



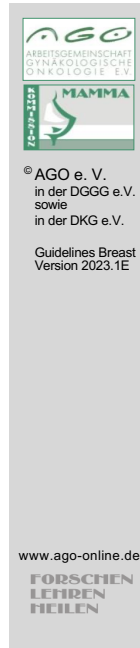
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Guidelines Breast
Version 2023.1E

FORSCHEN
LEHREN
HEILEN

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Adjuvant Radiotherapy



Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2022:**
Blohmer / Budach / Friedrich / Friedrichs / Göhring / Huober / Janni /
Krug / Kühn / Möbus / Rody / Scharl / Schmidt / Seegenschmiedt /
Souchon / Thomssen / Untch / Wenz
- **Version 2023:**
Budach / Krug / Solbach

Search Strategy

Search Terms: Radiotherapy Breast Cancer

Source: Pubmed 1/2010 – 1/2023

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.**

1. Sedlmayer F, Sautter-Bihl ML, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol. 2013 Oct;189(10):825-33.
2. Sautter-Bihl ML, Sedlmayer F, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer III--radiotherapy of the lymphatic pathways. Strahlenther Onkol. 2014 Apr;190(4):342-51.
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5. Harms W, Budach W, Dunst J, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. Strahlenther Onkol. 2016;192(4):199-208

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10. Krug D, Baumann R, Combs SE et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. *Strahlenther Onkol* 2021 <https://doi.org/10.1007/s00066-020-01744-3>

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

	Oxford		
	LoE	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	+
▪ Ultra-hypofractionated RT (total dose 26 or 28,5 Gy in 5 fractions in 1 or 5 weeks)	1b	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.	1a	B	+

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.
2. Whelan TJ, Pignol JP, Levine M et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010 Feb 11;362(6):513-20.
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Ultra-Hypofractionation

1. Brunt AM, Haviland JS, Sydenham M et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. *J Clin Oncol.* 2020 Oct 1;38(28):3261-3272.
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Elderly patients with low-risk features

1. Fyles A, McCready DR, Manchul MA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70.
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FAST / FAST-Forward		
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2023.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>		
	FAST	FAST Forward
	Timeframe	2004-2007
	Sample size	915
	Dose / Fractionation	40 Gy / 2,67 Gy / 3 weeks 27 Gy / 5,4 Gy / 1 weeks 26 Gy / 5,2 Gy / 1 weeks
	Median follow-up	119.8 months
	Primary endpoint	change in photographic breast appearance
	Inclusion criteria	pT1-2 (< 3 cm) pN0 Age ≥ 50 years Breast conserving surgery No chemotherapy
	Boost	No
		Approx. 25% adj. chemotherapy
		Approx. 25%, 5-8x 2 Gy

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

Ultra-Hypofractionation

1. Brunt AM, Haviland JS, Sydenham M et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.
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FAST / FAST-Forward						
	FAST (10 year-data)			FAST Forward (5 year-data)		
	Dose	Frequency	Hazard ratio (95%-CI)	Dose	Frequency	Hazard ratio (95%-CI)
Ipsilateral in-breast recurrence	50 Gy	0.7%	-	40 Gy	2.1%	-
	30 Gy	1.4%	HR 1.36 (0.3-6.06)	27 Gy	1.7%	HR 0.86 (0.51-1.44)
	28.5 Gy	1.7%	HR 1.35 (0.3-6.05)	26 Gy	1.4%	HR 0.67 (0.38-1.16)
Moderate / marked normal tissue effects breast / chestwall	50 Gy	33.6%	-	40 Gy	26.8%	-
	30 Gy	50.4%	HR 1.79 (1.37-2.34)	27 Gy	35.1%	HR 1.41 (1.23-1.61)
	28.5 Gy	47.6%	HR 1.45 (1.10-1.91)	26 Gy	28.5%	HR 1.09 (0.95-1.27)

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

Ultra-Hypofractionation

1. Brunt AM, Haviland JS, Sydenham M et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.
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4. Krug D, Baumann R, Combs SE et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. Strahlenther Onkol. 2021;197:269–280.

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%	5.2

1. Fyles A, McCready DR, Manchul MA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70.
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6. Kunkler et al. GS2-03. Prime 2 randomised trial (postoperative radiotherapy in minimum-risk elderly): Wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women ≥/ 65 years with early invasive breast cancer: 10 year results. SABCS 2020

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

	Oxford		
	LoE	GR	AGO
Boost-RT (improves local control, no survival benefit) <ul style="list-style-type: none"> Premenopausal Postmenopausal, if > T1⁺ G3, HER2-positive, triple negative, EIC (at least 1 factor) 	1b 2b	B B	++ +
Techniques <ul style="list-style-type: none"> Percutaneous boost (photons, electrons) as sequential boost Multicatheter brachytherapy-boost Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation) Percutaneous boost as simultaneous integrated boost (with conventionally fractionated whole-breast irradiation) Intraoperative boost irradiation (followed by whole-breast irradiation) 	1a 1a 1b ^a 1b 2b	A A B B B	++ ++ + + +
Intraoperative clip placement at the tumor bed if boost irradiation is indicated <ul style="list-style-type: none"> * continuous parameter with regard to risk of relapse 	2b	B	+

Boost in general (EBRT/Brachytherapy, sequential)

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Boost-RT in premenopausal p.

Boost-RT in postmenopausal p.

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Simultaneous-integrated boost (conventionally fractionated RT)

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Simultaneous-integrated boost (hypofractionated RT)

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Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI

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- (HIOB): First Clinical Results of a Prospective Multicenter Trial (NCT01343459). *Cancers (Basel)*. 2022 Mar 9;14(6):1396.
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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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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.
2. Vrieling C et al. European Organisation for Research and Treatment of Cancer, Radiation Oncology and Breast Cancer Groups. Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial. JAMA Oncol. 2017 Jan 1;3(1):42-48



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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 ($\Delta \geq 4\%$)	@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.

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.
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Moderate hypofractionation with simultaneous-integrated boost		
 <p>© AGO e. V. in der DGKG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2023.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>	RTOG 1005 (ASTRO 2022)	IMPORT-HIGH (ESTRO 2021)
	Patient number	2262
	Schedule Breast	40 Gy in 15 fx
	Schedule Boost	48 Gy in 15 fx vs. 53 Gy in 15 fx
	Ipsilateral in-breast recurrence at 5 years	HR 1.32 (0.8-2.1) → Non-inferiority for SIB
	Toxicity	Toxicity grade ≥3 (ROTG) p = 0.79
<p>HR 1.04 (0.56-1.92) → Non-inferiority for 48 Gy (absolute diff.)</p> <p>HR 1.76 (1.01-3.04) → Inferiority for SIB 53 Gy (absolute + relat.)</p> <p>p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB) p = 0.823 for SIB 53 Gy vs. sequential boost</p>		

1. Coles C, Haviland JS, Kirby AM, et al OC-0291 IMPORT HIGH trial: Dose escalated simultaneous integrated boost radiotherapy in early breast cancer. Radiother Oncol 2021. 161:S197–S1992.
2. Vicini FA, Winter K, Freedman GM, et al. NRG RTOG 1005: A Phase III Trial of Hypo Fractionated Whole Breast Irradiation with Concurrent Boost vs. Conventional Whole Breast Irradiation Plus Sequential Boost Following Lumpectomy for High Risk Early-Stage Breast Cancer. Int J Radiat Oncol Biology Phys 2022. 114:S1.

Techniques for Partial Breast Irradiation (PBI) after Breast Conserving Surgery (Invasive Cancer)

	Oxford		
	LoE	GR	AGO
Intraoperative Radiotherapy (low-risk)* <ul style="list-style-type: none"> As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT) <ul style="list-style-type: none"> > 50 years > 70 years 	1b 1b	A A	+/- +
Postoperative partial breast irradiation (low-risk)* <ul style="list-style-type: none"> Interstitial Multicatheter-Brachytherapy Intracavitary balloon-technique Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 1.5 weeks) 3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks) 3D-conformal radiotherapy (10 x 3.8-4 Gy in 2 weeks) 3D-conformal radiotherapy (10 x 3.85 Gy in 1 week) 	1b 2b 1b 1b 2b 1b	A B A A B A	+ - + ++ +/- +/-
Intraoperative clip placement at the tumor bed if partial breast irradiation is indicated <p>For definition of target volume and practical conduct see DEGRO practical guidelines</p>	2b	B	+

* only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS

Intraoperative irradiation (IORT/IOERT)

IORT using 50 kV or IOERT (pT1 pN0 R0 G1-2, non-lobular, age >50 y, no extensive DCIS, IORT during first surgery, HR+)

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.
2. Vaidya JS, Bulsara M, Saunders C et al. Effect of Delayed Targeted Intraoperative Radiotherapy vs Whole-Breast Radiotherapy on Local Recurrence and Survival: Long-term Results From the TARGIT-A Randomized Clinical Trial in Early Breast Cancer. JAMA Oncol. 2020 Jul 1;6(7):e200249.
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>70 yrs

1. Abbott AM, Dossett LA, Loftus L, et al: Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. Am J Surg. 2015 Oct;210(4):624-8.

2. Vaidya JS, Wenz F, Bulsara M, et al: TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
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Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)

Interstitial brachytherapy

1. Aristei C, Palumbo I, Capezzali G, et al. Outcome of a phase II prospective study on partial breast irradiation with interstitial multi-catheter highdose rate brachytherapy. *Radiother Oncol* 2013;108:236-241.
2. Strnad V, Ott OJ, Hildebrandt G, et al: Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet*. 2016 Jan 16;387(10015):229-38.
3. Schäfer R, Strnad V, Polgár C et al. Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. *Lancet Oncol*. 2018 Jun;19(6):834-844.
4. Polgár C, Ott OJ, Hildebrandt G et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017 Feb;18(2):259-268.
5. Strnad V, Major T, Polgar C et al. ESTRO-ACROP guideline: Interstitial multi-catheter breast brachytherapy as Accelerated Partial Breast Irradiation alone or as boost - GEC-ESTRO Breast Cancer Working Group practical recommendations. *Radiother Oncol*. 2018 Sep;128(3):411-420.
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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.
2. Meattini I, Saieva C, Miccinesi G et al. Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation: Health-related quality of life final analysis from the Florence phase 3 trial. Eur J Cancer. 2017 May;76:17-26.
3. Meattini I, Marrazzo L, Saieva C et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. J Clin Oncol. 2020 Dec 10;38(35):4175-4183.

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.
2. Bhattacharya IS, Haviland JS, Kirby AM et al. Patient-Reported Outcomes Over 5 Years After Whole- or Partial-Breast Radiotherapy: Longitudinal Analysis of the IMPORT LOW (CRUK/06/003) Phase III Randomized Controlled Trial. J Clin Oncol. 2019 Feb 1;37(4):305-317.
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3D-conformal RT (10x3.85-4 Gy over two weeks)

1. Ott OJ, Strnad V, Stillkrieger W et al. Accelerated partial breast irradiation with external beam radiotherapy : First results of the German phase 2 trial. *Strahlenther Onkol*. 2017 Jan;193(1):55-61.
2. Boutrus RR, Sherif SE, Abdelazim Y, et al (2021) Once Daily Versus Twice Daily External Beam Accelerated Partial Breast Irradiation: A Randomized Prospective Study. *Int J Radiat Oncol Biology Phys* 109:1296–1300.
3. Song Y-C, Sun G-Y, Fang H, et al (2021) Quality of Life After Partial or Whole-Breast Irradiation in Breast-Conserving Therapy for Low-Risk Breast Cancer: 1-Year Results of a Phase 2 Randomized Controlled Trial. *Frontiers Oncol* 11:738318.

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.
3. Vicini FA, Cecchini RS, White JR et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet*. 2019 Dec 14;394(10215):2155-2164.
4. Ganz PA, Cecchini RS, White JR et al. Patient-reported outcomes (PROs) in NRG oncology/NSABP B-39/RTOG 0413: A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) in stage 0, I, or II breast cancer. *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 508-508. Presented at ASCO Annual Meeting 2019

Clip placement

1. Freitas TB de, Lima KML de B, Carvalho H de A, et al (2018) What a difference a clip makes! Analysis of boost volume definition in radiation therapy for conservative breast surgery. *Eur J Surg Oncol* 44:1312–1317.
2. Dzhugashvili M, Tournay E, Pichenot C, et al (2009) 3D-conformal Accelerated Partial Breast Irradiation treatment planning: the value of surgical clips in the delineation of the lumpectomy cavity. *Radiat Oncol* 4:70.
3. Aldosary G, Caudrelier J-M, Arnaout A, et al (2021) Can we rely on surgical clips placed during oncoplastic breast surgery to accurately delineate the tumor bed for targeted breast radiotherapy? *Breast Cancer Res Tr* 186:343–352.

4. Mourik AM van, Elkhuisen PHM, Minkema D, et al (2010) Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 94:286–291.
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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 (elsewhere)	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

1. Haussmann J, Budach W, Strnad V et al. Comparing Local and Systemic Control between Partial- and Whole-Breast Radiotherapy in Low-Risk Breast Cancer-A Meta-Analysis of Randomized Trials. *Cancers (Basel)*. 2021 Jun 13;13(12):2967.
2. Haussmann J, Budach W, Corradini S et al. No Difference in Overall Survival and Non-Breast Cancer Deaths after Partial Breast Radiotherapy Compared to Whole Breast Radiotherapy-A Meta-Analysis of Randomized Trials. *Cancers (Basel)*. 2020 Aug 17;12(8):2309.

Comparison of different techniques for partial breast irradiation

	Intraoperative radiotherapy	Multicatheter interstitial brachytherapy	External-beam radiotherapy
Advantages	<ul style="list-style-type: none"> • Shortest possible treatment time • Direct visualization of the tumor bed 	<ul style="list-style-type: none"> • High conformality • Longest available follow-up 	<ul style="list-style-type: none"> • Broad availability • Reproducibility
Disadvantages	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Availability limited to specialized centers with high expertise • Additional invasive procedure • Additional hospital stay • Risk of target miss due to visualization of the tumor bed 	<ul style="list-style-type: none"> • Risk of target miss due to visualization of the tumor bed • Larger irradiated volume due to intra- and interfractional motion

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

- > 3 tumor infiltrated lymph nodes (LN)
 - 1–3 tumor infiltrated LN (high-risk)
 - 1–3 tumor infiltrated LN (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**
- Inflammatory breast cancer: PMRT and regional nodal irradiation**

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

* For definition of low-risk, see next slide Radiotherapy of the Chest Wall After Mastectomy (PMRT)

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. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997 Oct 2;337(14):949-55.
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4. Truong PT, Olivetto 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.
5. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
6. Kyndi M, Overgaard M, Nielsen HM, et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009 Jan;90(1):74-9.
7. 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]

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.
3. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997 Oct 2;337(14):949-55.
4. Overgaard M, Jensen MB, Overgaard J, et al: Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999 May 15;353(9165):1641-8.
5. Truong PT, Olivetto 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.
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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]

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.
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.

3. 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.
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg*. 2013 Sep 11;2013:212979.
5. Kyndi M, Overgaard M, Nielsen H et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. *Radiother Oncol*. 2009 Jan;90(1):74-9.

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.
2. Boutrus R, Taghian AG; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Post mastectomy radiation for large node negative breast cancer: time for a second look. *Crit Rev Oncol Hematol*. 2012 Dec;84 Suppl 1:e75-8.
3. 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 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.
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg*. 2013 Sep 11;2013:212979.
5. Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. *Breast*. 2010 Feb;19(1):14-22.
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.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features

1. Garg AK, Oh JL, Oswald MJ, et al. Effect 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, Paganì 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.
3. Dragun AE, Huang B, Gupta S, et al: One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. *Int J Radiat Oncol Biol Phys* 2012;83:e591-6.
4. Mallon PT, McIntosh SA. Post mastectomy radiotherapy in breast cancer: a survey of current United Kingdom practice. *J BUON* 2012;17:245-8.
5. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. *Breast Cancer Res Treat* 2011;127:207-15.

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.

2. Ueno NT, Fernandez JRE, Cristofanilli M et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. J Cancer. 2018; 9(8): 1437–1447.
3. Rueth NM, Lin HY, Bedrosian I et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. J Clin Oncol. 2014;32(19):2018-24.
4. Dawood S, Lei X, Dent R et al. Survival of women with inflammatory breast cancer: a large population-based study. Ann Oncol. 2014;25(6):1143-51.
5. Dawood S, Merajver SD, Viens P et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011;22(3):515-523.

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

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.
2. Hehr T, Baumann R, Budach W et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Radiotherapy after skin-sparing mastectomy with immediate breast reconstruction in intermediate-risk breast cancer : Indication and technical considerations. Strahlenther Onkol. 2019 Nov;195(11):949-963.

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

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks) <ul style="list-style-type: none"> After breast reconstruction 	1a	A	++
<ul style="list-style-type: none"> 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) 	2b	B	+
<ul style="list-style-type: none"> 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“.

Moderate Hypofractionation

- 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.
- Hickey BE, James ML, Lehman M et al. Fraction size in radiation therapy for breast conservation in early breast cancer. *Cochrane Database Syst Rev.* 2016 Jul 18;7:CD003860.
- Wang SL, Fang H, Song YW et al. 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.
- 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.

Moderate hypofractionation and breast reconstruction


- 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.
3. Rojas DP, Leonardi MC, Frassoni S, et al (2021) Implant risk failure in patients undergoing postmastectomy 3-week hypofractionated radiotherapy after immediate reconstruction. *Radiother Oncol* 163:105–113.

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.

	Radiotherapy of the Chest Wall After Mastectomy (PMRT) in Case of 1-3 Axillary Lymph Node Metastases		
© AGO e. V. in der DGOG e.V. sowie in der DKG e.V.	PMRT can be omitted LoE 3b B AGO +	PMRT to be discussed LoE 3b B AGO +/-	PMRT recommended LoE 3b B AGO +
Guidelines Breast Version 2023.1E	<div>ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)</div> <div>Kyndi et al. 2009</div>	<div>Patients, who don't fulfill the mentioned criteria for high or low risk</div>	<div>≥ 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</div> <div>< 40 y. OR HER2 pos. OR lymphovascular invasion Shen H et al. 2015</div> <div>G3 OR lymphovascular invasion OR triple negative Different publications</div>
www.ago-online.de FORSCHEN LEBEN HEILEN	Comment: In case of an indication for radiotherapy of regional lymph nodes, radiotherapy of the chest wall should also be administered		

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. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997 Oct 2;337(14):949-55.
3. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999 May 15;353(9165):1641-8.
4. 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.
5. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
6. Kyndi M, Overgaard M, Nielsen HM, et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009 Jan;90(1):74-9.
7. NCCN Guidelines for Treatment of Cancer by Site
"http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf" download 2016
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]

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.
3. Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997 Oct 2;337(14):949-55.
4. Overgaard M, Jensen MB, Overgaard J et al: Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999 May 15;353(9165):1641-8.
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.
7. Kyndi M, Overgaard M, Nielsen HM et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009 Jan;90(1):74-9.
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]

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.

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.
3. 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.
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
5. Kyndi M, Overgaard M, Nielsen HM, et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009 Jan;90(1):74-9.
6. NCCN Guidelines for Treatment of Cancer by Site
“http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf” download 2016

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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.
2. Boutrus R, Taghian AG; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Post mastectomy radiation for large node negative breast cancer: time for a second look. Crit Rev Oncol Hematol. 2012 Dec;84 Suppl 1:e75-8.
3. 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 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.
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4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
5. Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. Breast. 2010 Feb;19(1):14-22.
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.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features

1. Garg AK, Oh JL, Oswald MJ, et al. Effect 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.
3. Dragun AE, Huang B, Gupta S, et al. One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. Int J Radiat Oncol Biol Phys 2012;83:e591-6.
4. Mallon PT, McIntosh SA. Post mastectomy radiotherapy in breast cancer: a survey of current United Kingdom practice. J BUON 2012;17:245-8.
5. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. Breast Cancer Res Treat 2011;127:207-15.

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.

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

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.
2. Hehr T, Baumann R, Budach W et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Radiotherapy after skin-sparing mastectomy with immediate breast reconstruction in intermediate-risk breast cancer : Indication and technical considerations. Strahlenther Onkol. 2019 Nov;195(11):949-963.

Boost in PMRT

	Oxford		
	LoE	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 R1 / R2-resection, if secondary resection is not feasible	5	D	++
▪ In case of tumor extension to the pectoral resection margin, but no clinical signs of extension 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	++

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

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

1-2 pos SLN: BCT: No further treatment to the axilla neither axillary dissection nor RT of the axilla (criteria according ACOSOG Z0011)

1. Giuliano AE, Hunt KK, Ballmann KV, et al Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
2. 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.
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

1-2 pos SLN: BCT: Axillary dissection

1. Giuliano AE, Hunt KK, Ballmann KV, et al. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
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

1-2 pos SLN: BCT: radiotherapy of the axilla

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>

1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, axillary dissection or radiotherapy of the axilla

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.
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<https://doi.org/10.1200/jco.22.01565>

1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, no axillary treatment (criteria ACOSOG Z011)

EXPERT OPINION, extrapolated from:

1. Giuliano AE, Hunt KK, Ballmann KV, et al. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-5753.
2. 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.

1-2 pos SLN: Mastectomy: If RT of chestwall is not planned, axillary dissection or radiotherapy of the axilla

EXPERT OPINION, extrapolated from:

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.
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<https://doi.org/10.1200/jco.22.01565>

>=3 positive SLN: Axillary LN dissection


1. Giuliano AE, Hunt KK, Ballmann KV, et al. Axillary dissection vs no axillary dissection in women with breast invasive cancer and

sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.

2. 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.
3. 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>
4. 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.

>=3 positive SLN: Radiotherapy of the axilla

1. Giuliano AE, Hunt KK, Ballmann KV, et al: Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
2. 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.
3. 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>
4. 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.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2023.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>	Additional RT 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)		
	Expansion of the PTV (planning target volume) to level I-II ³		
	pN-status		
	pN0(sn) / pN1mic(sn)	1b	B
	pN0/+ after ALND	1a	A
	pN+(sn) in analogy to ACOSOG Z0011 (no ALND)	2b	B
	pN+(sn) not fitting ACOSOG Z0011-criteria → RT in analogy to AMAROS ⁴ (no ALND)	1b	B
	R2-situation in the axilla	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 < T3, no palpable LN, R0, 1-2 positive SN, no NACT, always in conjunction with supra-/infraclavicular RT			

Sentinel node negative

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 findings 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.

Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies


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.
2. Giuliano AE, Ballman KV, McCall L, et al. 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. 2017 Sep 12;318(10):918-926.
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

Regional nodal irradiation without ALND in non-Z0011-eligible patients

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>

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		Oxford		
		LoE	GR	AGO		
(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					
cN0 / ycN0	ypN0(sn)	5	D	-		
cN0 / ycN0	ypN1mic(sn) / ypN+(sn) (no ALND)	5	D	+ ⁴		
cN+cNB / ycN0	ypN0(sn/TAD)	5	D	+/- ⁴		
cN+cNB/ycN0	ypN1mic(sn/TAD) / ypN+(sn/TAD) (no ALND)	5	D	+ ⁴		
cN0/cN+	ypN0/+ after ALND	2b	B	-		
	R2-situation in the axilla	5	D	++		

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

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.


Axillary intervention after PST

1. 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.
2. 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.

3. 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.
4. Moo TA, Edelweiss M, Hajiyevea 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.
5. 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.

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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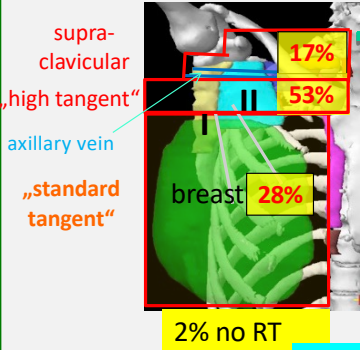
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Dose in the Axillary LN-levels I + II Using Different RT-Techniques

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



supra-clavicular 17%
„high tangent“ 53%
axillary vein 28%
breast 28%
2% no RT

RT-volume % of patients

AMAROS

LN level 1	mean dose*	encompassed volume**
AMAROS	> 95%	> 95%
high tangent	86%	79%
standard tangent	66%	51%
IMRT ⁺	29%	1%

LN-level 2	mean dose*	encompassed volume**
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"

1. Giuliano et al. 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. 2017 Sep 12;318(10):918-926
2. Jagsi R et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. J Clin Oncol. 2014 Nov 10;32(32):3600-6
3. Lee J et al.. Dosimetric evaluation of incidental irradiation to the axilla during whole breast radiotherapy for patients with left-sided early breast cancer in the IMRT era. Medicine (Baltimore). 2016 Jun;95(26):e403

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

	Oxford		
	LoE	GR	AGO
<u>RT to supra- / infraclavicular lymphatic regions</u>			
▪ ≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in supra- / infraclavicular LN	1b	A	++
▪ 1–3 positive axillary lymph nodes¹ in case of - central or medial tumor and G2-3 or HR-negative - premenopausal patient and G2-3 or HR-negative	2a	B	+
▪ pN0 with central or medial tumors, if premenopausal and G2-3 and HR-negative	2a	B	+/-

¹ not applicable for micrometastases

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

1. Yates L, Kirby A, Crichton S, et al. Risk factors for regional nodal relapse in breast cancer patients with one to three positive axillary nodes. *Int J Radiat Oncol Biol Phys.* 2012 Apr 1;82(5):2093-103.
2. Viani GA, Godoi da Silva LB, Viana BS. Patients with N1 breast cancer: who could benefit from supraclavicular fossa radiotherapy? *Breast.* 2014 Dec;23(6):749-53.

Supra-/infraclavicular lymphatic regions

RT to Supra-/infraclavicular lymphatic regions if ≥ pN2a

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. 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.
3. 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.
4. Whelan TJ, Olivetto IA, Parulekar WR et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med.* 2015 Jul

23;373(4):307-16.

5. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. *Radiat Oncol*. 2013 Nov 14 ;8:267.
6. P. F. Nguyen-Tan, L. Vincent, F. Methot et al., "The incidence of supraclavicular failure in patients with T1-2 breast cancer an four or more positive nodes treated by conservative surgery and tangential breast irradiation without regional nodal irradiation," *International Journal of Radiation Oncology Biology Physics*, vol. 42, supplement 1, p. 249, 1998.
7. Whelan TJ, Olivotto IA, Parulekar WR, et al. MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.
8. Budach W, Bölke E, Kammers K, et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. *Radiat Oncol*. 2015 Dec 21;10(1):258.
9. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

RT to Supra-/infraclavicular lymphatic regions if Level III involved

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. 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.
3. 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.
4. Budach W, Bölke E, Kammers K, et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. *Radiat Oncol*. 2015 Dec 21;10(1):258.
5. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. *Radiat Oncol*. 2013 Nov 14 ;8:267.
6. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

RT to Supra-/infraclavicular lymphatic regions if pN1a high risk

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. 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.
3. 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.
4. Budach W, Bölke E, Kammers K et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
5. Whelan TJOI, Ackerman I, Chapman JW, et al: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
6. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

RT to Supra-/infraclavicular lymphatic regions if pN1a low risk

1. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.
2. 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.
3. Whelan TJ, Olivotto IA, Parulekar WR, et al. MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
4. Budach W, Bölke E, Kammers K, et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
5. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

RT to Supra-/infraclavicular lymphatic regions if pN0 high risk, if radiotherapy of the internal mammaria Inn. chain is indicated (see below)

1. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial

Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.

2. 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.
3. Whelan TJ, Olivetto IA, Parulekar WR, et al; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
4. Budach W, Bölke E, Kammers K et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
5. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
6. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

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

1. Please check slide on radiotherapy after NACT

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

	Oxford		
	LoE	GR	AGO
Internal mammary lymph node region (IMN)			
▪ pN0 high-risk with central or medial tumor and premenopausal and G2-3 and ER/PR-negative	1b	B	+/-
▪ 1–3 positive axillary lymph nodes ¹ in case of - central or medial tumor - HR-negative	2a	B	+
▪ ≥ 4 positive axillary lymph nodes	2a	B	+
▪ involved internal mammary lymph nodes	2a	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			

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

Internal mammary lymph node region (IMN)

RT to Internal mammary lymph node region (IMC) if pN0 high risk with central/medial tumors

1. 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.
2. Chang JS, Park W, YB Kim, et al. Long-term Survival Outcomes Following Internal Mammary Node Irradiation in Stage II-III Breast Cancer: Results of a Large Retrospective Study With 12-Year Follow-up. *Int J Radiation Oncol Biol Phys*, 2013; 86 (5): 867-872.
3. 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.
4. 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.
5. 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.
6. Whelan TJ, Olivetto IA, Parulekar WR et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.

7. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

RT to Internal mammaria lymph node region (IMN) if pN1-pN2

1. 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.
2. Chang JS, Park W, YB Kim, et al. Long-term Survival Outcomes Following Internal Mammary Node Irradiation in Stage II-III Breast Cancer: Results of a Large Retrospective Study With 12-Year Follow-up. *Int J Radiation Oncol Biol Phys*, 2013; 86 (5): 867-872.
3. 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.
4. 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.
5. 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.
6. 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.
7. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018
8. 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.
9. 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>

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.
4. Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol* 2009;27:2638-44.
5. Jacob J, Belin L, Pierga JY, et al: Concurrent administration of trastuzumab with locoregional breast radiotherapy: long-term results of a prospective study. *Breast Cancer Res Treat*. 2014 Nov;148(2):345-53.
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.



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Radiotherapy to the internal mammary nodes

	DBCG-IMN	KROG 15-03	
Patient number	3089	735	
Timeframe	2003-2007	2008-2013	
Median FU	14.8 years	8.3 years	
Design	Prospective cohort study, right-sided treated with IMNI, left-sided without IMNI. All received SCV-RT.	Randomized controlled trial All received SCV-RT, randomization to +/- IMNI.	
Inclusion criteria	N+, no NACT	N+, ALND with ≥8 lymph nodes, no NACT	
Stratification	All patients	Medial/central	lateral
Distant recurrence	HR 0.88 (0.78-0.99)	HR 0.44 (0.23-0.85)	HR 1.07 (0.68-1.68)
Breast-cancer mortality	HR 0.88 (0.78-1.00)	HR 0.41 (0.17-0.99)	0.91 (0.53-1.57)
Overall survival	HR 0.86 (.77-0.96)	HR 0.51 (0.24-1.11)	1.07 (0.64-1.77)
Subgroup analysis	No benefit in 1-3 LN+ with lateral tumor, larger benefit with N2-3	Benefit for ER/PR-negative tumors (p-interaction = 0.03)	

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Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

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

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Hypofractionated regional nodal irradiation

	START-P/A/B subgroups	Wang et al.	DBCG Skagen 1 (Abstract)	FAST-Forward Nodal substudy (Abstract)
Patient number	864	820	2963	469
Fractionation	39-42.9 Gy in 13-15 fx	43.5 Gy in 15 Fx	40 Gy in 15 Fx	26 Gy / 27 Gy in 5 Fx
Median FU	10 years	58.5 months	3 years	?
Primary endpoint	Late normal tissue effects	Locoregional recurrence	Lymphedema at 3 years	Arm/hand swelling at 5 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)	No increased risk of late normal tissue effects (preliminary data at 2-3 years)

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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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Radiotherapy following NACT

Pretreatment	Post-treatment	RT-BCS	PMRT	RNI*	Oxford		
					AGO	LoE	GR
Locally advanced	pCR / no pCR	yes	yes	yes	++/+/+	1a/1a/1a	A/A/A
cT1/2 cN1+*	ypT1+ or ypN1 + (no pCR)	yes	yes	yes	++/+/+	1a/2b/2b	A/B/B
cT1/2 cN1+*	ypT0/is ypN0	yes	Increased risk of relapse ¹		+/-/+	2b/2b/2b	B/B/B
cT1/2 cN0 (Sonogr. obligatory)	ypN+ or ypT3/4	yes	yes	yes	+/-/+	2b/2b/2b	B/B/B
cT1/2 cN0 (Sonogr. obligatory)	ypT0/is ypN0	yes	no	no	+/-/-	2b/2b/2b	A/B/B
cT1/2 cN0 (Sonogr. obligatory)	ypT1-2 ypN0	yes	no	no	+/-/-	2b/2b/2b	A/B/B

Locally advanced: T3-4 or cN2-N3

¹ Criteria for increased risk of relapse:

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

* 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

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Molecular Predictors and Use of Radiotherapy

- Results of gene expression profiling should not be used for indication of radiotherapy

Oxford		
LoE	GR	AGO
2b	B	++

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Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

- Trastuzumab / Pertuzumab*
- T-DM1
- Tamoxifen
- Aromatase inhibitors
- Checkpoint inhibitors
- Capecitabine**
- CDK4/6-inhibitors***
- Olaparib****

- * 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.

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

Trastuzumab +/- Pertuzumab concurrent with radiotherapy

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Tamoxifen concurrent with radiotherapy

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AI (letrozole, anastrozole) concurrent with radiotherapy

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Checkpoint-inhibitors concurrent with radiotherapy

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Simultaneous Capecitabine with Locoregional Radiotherapy

Woodward et al. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):777-783

- Prospective phase trial, 32 pat. with LABC, sim. def. / neoadj. chemoradiotherapy, median total dose 66 Gy
- “The first 9 patients analyzed [...] received CAP 825 mg/m² twice daily continuously beginning on the first day of RT. **Because of observed excess grade 3 toxicity the protocol was amended**, and subsequent patients received CAP only on RT days (5 days per week).”
- “Noncontinuous CAP dosing was much better tolerated than continuous dosing. **Thirteen of 26 patients (50%) had grade ≥ 3 and higher treatment-related dermatologic toxicity.**”

Alhanafy et al. Menoufia Medical Journal 2015, 28:325-332

- Randomised phase II-trial, 100 pat., adj. Radiotherapy 40 Gy / 15 fr. +/- CAP 825 mg/m² Mo-Fr, LABC
- “ [...] **concurrent capecitabine was feasible with a high percent of patients (96%),** [...] only two out of 50 (4%) patients had capecitabine dose modification ...”.
- “**All early toxicities were GI/GII.** Radiation dermatitis had a peak incidence in the last few fractions of the radiation therapy and the week after radiotherapy; no treatment interruption was needed and the incidence was close in both groups”.
- Radiation dermatitis grade I 14% vs. 18%; grade 2 4% vs. 4%

Smoking and Risk of Secondary Lung Cancer

- Increased risk of lung cancer secondary to breast cancer radiotherapy in smokers
- Inform patients about risk
- Recommend smoking cessation

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1. Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. Radiother Oncol. 2015 Jan;114(1):56-65
2. Taylor C, Correa C, Duane FK et al. Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. J Clin Oncol. 2017 May 20;35(15):1641-1649.