analysis (109/172 planned events)
  - Trial should have been designed as a non-inferiority trial
  - Underrepresented subgroups: cT3, ypT+
  - Not applicable to: cT4 cN2-3

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Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

	Oxford LoE	Oxford GR	AGO
▪ Trastuzumab / Pertuzumab*	1a	A	++
▪ T-DM1	1b	A	+
▪ Tamoxifen	2b	B	+
▪ Aromatase inhibitors	2b	B	+
▪ Checkpoint inhibitors	2b	C	+
▪ Capecitabine**	2b	B	+
▪ CDK4/6-inhibitors***	4	C	+/-
▪ Olaparib****	2b	C	+/-

* Simultaneous parasternal RT should be avoided in patients with HER2-positive tumors and tumor-localisation on the left side

** With hypofractionated RT approx. 40 Gy, consider dose reduction of Capecitabine, Pat. with high risk for locoregional recurrence

*** In currently available phase III-trials (monarchE, PALLAS, Penelope-B) RT was given before initiation of CDK4/6-inhibitors. No definitive signs of significantly increased toxicity with concomitant RT in the palliative setting.

**** In currently available phase III-trials, RT was given before initiation of Olaparib.

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Smoking and Risk of Secondary Lung Cancer

	Oxford LoE	Oxford GR	AGO
▪ **Increased risk of lung cancer secondary to breast cancer radiotherapy in smokers**	1a	A	
▪ **Inform patients about risk**			++
▪ **Recommend smoking cessation**			++

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