

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Adjuvant Radiotherapy



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Adjuvant Radiotherapy (RT)

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

- **Version 2019:**
Budach / Krug / Kühn

Search Strategy

Search Terms: Radiotherapy Breast Cancer

Source: Pubmed 1/2010 – 1/2020

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.



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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.
3. 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.
4. Budach W, Matuschek C, Bölke E et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer V: Therapy for locally advanced and inflammatory breast cancer, as well as local therapy in cases with synchronous distant metastases. Strahlenther Onkol. 2015 Aug;191(8):623-33.
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

6. Krug D, Baumann R, Budach W et al.: Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Neoadjuvant chemotherapy for breast cancer-background for the indication of locoregional treatment. Strahlenther Onkol. 2018 Sep;194(9):797-805.
7. Duma MN, Baumann R, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Heart-sparing radiotherapy techniques in breast cancer patients: a recommendation of the breast cancer expert panel of the German society of radiation oncology (DEGRO). Strahlenther Onkol. 2019 Oct;195(10):861-871.
8. Hehr T, Baumann R, Budach W, et al. 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.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation			
	Oxford		
	LoE	GR	AGO
▪ Radiotherapy of the affected breast	1a	A	++
▪ Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)	1a	A	++
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)	1a	B	+
▪ In case of life expectancy <10 years and pT1, pN0, R0, ER/PR-positive, HER2-negative, endocrine therapy (all criteria), radiotherapy can be omitted after individual counseling, resulting in an increased risk for in-breast recurrence	1a	B	+

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Hypofraktionierung

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.
3. Haffty BG¹, Buchholz TA. Hypofractionated breast radiation: preferred standard of care? *Lancet Oncol.* 2013 Oct;14(11):1032-4.
4. Hopwood P, Haviland JS, Sumo G et al; START Trial Management Group. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol.* 2010 Mar;11(3):231-40.
5. Bane AL, Whelan TJ, Pond GR, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. *Ann Oncol.* 2014 May;25(5):992-8.
6. Freedman GM, White JR, Arthur DW, et al. Accelerated fractionation with a concurrent boost for early stage breast cancer. *Radiother Oncol.* 2013 Jan;106(1):15-20.

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8. Dellas K, Vonthein R, Zimmer J, et al; ARO Study Group. Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01). *Strahlenther Onkol*. 2014 Jul;190(7):646-53.
9. Paelinck L, Gulyban A, Lakosi F, et al Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation? A randomized controlled trial. *Radiother Oncol*. 2017 Jan 3. pii: S0167-8140(16)34464-4. doi: 10.1016/j.radonc.2016.12.023. [Epub ahead of print]
10. Haviland JS, Bentzen SM, Bliss JM et al On behalf of the START Trial Management Group. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. *Radiotherapy and Oncology* 121 (2016) 420–423
11. Shaitelman SF, Lei X, Thompson A et al. Three-Year Outcomes With Hypofractionated Versus Conventionally Fractionated Whole-Breast Irradiation: Results of a Randomized, Noninferiority Clinical Trial. *J Clin Oncol*. 2018 Oct 31;JCO1800317.
12. 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.

Ältere Patientin mit Niedrig-Risiko-Karzinom

1. Hughes KS, Schnaper LA, Bellon J et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013 Jul 1;31(19):2382-7.
2. Kunkler IH, Williams LJ, Jack WJ, et al: On behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015 Jan 27.
3. Hughes KS, Schnaper LA. Can older women with early breast cancer avoid radiation? *The Lancet Oncology*, Available online 28 January 2015
4. Fastner G, Sedlmayer F, Widder J et al. Endocrine therapy with or without whole breast irradiation in low-risk breast cancer patients after breast-conserving surgery: 10-year results of the Austrian Breast and Colorectal Cancer Study Group 8A trial. *Eur J Cancer*. 2020 Jan 18;127:12-20



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

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

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

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

1. Hughes KS, Schnaper LA, Bellon J et al: Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013 Jul 1;31(19):2382-7.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Boost Irradiation			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ 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) ■ Techniques <ul style="list-style-type: none"> ■ Percutaneous boost (photons, electrons) as sequential boost ■ Multicatheter brachytherapy-boost ■ Percutaneous boost as simultaneous integrated boost (with normofractionated whole-breast irradiation) ■ Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation) ■ Intraoperative boost irradiation (followed by whole-breast irradiation) 	1b 2b	B B	++ +
	1a 1a	A A	++ ++
	2b	B	+
	2b	B	+/-
	2b	B	+

* continuous parameter with regard to risk of relapse



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Boost allgemein (perkutan/Brachytherapie, sequentiell)

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. Jones HA, Antonini N, Hart AA et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. J Clin Oncol. 2009 Oct 20;27(30):4939-47.
3. Romestaing P, Lehingue Y, Carrie C et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol. 1997 Mar;15(3):963-8.
4. Polgár C, Fodor J, Orosz Z et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial. Strahlenther Onkol. 2002 Nov;178(11):615-23.
5. Polo A, Polgar C, Hannoun-Levi JM et al. Risk factors and state-of-the-art indications for boost irradiation in invasive breast carcinoma. Brachytherapy. 2017 May - Jun;16(3):552-564.

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.
2. Livi L, Borghesi S, Saieva C et al. Benefit of radiation boost after whole-breast radiotherapy. *Int J Radiat Oncol Biol Phys.* 2009 Nov 15;75(4):1029-34.
3. Antonini et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiotherapy and Oncology* 82 (2007) 265–271

Simultan-integrierter Boost (normofraktionierte RT)

1. Bantema-Joppe EJ, Vredevelde EJ, de Bock GH, et al (2013) Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence. *Radiother Oncol* 108:269–272.
2. 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.

Simultan-integrierter Boost (hypofraktionierte 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.
2. Van Parijs H, Miedema G, Vinh-Hung V, et al (2012) Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. *Radiat Oncol* 7:80–10.
3. Freedman GM, White JR, Arthur DW, et al. Accelerated fractionation with a concurrent boost for early stage breast cancer. *Radiother Oncol.* 2013 Jan;106(1):15-20.
4. Cante D, Petrucci E, Sciacero P, et al (2017) Ten-year results of accelerated hypofractionated adjuvant whole-breast radiation with concomitant boost to the lumpectomy cavity after conserving surgery for early breast cancer. *Med Oncol* 34:152.

5. Dellas K, Vonthein R, Zimmer J, et al (2014) Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01). *Strahlenther Onkol* 190:646–653.
6. De Rose F, Fogliata A, Franceschini D, et al (2016) Phase II trial of hypofractionated VMAT-based treatment for early stage breast cancer: 2-year toxicity and clinical results. *Radiat Oncol* 11:120–9.


Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI

1. Fastner G, Sedlmayer F, Merz F et al. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: long term results of an ISORT pooled analysis. 2013 Aug;108(2):279-86.
2. Fastner G, Reitsamer R, Ziegler I et al. IOERT as anticipated tumor bed boost during breast-conserving surgery after neoadjuvant chemotherapy in locally advanced breast cancer--results of a case series after 5-year follow-up. *Int J Cancer*. 2015 Mar 1;136(5):1193-201.
3. Kaiser J, Kronberger C, Moder A et al. Intraoperative Tumor Bed Boost With Electrons in Breast Cancer of Clinical Stages I Through III: Updated 10-Year Results. *Int J Radiat Oncol Biol Phys*. 2018 Sep 1;102(1):92-101.
4. Blank E, Kraus-Tiefenbacher U, Welzel G et al. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. *Ann Surg Oncol*. 2010 Oct;17

	EORTC 22881-10882: Boost vs no Boost (Endpoint: Ipsilateral Breast Recurrence)			
© AGO e. V. in der DGOG e.V. sowie in der DKG e.V. Guidelines Breast Version 2020.1	@20 yrs (95% C.I.)	Boost (n=2.661)	No boost (n=2.657)	Hazard Ratio (95% C.I.)
www.ago-online.de 	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	

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

	Oxford		
	LoE	GR	AGO
■ Intraoperative Radiotherapy (low-risk)*			
■ As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT)			
■ >50 years	1b	A	+/-
■ >70 years	1b	A	+
■ Postoperative partial breast irradiation (low-risk)*			
■ Interstitial Multicatheter-Brachytherapy	1b	A	+
■ Intracavitary balloon-technique	2b	B	-
■ Intensity-modulated radiotherapy (IMRT) (5x6 Gy in 2 weeks)	1b	A	+
■ 3D-conformal radiotherapy (15x2.67 Gy in 3 weeks)	1b	A	+
■ 3D-conformal radiotherapy (10x3.8 Gy in 2 weeks)	2b	B	+/-
■ 3D-conformal radiotherapy (10x3.85 Gy in 1 week)	1b	A	+/-

For definition of target volume and practical conduct see DEGRO practical guidelines

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

Intraoperative irradiation (IORT/IOERT)

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

1. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet*. 2010 Jul 10;376(9735):91-102.
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.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77. #
4. Vaidya JS, Bulsar M, Wenz F, et al.: Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *Int J Radiation Oncol Biol Phys*, Vol. 96, No. 2, pp. 259e265, 2016
5. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess* 2016;20(73).

6. Gentilini O, Botteri E, Leonardi MC, et al. Ipsilateral axillary recurrence after breast conservative surgery: The protective effect of whole breast radiotherapy. *Radiother Oncol*. 2017 Jan 4. pii: S0167-8140(16)34462-0. doi: 10.1016/j.radonc.2016.12.021. [Epub ahead of print]

>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.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77.
4. Vaidya JS, Wenz F, Bulsara M et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess* 2016;20(73).

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 multicatheter 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.

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 Accelerated partial breasts irradiation or whole breast irradiation after breast-conserving surgery for patients with breast early cancer – 10-year follow up of the Florence APBI IMRT randomized phase >III trial. Presented at San Antonio Breast Cancer Symposium 2019

3D-konformale Radiotherapie (15x2,57 Gy über zwei Wochen)


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.

3D-konformale Radiotherapie (10x3,85 Gy über zwei Wochen)

1. Ott OJ, Strnad V, Stillkrieg 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.

3D-konformale Radiotherapie (10x3,85 Gy über eine Woche)

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



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New data on partial breast irradiation

NSABP B-39/RTOG 0413 (Vicini FA et al. Lancet. 2019 Dec 14;394(10215):2155-2164.)

- Randomised phase III equivalence trial, 4216 pat., 2005-2013, DCIS or invasive carcinoma ≤ 3 cm, 0-3 involved lymph nodes, age >18 y
- 50 Gy/25 fr. +/- boost vs. APBI with
 - 38.5 Gy/10 fr. in one week (external beam irradiation)
 - 34 Gy/10 fr. in one week (Multicatheter- or Single lumen-Brachytherapy)
- **"We observed an HR of 1.22 with a 90% CI of 0.94–1.58, which did not meet the equivalence criteria and favoured whole-breast irradiation.** The 10-year cumulative incidence of IBTR was 3.9% (95% CI 3.1–5.0) in the whole-breast irradiation group and 4.6% (3.7–5.7) in the APBI group for an absolute difference of 0.7%."
- **"Significantly more evaluable patients in the APBI group had recurrence-free interval events than patients in the whole-breast irradiation group** (figure 3). The 10-year point estimate of recurrence-free interval for the whole breast irradiation group was 93.4% (95% CI 92.1–94.6), and in the APBI group it was 91.8% (90.4–93.0; figure 3)".
- **"Our findings support whole-breast irradiation** but the absolute outcome difference compared with APBI is small, so **partial breast irradiation might also be an acceptable treatment for some patients.** "

1. 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.



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New data on partial breast irradiation

RAPID (Whelan TJ et al. Lancet. 2019 Dec 14;394(10215):2165-2172.)

- Randomised phase III non-inferiority trial, 2135 pat., 2006-2011, DCIS or invasive carcinoma ≤ 3 cm, pNO, age ≥40 y., no ILC
- 42.56/16 fr. or 50 Gy/25 fr. +/- Boost vs. APBI 38.5 Gy/10 fr. in one week (external beam irradiation)
- "In patients treated with **APBI**, the **5 year cumulative rate of IBTR was 2.3%** (95% CI 1.4–3.2) and the **8 year cumulative rate was 3.0%** (1.9–4.0). In patients treated with **whole breast irradiation**, the **5 year cumulative rate of IBTR was 1.7%** (0.9–2.5) and the **8 year cumulative rate was 2.8%** (1.8–3.9; figure 2). The HR for APBI versus whole breast irradiation was 1.27 (90% CI 0.84–1.91). Thus, **the upper bound of the estimated 90% CI did not exceed the non-inferiority margin of 2.02.**"
- "Late radiation toxicity (grade ≥2 [...]) was more common in patients treated with APBI (346 [32%] of 1070 patients) than whole breast irradiation (142 [13%] of 1065 patients; p<0.0001). **Adverse cosmesis [...]** was more common in patients treated with APBI than in those treated by whole breast irradiation at 3 years (absolute difference, 11.3%, 95% CI 7.5–15.0), 5 years (16.5%, 12.5–20.4), and 7 years (17.7%, 12.9–22.3)."

1. 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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Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

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

- **> 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

* 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.
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

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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, 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. 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.
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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.
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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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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.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. after neoadjuvant chemotherapy) based on the initial stage prior to NACT (cN+, cT3/4a-d)

1. Wright JL, Takita C, Reis IM, et al: Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer*. 2013 Jan 1;119(1):16-25.
2. Huang EH, Tucker SL, Strom E et al.: Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol*. 2004 Dec 1;22(23):4691-9.
3. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. *Lancet Oncol*. 2012 Jun;13(6):e270-6.
4. Rusthoven CG, Rabinovitch RA, Jones BL et al. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. *Ann Oncol*. 2016 Feb 9. pii: mdw046. [Epub ahead of print]
5. Krug D, Baumann R, Budach W et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Neoadjuvant chemotherapy for breast cancer-background for the indication of locoregional treatment. *Strahlenther Onkol*. 2018 Sep;194(9):797-805.

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Omission of Postmastectomy Radiotherapy (PMRT) to the Chest Wall after NACT in case of ypT0 ypN0 after NACT

1. Wright JL, Takita C, Reis IM et al: Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer*. 2013 Jan 1;119(1):16-25.
2. Huang EH, Tucker SL, Strom EA et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol*. 2004 Dec 1;22(23):4691-9.
3. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. *Lancet Oncol*. 2012 Jun;13(6):e270-6.
4. Rusthoven CG, Rabinovitch RA, Jones BL, et al. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. *Ann Oncol*. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

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 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.



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

PMRT can be omitted LoE 3b B AGO +	PMRT to be discussed LoE 3b B AGO +/-	PMRT recommended LoE 3b B AGO +
<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> <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) </div> <div>Truong et al. 2005</div> <div> <40 y. OR HER2 pos. OR lymphovascular invasion </div> <div>Shen H et al. 2015</div> <div> G3 OR lymphovascular invasion OR triple negative </div> </div>

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.
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“http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf” download 2016
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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.
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"](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.
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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"](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) download 2016

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, 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.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. after neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)

1. Wright JL, Takita C, Reis IM, et al. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer*. 2013 Jan 1;119(1):16-25.
2. Huang EH, Tucker SL, Strom EA et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol*. 2004 Dec 1;22(23):4691-9.
3. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. *Lancet Oncol*. 2012 Jun;13(6):e270-6.

4. Rusthoven CG, Rabinovitch RA, Jones BL et al: The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. Ann Oncol. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

Omission of Postmastectomy Radiotherapy (PMRT) to the Chest Wall after NACT in case of ypT0 ypN0 after NACT

1. Wright JL, Takita C, Reis IM et al. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. Cancer. 2013 Jan 1;119(1):16-25.
2. Huang EH, Tucker SL, Strom EA, et al: Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol. 2004 Dec 1;22(23):4691-9.
3. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. Lancet Oncol. 2012 Jun;13(6):e270-6.
4. Rusthoven CG, Rabinovitch RA, Jones BL, et al: The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. Ann Oncol. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

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.



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Boost in PMRT

- An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival
- 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
- 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

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

Thoracic wall boost irradiation

- 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 after axillary lymph node dissection or negative sentinel lymph node excision

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

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

1. Bromham N, Schmidt-Hansen M, Astin M et al.: Axillary treatment for operable primary breast cancer. Cochrane Database Syst Rev. 2017 Jan 4;1:CD004561. doi: 10.1002/14651858.CD004561.pub3. [Epub ahead of print]

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.

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. Helms G, Kuhn T, Moser L, et al. Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection:

data from a prospective randomised trial. Eur J Surg Oncol 2009; 35: 697–701.

3. Kuehn T, Bembenek A, Decker T, et al, for the Consensus Committee of the German Society of Senology. A concept for the clinical implementation of sentinel lymph node biopsy (SLNB) in breast cancer patients with special regard to quality assurance. Cancer 2005; 103: 451–61.
4. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early stage breast cancer. J Clin Oncol 2005; 23: 7703–20.
5. 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.

Axillary dissection not indicated e.g. cN0, SLN positive (see surgical chapter)

1. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis. A Randomized Clinical Trial. JAMA. 2011;305(6):569-575

Extracapsular tumor spread (ECS)

1. Stranzl H, Ofner P, Peintinger F. Postoperative irradiation in breast cancer patients with one to three positive axillary lymph nodes. Is there an impact of axillary extranodal tumor extension on locoregional and distant control? Strahlenther Onkol. 2006 Oct;182(10):583-8.
2. Stranzl H, Mayer R, Ofner P, et al: Extracapsular extension in positive axillary lymph nodes in female breast cancer patients. Patterns of failure and indications for postoperative locoregional irradiation. Strahlenther Onkol. 2004 Jan;180(1):31-7.

Axillary micrometastases or isolated cells found in regional lymph nodes

1. Pernas S1, Gil M, Benítez A, et al: Avoiding axillary treatment in sentinel lymph node micrometastases of breast cancer: a prospective analysis of axillary or distant recurrence. Ann Surg Oncol. 2010 Mar;17(3):772-7.
2. Yegiyants S, Romero LM, Haigh PI et al: Completion axillary lymph node dissection not required for regional control in patients with

breast cancer who have micrometastases in a sentinel node. Arch Surg. 2010 Jun;145(6):564-9.

	Oxford		
	LoE	GR	AGO
BCS and ACOSOG Z0011-criteria ⁺ met			
▪ Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)	2b	B	+*
BCS and ACOSOG Z0011-criteria ⁺ <u>not</u> met			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	++*
ME and chest wall RT indicated and ACOSOG Z011-criteria ⁺ <u>not</u> met or ME and chest wall RT <u>not planned</u>			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS) <u>>=3 pos. SLN</u>	1b	B	++
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	+

* = Study participation recommended
 ** = Macrometastases

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

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. Rutgers et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients – 10-year results of the EORTC AMAROS trial. Presented at SABCS 2018.

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.
2. Rutgers et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients – 10-year results of the EORTC AMAROS trial. Presented at SABCS 2018.

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, Zurrada 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.

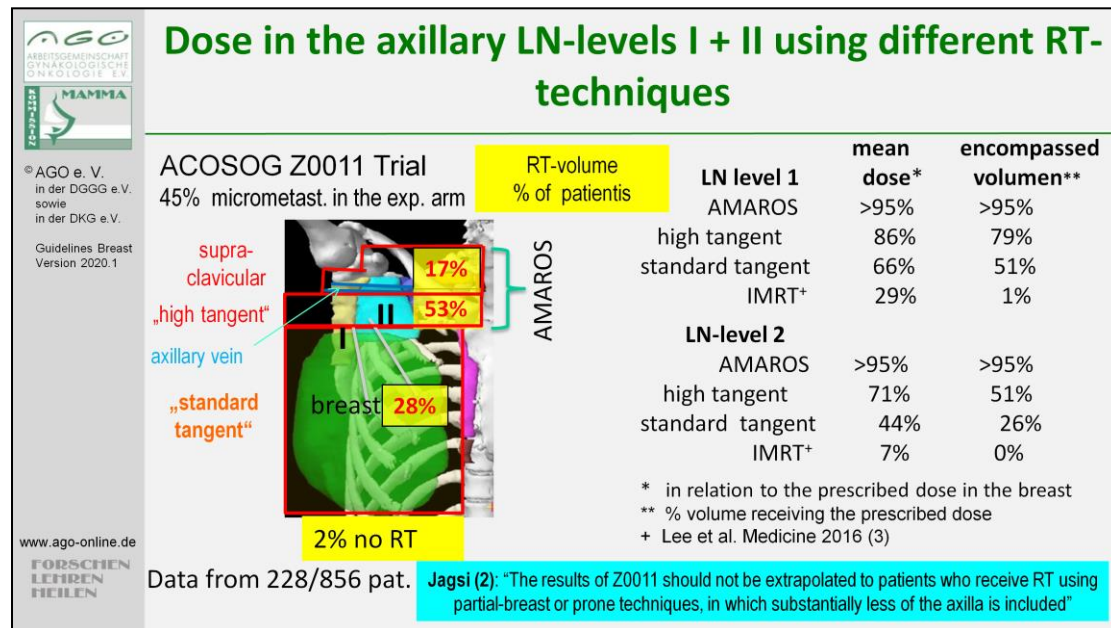
2. Rutgers et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients – 10-year results of the EORTC AMAROS trial. Presented at SABCS 2018.

>=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. Rutgers et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients – 10-year results of the EORTC AMAROS trial. Presented at SABCS 2018.
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. Rutgers et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients – 10-year results of the EORTC AMAROS trial. Presented at SABCS 2018.
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.



: 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):e4036

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 nodes ¹ in case of - central or medial tumor and G2-3 or ER/PgR-negative - premenopausal patient and G2-3 or ER/PgR-negative	2a	B	+
▪ pN0 with central or medial tumors, if premenopausal and G2-3 and ER/PgR-negative	2a	B	+/-

¹ not applicable for micrometastases



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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 et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20,

2018) 504-504. Presented at ASCO Annual Meeting 2018.

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, 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.
5. 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.
6. 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.
7. 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.
8. 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 et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 504-504. Presented at ASCO Annual Meeting 2018.
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 et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 504-504. Presented at ASCO Annual Meeting 2018.
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 TJ, 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 et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 504-504. Presented at ASCO Annual Meeting 2018
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 mammae 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 et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 504-504. Presented at ASCO Annual Meeting 2018
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. 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/PgR-negative	1b	B	+/-
▪ 1–3 positive axillary lymph nodes ¹ in case of - central or medial tumor and G2-3 or ER/PgR-negative - premenopausal patient and G2-3 or ER/PgR-negative	2a	B	+
▪ ≥ 4 positive axillary lymph nodes	2a	B	+
▪ involved internal mammary lymph nodes	2a	B	+
▪ In case of cardiac risk factors or if trastuzumab is given	2b	A	--

¹ not applicable for micrometastases

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

Internal mammaria lymph node region (IMN)

RT to Internal mammaria 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.
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supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 504-504. Presented at ASCO Annual Meeting 2018.


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. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
7. 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.
8. 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 and HR positive in patients who had systemic chemotherapy

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 et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 504-504. Presented at ASCO Annual Meeting 2018.
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. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg.* 2013 Sep 11;2013:212979.
7. 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.
8. 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



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Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks) 	1a	A	++
<ul style="list-style-type: none"> Hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks) 	2b	B	+/-

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.
3. 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.
4. Bellefqih S, Elmajjaoui S, Aarab J et al. Hypofractionated Regional Nodal Irradiation for Women With Node-Positive Breast Cancer. Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):563-570.
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Hypofractionated post-mastectomy radiotherapy and regional nodal irradiation

Wang et al. Lancet Oncol. 2019 Mar;20(3):352-360.


- Randomised phase III non-inferiority trial, 820 pat., 2008-2016, T3/4 and/or ≥ 4 involved lymph nodes, 50 Gy/25 fr. vs. 43.5 Gy/15 fr.
- 98% 2D-planned radiotherapy, no treatment of the internal mammary lymph nodes
- “The 5-year cumulative incidence of locoregional recurrence was 8.3% (90% CI 5.8–10.7) in the hypo- fractionated radiotherapy group compared with 8.1% (90% CI 5.4–10.6) in the conventional fractionated radiotherapy group (absolute difference 0.2%, 90% CI –3.0 to 2.6; HR 1.10, 90% CI 0.72 to 1.69; figure 2).
- “In conclusion, this study provides high-level evidence for the clinical use of hypofractionated postmastectomy radiotherapy for patients with high-risk breast cancer. It can be recommended in clinical practice to patients who do not plan breast reconstruction and will not receive internal mammary node irradiation.”

1. 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.

	<h2>Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes</h2>		
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p>	<p>(median follow-up 10.9 yrs)</p>		
	Adjuvant treatment	n*	Hazard ratio (95%CI)
	No adjuvant reported	625	0.91 (0.59 - 1.39)
	Chemotherapy	954	1.05 (0.84 - 1.32)
	Endocrine therapy	1185	0.82 (0.63 - 1.06)
	Both (endocrine th. and chemotherapy)	1200	0.72 (0.55 – 0.94)
	Total	4004	0.88 (0.76 – 1.01)
<p>www.ago-online.de</p>	<p>* missing data on 40 patients</p>		
<p>FORSCHEN LEHREN HEILEN</p>	<p>Poortmans et al. ECCO Amsterdam 2013</p>		

1. Poortmans P, Struikmans H, Kirkove C, et al: Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer, 2013; 49 (Suppl. 3): abstr. #2BA.



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Radiotherapy following NACT

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

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

Locally advanced: T3-4 or cN2-N3,

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

¹ Criteria for increased risk of relapse:

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

* = confirmed by core biopsy

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Molecular predictors and use of radiotherapy

	Oxford LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Results of gene expression profiling should not be used for indication of radiotherapy 	2b	B	++

1. Krug D, Baumann R, Budach W et al. Commercially available gene expression assays as a predictive tool for adjuvant radiotherapy? A critical review. Breast Care 2020



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Use of concomitant Systemic Therapy with adjuvant locoregional Radiotherapy

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

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

* concurrent Trastuzumab/Pertuzumab and parasternal radiotherapy should be avoided

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

Trastuzumab* concurrent with radiotherapy (*in HER2 pos tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT)

1. 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).
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Tamoxifen concurrent with radiotherapy

1. Chargari C, Toillon RA, Macdermed D, et al: Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? *Lancet Oncol*. 2009 Jan;10(1):53-60.
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AI (letrozole, anastrozole) concurrent with radiotherapy

1. Chargari C, Toillon RA, Macdermed D, et al: Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? *Lancet Oncol*. 2009 Jan;10(1):53-60.
2. Belkacémi Y, Fourquet A, Cutuli B, et al. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. *Crit Rev Oncol Hematol* 2011;79:91-102
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Pertuzumab concurrent with radiotherapy

1. Von Minckwitz G, Procter M, de Azambuja E et al., Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer, *N Engl J Med*. 2017 Jul 13;377(2):122-131

T-DM1 concurrent with radiotherapy

1. Von Minckwitz G, Huang CS, Mano MS et al., Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer, *N Engl J Med*. 2018 Dec

Checkpointinhibitors concurrent with radiotherapy

Extrapolated from trial results in other tumor entities and from current clinical trial in breast cancer

Capecitabine and radiotherapy

1. Masuda N, Lee SJ, Ohtani S et al., Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy, *N Engl J Med*. 2017 Jun 1;376(22):2147-2159
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Advanced Breast Cancer. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):777-783

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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%



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Smoking and Risk of secondary lung cancer

Oxford		AGO
LoE	GR	
1a	A	
		++
		++

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

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.