Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Guidelines Breast
Version 2023.1D

FORSCHEN
LEHREN
HEILEN

Adjuvante Strahlentherapie

Adjuvante Radiotherapie (RT)

- **Versionen 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.

Guidelines Breast
Version 2023.1D

Vorbemerkung

- **Diese Empfehlungen zur adjuvanten Strahlentherapie bei Brustkrebs basieren auf einer Konsensusdiskussion zwischen Experten der Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) und der Deutschen Gesellschaft für Radioonkologie (DEGRO).**
- **Für technische Details zur Durchführung der Strahlentherapie verweisen wir auf die entsprechenden aktualisierten Leitlinien der DEGRO.**

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.
9. Piroth MD, Krug D, Sedlmayer F et al. Post-neoadjuvant treatment with capecitabine and trastuzumab emtansine in breast cancer patients-sequentially, or better simultaneously? Strahlenther Onkol. 2021 Jan;197(1):1-7.
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

Radiotherapie (RT) nach brusterhaltenden Operationen (BEO; invasive Karzinome)

	Oxford		
	LoE	GR	AGO
▪ **Bestrahlung der operierten Brust**	1a	A	++
▪ **Moderat hypofraktionierte RT (Gesamtdosis ca. 40 Gy in ca. 15-16 Fraktionen in ca. 3 bis 5 Wochen)**	1a	A	++
▪ **Ultra-hypofraktionierte RT (Gesamtdosis 26 Gy, d.h. 5 Fraktionen in einer Woche = 1 Fraktion/Tag bzw. 28,5 Gy, d.h. 5 Fraktionen in 5 Wochen = 1 Fraktion/Woche)**	1b	B	+/-
▪ **Konventionell fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25-28 Fraktionen in ca. 5-6 Wochen)**	1a	B	+
▪ **Bei Lebenserwartung < 10 Jahre und pT1, pN0, R0, ER / PR positiv, HER2-negativ, endokriner adjuvanter Therapie (alle Faktoren) kann unter Inkaufnahme eines erhöhten Lokalrezidivrisikos nach individueller Beratung auf die RT verzichtet werden.**	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.
3. 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
4. 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.
5. 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.
6. Offersen B, Alsner J, Nielsen HM et al., Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial . J Clin Oncol. 2021;38:3615–3625.

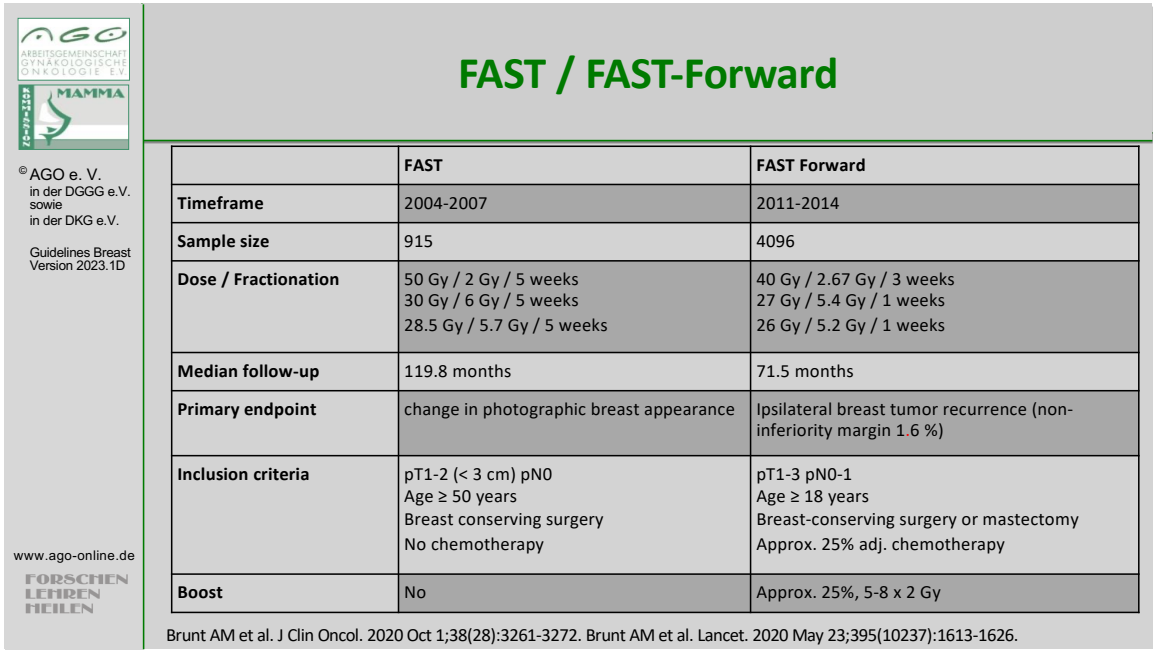
7. Wang SL, Fang H, Hu C et al., Hypofractionated Versus Conventional Fractionated Radiotherapy After Breast-Conserving Surgery in the Modern Treatment Era: A Multicenter, Randomized Controlled Trial From China. J Clin Oncol. 2021;38:3604–3614.
8. Jagsi R, Griffith KA, Vicini FA et al. Disease Control After Hypofractionation Versus Conventional Fractionation for Triple Negative Breast Cancer: Comparative Effectiveness in a Large Observational Cohort. Int J Radiat Oncol Biol Phys. 2021;S0360-3016(21)02918-7. doi: 10.1016/j.ijrobp.2021.10.012.
9. Fodor A, Brombin C, Mangili P et al. Impact of molecular subtype on 1325 early-stage breast cancer patients homogeneously treated with hypofractionated radiotherapy without boost: Should the indications for radiotherapy be more personalized? Breast. 2021;55:45-54.
10. Purswani JM, Oh C, Jaros B et al. Breast Conservation in Women with Autoimmune Disease: The Role of Active Autoimmune Disease and Hypofractionation on Acute and Late Toxicity in a Case-Controlled Series. Int J Radiat Oncol Biol Phys. 2021;110(3):783-791.
11. Meattini I, Becherini C, Boersma L et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 2022;23(1):e21-e31.

Ultra-Hypofractionation

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.
2. 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.
3. Whelan T, Levine M, Sussman J. Hypofractionated Breast Irradiation: What's Next? J Clin Oncol. 2020 Oct 1;38(28):3245-3247.
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.
5. 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.

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.
2. Blamey RW, Bates T, Chetty U et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. Eur J Cancer. 2013 Jul;49(10):2294-302.
3. 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.
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.
5. 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.
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
7. Matuschek C, Bölke E, Haussmann J, et al (2017) The benefit of adjuvant radiotherapy after breast conserving surgery in older patients with low risk breast cancer- a meta-analysis of randomized trials. Radiation oncology (London, England) 12:60–8.



FAST / FAST-Forward

	FAST	FAST Forward
Timeframe	2004-2007	2011-2014
Sample size	915	4096
Dose / Fractionation	50 Gy / 2 Gy / 5 weeks 30 Gy / 6 Gy / 5 weeks 28.5 Gy / 5.7 Gy / 5 weeks	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	71.5 months
Primary endpoint	change in photographic breast appearance	Ipsilateral breast tumor recurrence (non-inferiority margin 1.6 %)
Inclusion criteria	pT1-2 (< 3 cm) pN0 Age ≥ 50 years Breast conserving surgery No chemotherapy	pT1-3 pN0-1 Age ≥ 18 years Breast-conserving surgery or mastectomy Approx. 25% adj. chemotherapy
Boost	No	Approx. 25%, 5-8 x 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.
2. 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.
3. Whelan T, Levine M, Sussman J. Hypofractionated Breast Irradiation: What's Next? J Clin Oncol. 2020 Oct 1;38(28):3245-3247.
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.

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.

<u>Ultra-Hypofractionation</u>

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.
2. 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.
3. Whelan T, Levine M, Sussman J. Hypofractionated Breast Irradiation: What's Next? J Clin Oncol. 2020 Oct 1;38(28):3245-3247.
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.
2. Blamey RW, Bates T, Chetty U et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. Eur J Cancer. 2013 Jul;49(10):2294-302.
3. 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.
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.
5. 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.
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

Guidelines Breast
Version 2023.1D

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Boostbestrahlung nach BEO beim invasiven Karzinom

	Oxford LoE	GR	AGO
Boost-RT des Tumorbettes (verbesserte lokale Kontrolle, kein Überlebensvorteil)			
Prämenopausal	1b	B	++
Postmenopausal, sofern > T1*, G3, HER2-positiv, tripel-negativ, EIC (mindestens 1 Faktor)	2b	B	+
Techniken			
Perkutan (Photonen, Elektronen) als sequentieller Boost	1a	A	++
Multikatheter-Brachytherapie	1a	A	++
Perkutan als simultan integrierter Boost (bei konventionell fraktionierter RT)	1b	B	+
Perkutan als simultan integrierter Boost (bei hypofraktionierter RT)	1b[a]	B	+
Intraoperative Radiotherapie (als vorgezogener Boost)	2b	B	+
Intraoperative Clipmarkierung des Tumorbetts bei Indikation für Boostbestrahlung	2b	B	+

*kontinuierliche Variable bzgl. Rezidiv

Boost in general (EBRT/Brachytherapy, sequential)

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

Simultaneous-integrated boost (conventionally fractionated RT)

1. Hörner-Rieber J, Forster T, Hommertgen A et al. Intensity-modulated radiotherapy (IMRT) with simultaneously integrated boost shortens treatment time and is non-inferior to conventional radiotherapy followed by sequential boost in adjuvant breast cancer treatment: results of a large randomized phase III trial (IMRT-MC2 trial). Int J Radiat Oncol Biol Phys. 2020 Dec 12:S0360-3016(20)34651-4.
2. Choi KH, Ahn SJ, Jeong JU et al. Postoperative radiotherapy with intensity-modulated radiation therapy versus 3-dimensional conformal radiotherapy in early breast cancer: A randomized clinical trial of KROG 15-03. Radiother Oncol. 2020 Sep 24;154:179-186.
3. Krug D, Köder C, Häfner MF et al. Acute toxicity of normofractionated intensity modulated radiotherapy with simultaneous integrated boost compared to three-dimensional conformal radiotherapy with sequential boost in the adjuvant treatment of breast cancer. Radiat Oncol. 2020 Oct 13;15(1):235.
4. Bantema-Joppe EJ, Vredeveld 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.
5. Bantema-Joppe EJ, Schilstra C, de Bock GH, et al (2012) Simultaneous integrated boost irradiation after breast-conserving surgery: physician-rated toxicity and cosmetic outcome at 30 months' follow-up. Int J Radiat Oncol Biol Phys 83:e471–7.

Simultaneous-integrated boost (hypofractionated RT)

1. Paelinck L, Gulyban A, Lakosi F, et al (2017) Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation? A randomized controlled trial. Radiother Oncol 122:30–36.
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. Krug D, Baumann R, Krockenberger K et al. Adjuvant hypofractionated radiotherapy with simultaneous integrated boost after breast-conserving surgery: results of a prospective trial. Strahlenther Onkol. 2021;197(1):48-55..
6. 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.
7. Franceschini D, Fogliata A, Spoto R, Dominici L, Lo Faro L, Franzese C, u. a. Long term results of a phase II trial of hypofractionated adjuvant radiotherapy for early-stage breast cancer with volumetric modulated arc therapy and simultaneous integrated boost. Radiother Oncol. 2021;164:50–6.
8. Pfaffendorf C, Vonthein R, Krockenberger-Ziegler K et al. Hypofractionation with simultaneous integrated boost after breast-conserving surgery: Long term results of two phase-II trials. Breast. 2022 Aug;64:136-142.
9. 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.
10. 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.

Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI

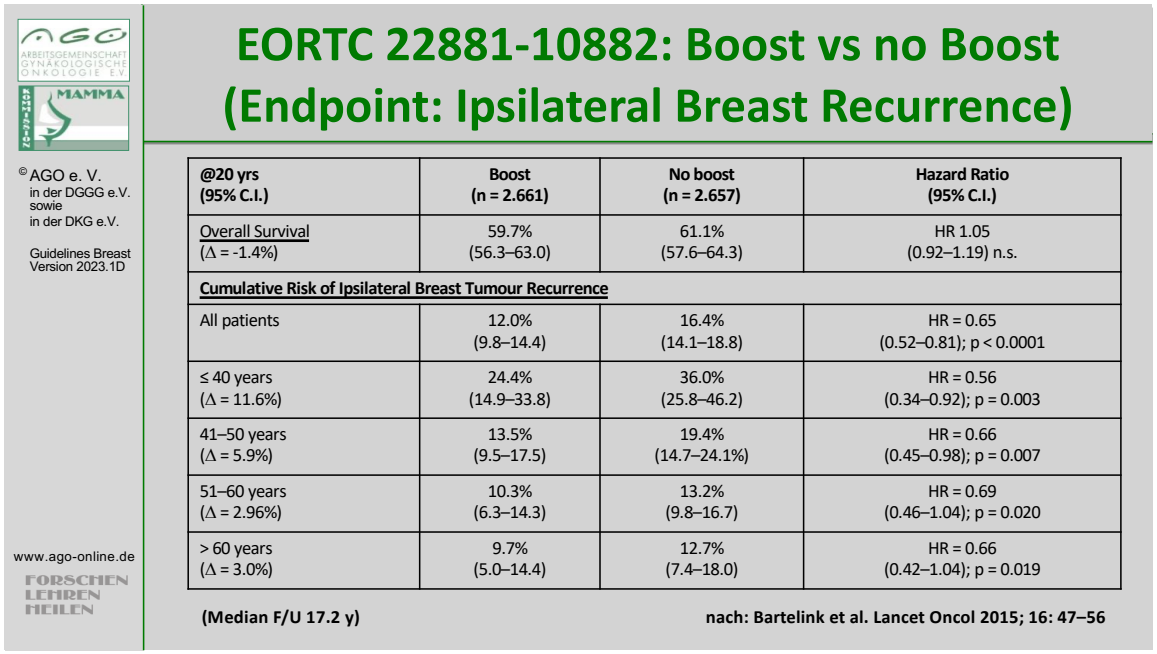
1. Ciabattoni A, Gregucci F, Fastner G et al. IOERT versus external beam electrons for boost radiotherapy in stage I/II breast cancer: 10-year results of a phase III randomized study. Breast Cancer Res. 2021;23(1):46.
2. Fastner G, Reitsamer R, Urbański B et al. Toxicity and cosmetic outcome after hypofractionated whole breast irradiation and boost-IOERT in early stage breast cancer (HIOB): First results of a prospective multicenter trial (NCT01343459). Radiother Oncol. 2020 May;146:136-142.
3. Fastner G, Reitsamer R, Gaisberger C et al. Hypofractionated Whole Breast Irradiation and Boost-IOERT in Early Stage Breast Cancer

(HIOB): First Clinical Results of a Prospective Multicenter Trial (NCT01343459). Cancers (Basel). 2022 Mar 9;14(6):1396.
4. 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 ISIORT pooled analysis. 2013 Aug;108(2):279-86.
5. 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.
6. 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.
7. Ahn SG, Bae SJ, Lee HW et al. A phase II study investigating the acute toxicity of targeted intraoperative radiotherapy as tumor-bed boost plus whole breast irradiation after breast-conserving surgery in Korean patients. Breast Cancer Res Treat. 2019;174(1):157-163.
8. Stoian R, Erbes T, Zamboglou C et al. Intraoperative radiotherapy boost as part of breast-conservation therapy for breast cancer: a single-institution retrospective analysis. Strahlenther Onkol. 2021;197(9):812-819.
9. Pez M, Keller A, Welzel G et al. Long-term outcome after intraoperative radiotherapy as a boost in breast cancer. Strahlenther Onkol. 2020;196(4):349-355.

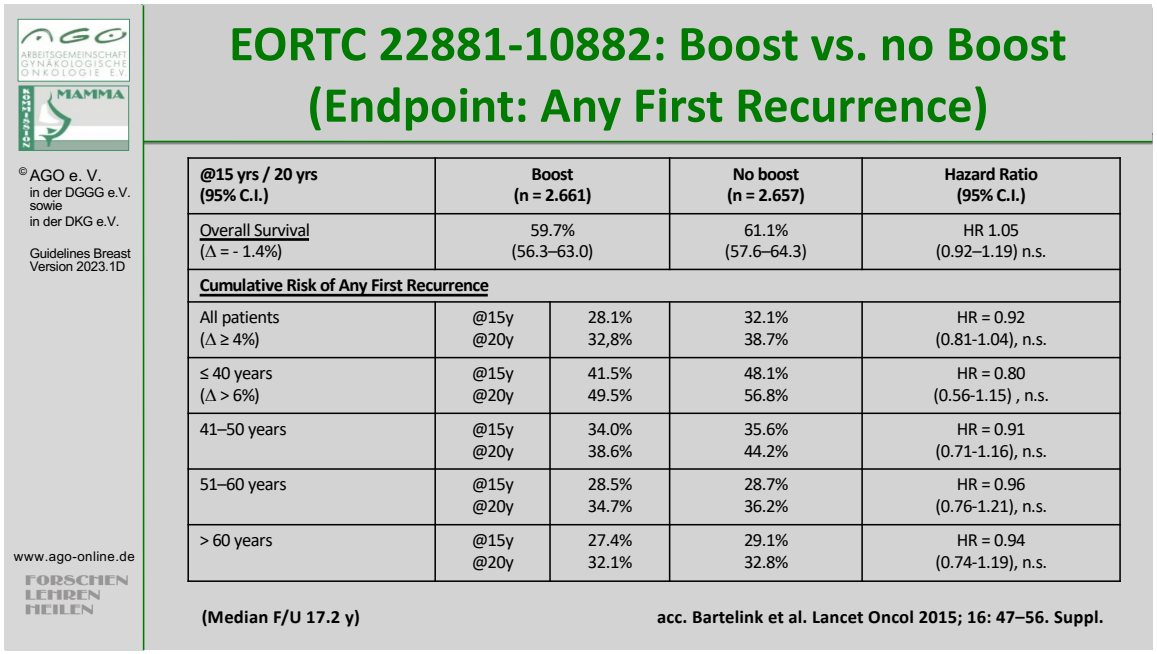
<u>Clip placement</u>

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, Elkhuizen 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.
5. Major T, Gutiérrez C, Guix B, et al (2015) Interobserver variations of target volume delineation in multicatheter partial breast brachytherapy after open cavity surgery. Brachytherapy 14:925–932.

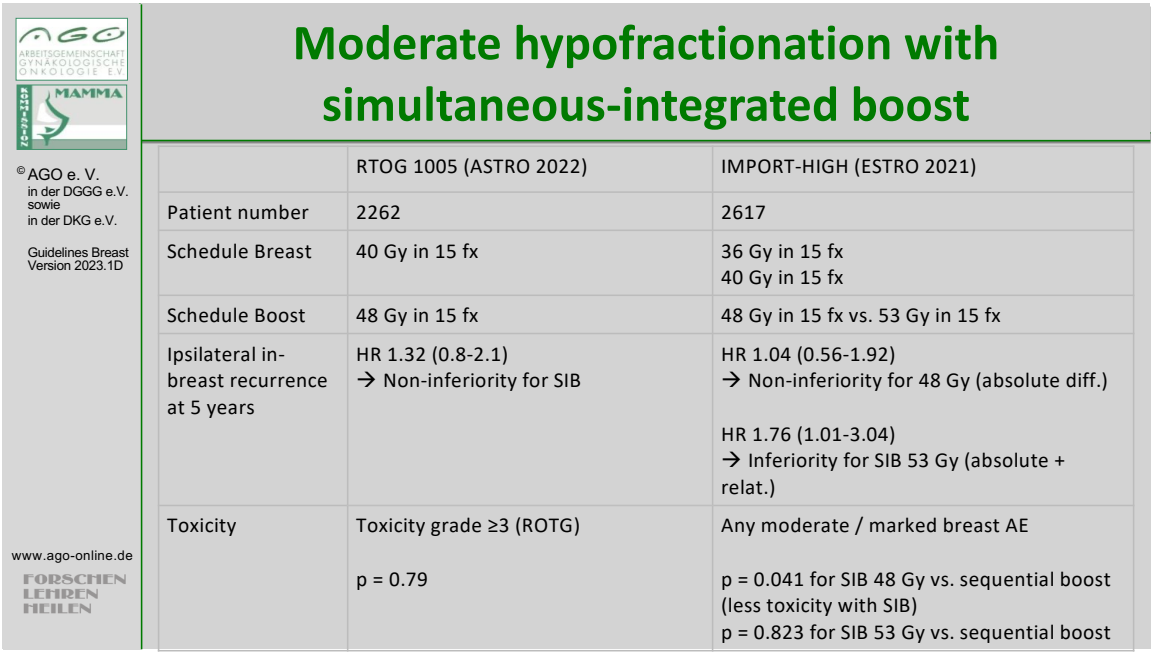
6. Major T, Gutiérrez C, Guix B, et al (2016) Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol 118:199–204.
7. Strnad V, Hannoun-Levi J-M, Guinot J-L, et al (2015) Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery. Radiother Oncol 115:342–348.



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



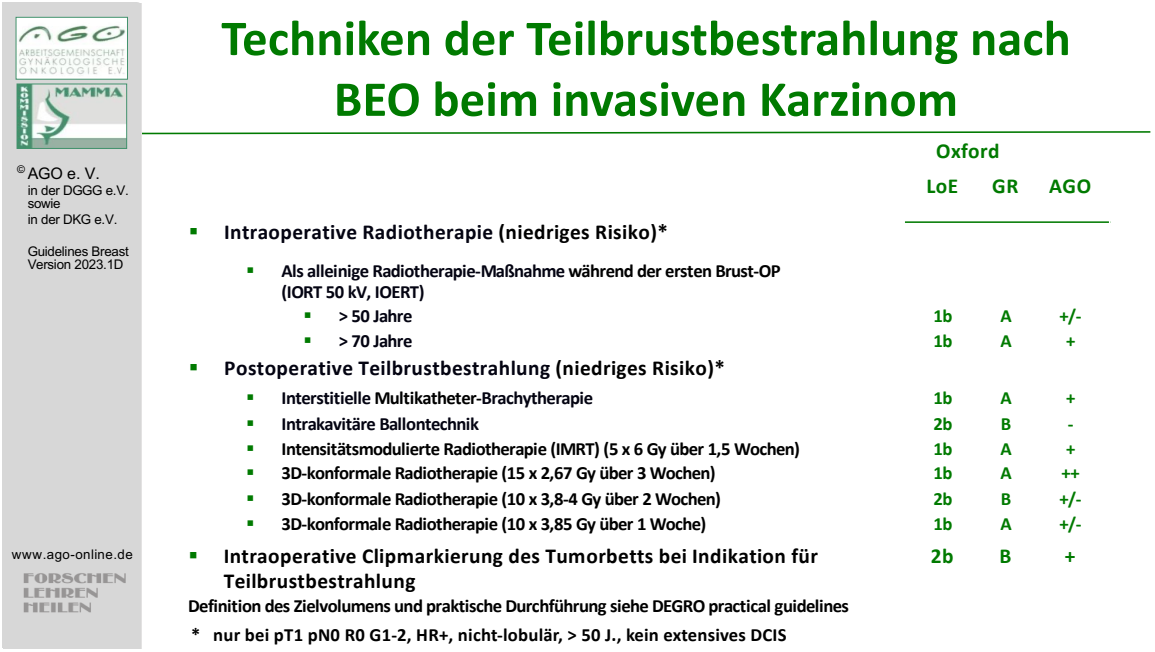
1. Bartelink H, Maingon P, Poortmans P, et al; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised 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



Moderate hypofractionation with simultaneous-integrated boost

	RTOG 1005 (ASTRO 2022)	IMPORT-HIGH (ESTRO 2021)
Patient number	2262	2617
Schedule Breast	40 Gy in 15 fx	36 Gy in 15 fx 40 Gy in 15 fx
Schedule Boost	48 Gy in 15 fx	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	HR 1.04 (0.56-1.92) → Non-inferiority for 48 Gy (absolute diff.) HR 1.76 (1.01-3.04) → Inferiority for SIB 53 Gy (absolute + relat.)
Toxicity	Toxicity grade ≥3 (ROTG) p = 0.79	Any moderate / marked breast AE p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB) p = 0.823 for SIB 53 Gy vs. sequential boost

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.



Techniken der Teilbrustbestrahlung nach BEO beim invasiven Karzinom

	Oxford LoE	GR	AGO
▪ **Intraoperative Radiotherapie (niedriges Risiko)***			
▪ Als alleinige Radiotherapie-Maßnahme während der ersten Brust-OP (IORT 50 kV, IOERT)			
▪ > 50 Jahre	1b	A	+/-
▪ > 70 Jahre	1b	A	+
▪ **Postoperative Teilbrustbestrahlung (niedriges Risiko)***			
▪ Interstitielle Multikatheter-Brachytherapie	1b	A	+
▪ Intrakavitäre Ballontechnik	2b	B	-
▪ Intensitätsmodulierte Radiotherapie (IMRT) (5 x 6 Gy über 1,5 Wochen)	1b	A	+
▪ 3D-konformale Radiotherapie (15 x 2,67 Gy über 3 Wochen)	1b	A	++
▪ 3D-konformale Radiotherapie (10 x 3,8-4 Gy über 2 Wochen)	2b	B	+/-
▪ 3D-konformale Radiotherapie (10 x 3,85 Gy über 1 Woche)	1b	A	+/-
▪ **Intraoperative Clipmarkierung des Tumorbetts bei Indikation für Teilbrustbestrahlung**	2b	B	+

Definition des Zielvolumens und praktische Durchführung siehe DEGRO practical guidelines

* nur bei pT1 pN0 R0 G1-2, HR+, nicht-lobulär, > 50 J., kein extensives 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.
3. Vaidya JS, Bulsara M, Baum M et al. New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer Brit J Cancer. 2021. 125:380–389.
4. Orecchia R, Veronesi U, Maisonneuve P et al., Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. Lancet Oncol. 2021. 22:597–608.

>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 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.
6. Polgár C, Major T, Takácsi-Nagy Z et al. Breast-Conserving Surgery Followed by Partial or Whole Breast Irradiation: Twenty-Year Results of a Phase 3 Clinical Study. Int J Radiat Oncol Biol Phys. 2020 Nov 10;S0360-3016(20)34492-8

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.
3. Offersen BV, Alsner J, Nielsen HM, et al (2022) Partial Breast Irradiation Versus Whole Breast Irradiation for Early Breast Cancer Patients in a Randomized Phase III Trial: The Danish Breast Cancer Group Partial Breast Irradiation Trial. J Clin Oncol 40:4189–4197.
4. Thomsen MS, Alsner J, Nielsen HM, et al (2022) Volume matters: Breast induration is associated with irradiated breast volume in the Danish Breast Cancer Group phase III randomized Partial Breast Irradiation trial. Radiother Oncol 177:231–235.

3D-conformal RT (10x3.85-4 Gy over two weeks)

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.
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.

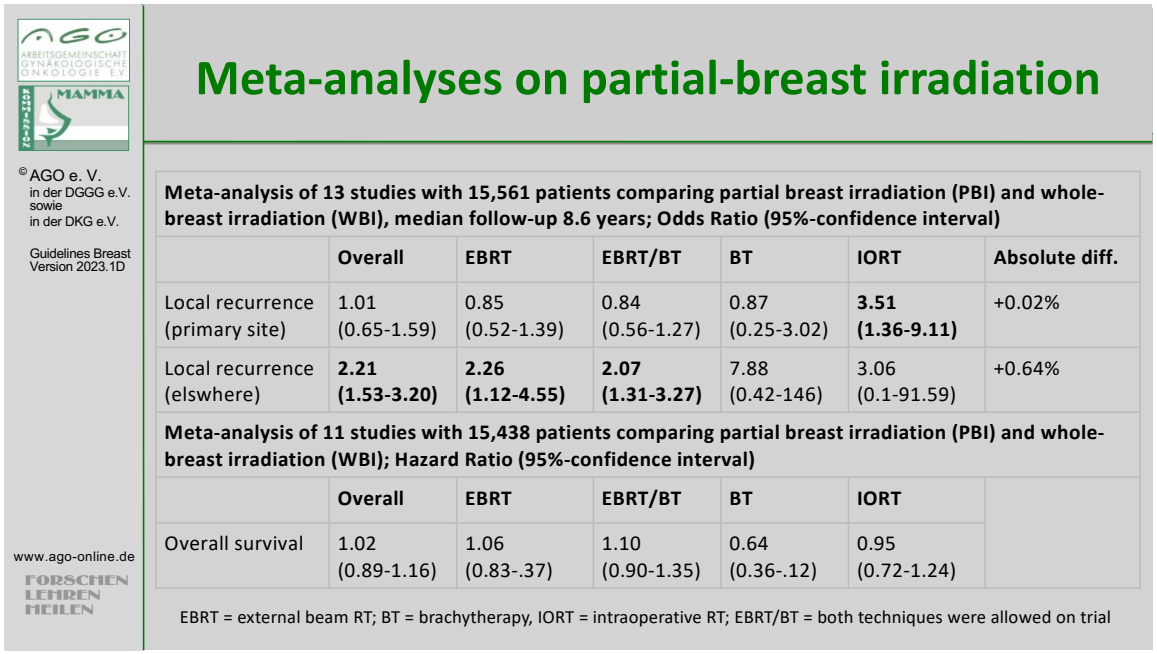
<u>3D-conformal RT (10x3.85 Gy over one week)</u>

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

<u>Clip placement</u>

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, Elkhuizen 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.
5. Major T, Gutiérrez C, Guix B, et al (2015) Interobserver variations of target volume delineation in multicatheter partial breast brachytherapy after open cavity surgery. Brachytherapy 14:925–932.
6. Major T, Gutiérrez C, Guix B, et al (2016) Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol 118:199–204.
7. Strnad V, Hannoun-Levi J-M, Guinot J-L, et al (2015) Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery. Radiother Oncol 115:342–348.



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

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

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

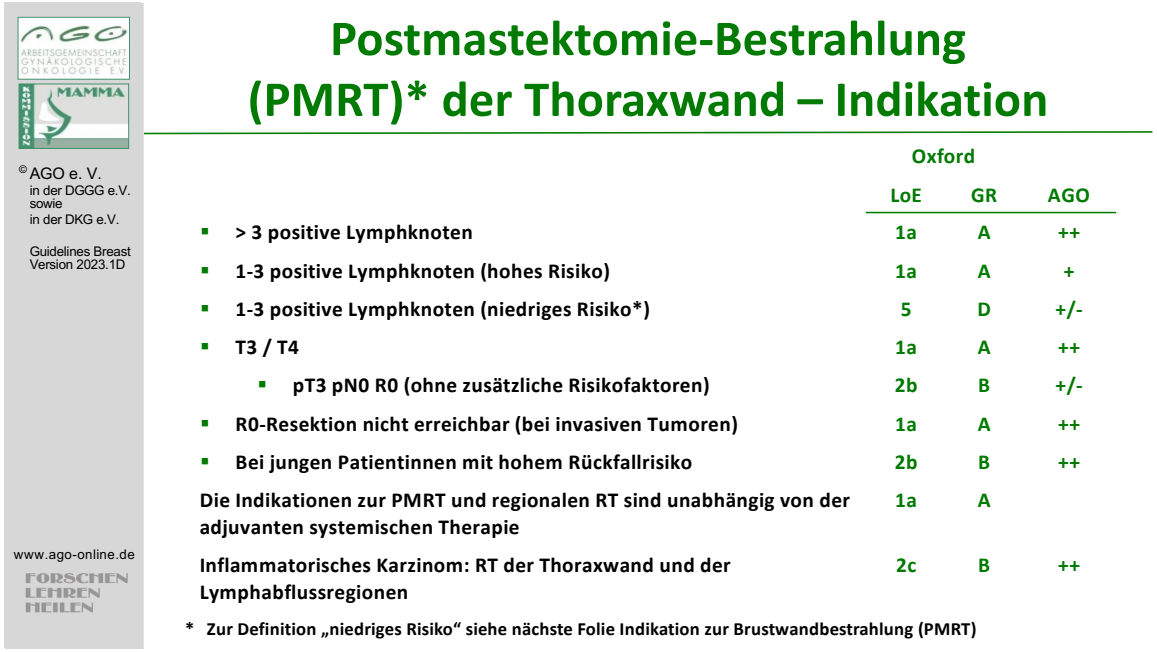
	Overall	EBRT	EBRT/BT	BT	IORT
Overall survival	1.02 (0.89-1.16)	1.06 (0.83-.37)	1.10 (0.90-1.35)	0.64 (0.36-.12)	0.95 (0.72-1.24)

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

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



Postmastektomie-Bestrahlung (PMRT)* der Thoraxwand – Indikation

	Oxford		
	LoE	GR	AGO
▪ > 3 positive Lymphknoten	1a	A	++
▪ 1-3 positive Lymphknoten (hohes Risiko)	1a	A	+
▪ 1-3 positive Lymphknoten (niedriges Risiko*)	5	D	+/-
▪ T3 / T4	1a	A	++
▪ pT3 pN0 R0 (ohne zusätzliche Risikofaktoren)	2b	B	+/-
▪ R0-Resektion nicht erreichbar (bei invasiven Tumoren)	1a	A	++
▪ Bei jungen Patientinnen mit hohem Rückfallrisiko	2b	B	++
Die Indikationen zur PMRT und regionalen RT sind unabhängig von der adjuvanten systemischen Therapie	1a	A	
Inflammatorisches Karzinom: RT der Thoraxwand und der Lymphabflussregionen	2c	B	++

* Zur Definition „niedriges Risiko“ siehe nächste Folie Indikation zur Brustwandbestrahlung (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 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, 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.
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. Eff ect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 2007; 69: 1478–83.
2. Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77.
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.

Postmastektomie-Bestrahlung (PMRT) der Thoraxwand* – Fraktionierung

	Oxford		
	LoE	GR	AGO
▪ **Moderat hypofraktionierte RT (Gesamtdosis ca. 40 Gy in ca. 15-16 Fraktionen in ca. 3 bis 5 Wochen)**	1a	A	++
▪ **Nach Brustrekonstruktion**	2b	B	+
▪ **Ultra-hypofraktionierte RT (Gesamtdosis 26 Gy, d.h. 5 Fraktionen in einer Woche = 1 Fraktion/Tag bzw. 28,5 Gy, d.h. 5 Fraktionen in 5 Wochen = 1 Fraktion/Woche)**	1b	B	+/-
▪ **Konventionell fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25-28 Fraktionen in ca. 5-6 Wochen)**	1a	B	+

* **Zur Fraktionierung bei Bestrahlung der Lymphabflusswege siehe Folie „Fraktionierung der Radiotherapie lokoregionärer Lymphabflussregionen“.**

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. 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.
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. 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.

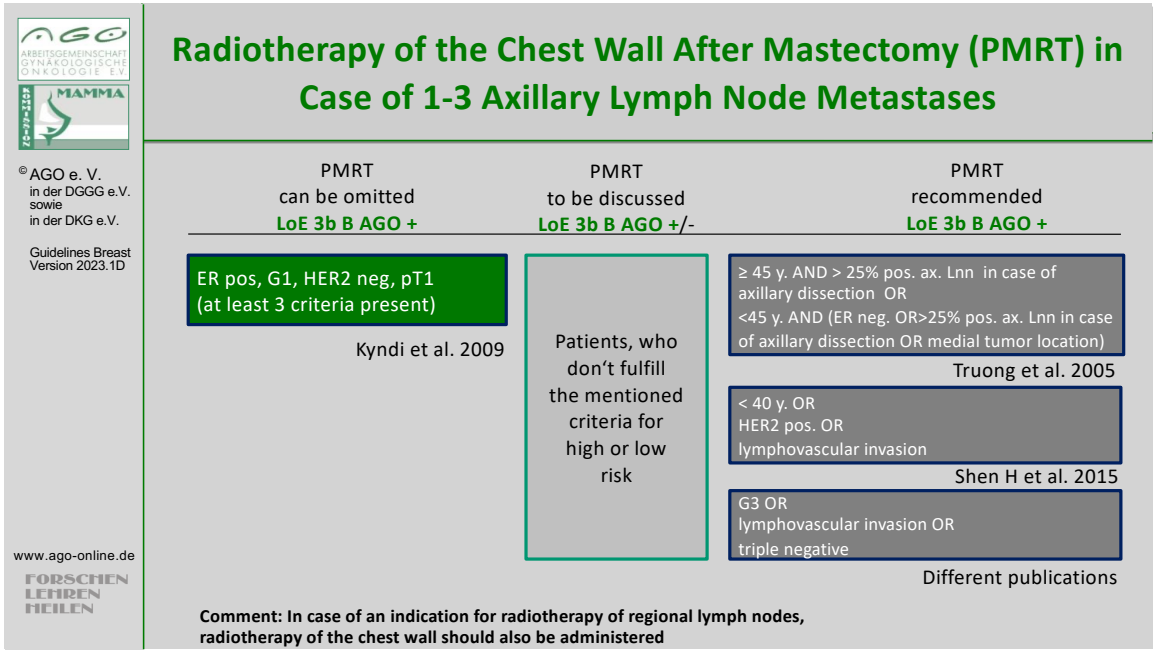
Moderate hypofractionation and breast reconstruction

1. Kim D-Y, Park E, Heo CY, et al (2022) Influence of Hypofractionated Versus Conventional Fractionated Postmastectomy Radiation

Therapy in Breast Cancer Patients With Reconstruction. Int J Radiat Oncol Biology Phys 112:445–456.
2. Kim D-Y, Park E, Heo CY, et al (2021) Hypofractionated versus conventional fractionated radiotherapy for breast cancer in patients with reconstructed breast: Toxicity analysis. Breast 55:37–44.
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.



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

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. Eff ect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 2007; 69: 1478–83.
2. Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77.
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 bei PMRT

	Oxford		
	LoE	GR	AGO
▪ Eine Boost-Bestrahlung der Thoraxwand hat keinen Einfluss auf das brustkrebsspezifische und Gesamtüberleben	2a	B	
▪ Eine Boost-Bestrahlung der Thoraxwand sollte nur bei nachgewiesener R1 / R2-Situation ohne Möglichkeit einer Nachresektion erfolgen	5	D	++
▪ Reicht der Tumor nach Mastektomie (unter Mitnahme der Pectoralisfaszie) an den pectoralen Absetzungsrand heran und ist ein faszienüberschreitendes Tumorwachstum klinisch nicht zu erkennen, ist von einer R0-Situation auszugehen. Eine Boostbestrahlung ist nicht erforderlich	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

Radiotherapie der Axilla bei Patientinnen mit positiven Sentinel-Lymphknoten** ohne axilläre Dissektion

	Oxford		
	LoE	GR	AGO
BET und ACOSOG Z0011-Kriterien⁺ erfüllt	2b	B	+*
▪ **Radiotherapie der Brust unter Einschluss von Level 1 + 2 bis 5 mm unterhalb der Vena axillaris (PTV)**			
BET und ACOSOG Z0011-Kriterien⁺ nicht erfüllt	1b	B	++*
▪ **Radiotherapie der Axilla (analog AMAROS)**			
Nach ME, RT der Thoraxwand indiziert und ACOSOG Z011-Kriterien⁺ nicht erfüllt oder ME und RT der Thoraxwand nicht geplant			
▪ **Radiotherapie der Axilla (analog AMAROS)**	1b	B	++
≥ 3 pos. SLN			
▪ **Radiotherapie der Axilla (analog AMAROS)**	1b	B	+

* Studienteilnahme empfohlen
** Makrometastasen
⁺ < T3, keine palpablen LK, R0, 1-2 befallene SN, keine NACT

1-2 pos SLN: BCT: No further treatment to the axilla neither axillary dissection nor RT of the axilla (criteria according ACOSOG Z011)

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.
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, 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.
2. Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https://doi.org/10.1200/jco.22.01565

>=3 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.

Zusätzliche RT der Axilla nach primärer Operation (bei Indikation zur Radiotherapie der Mamma/Brustwand[1] +/- supra- / infraklavikulärer und parasternaler RT[2]) Erweiterung des PTV (planning target volume) zur Erfassung von Level I-II[3]	Oxford		
	LoE	GR	AGO
pN-Status			
pN0(sn) / pN1mic(sn)	1b	B	--
pN0/+ nach ALND	1a	A	--
pN+(sn) analog ACOSOG Z0011 (keine ALND)	2b	B	+
pN+(sn) nicht analog ACOSOG Z0011 → gemäß AMAROS-Studie[4] (ALND nicht erfolgt)	1b	B	++
R2-Situation Axilla	5	D	++

[1]Eine inzidentelle Dosisbelastung in Teilen von Level I/II ist technisch nicht zu umgehen. [2]Die Indikation für eine RT der SCG/ICG und der IMC ist separat zu prüfen. [3]Bis 5 mm unterhalb der Vena axillaris. [4] < T3, keine palpablen LK, R0, 1-2 befallene SN, RT immer in Kombination mit supra- und infraklavikulärer 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 fi ndings from the NSABPB-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927–33.
2. Galimberti V, Manika A, Maisonneuve P, et al. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. Eur J Surg Oncol. 2014 Oct;40(10):1203-8.

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

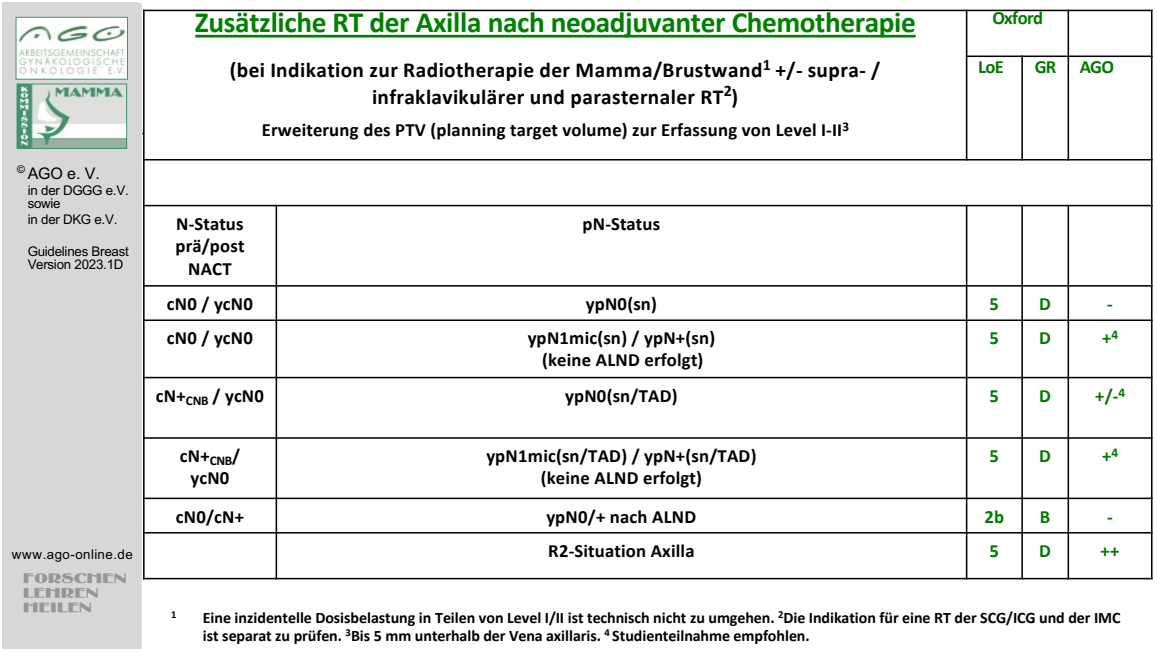
1. Galimberti V, Cole BF, Zurrida S, et al. International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305.
2. 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.



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2023.1D

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Zusätzliche RT der Axilla nach neoadjuvanter Chemotherapie

(bei Indikation zur Radiotherapie der Mamma/Brustwand[1] +/- supra- / infraklavikulärer und parasternaler RT[2])

Erweiterung des PTV (planning target volume) zur Erfassung von Level I-II[3]

N-Status prä/post NACT	pN-Status	Oxford LoE	Oxford GR	AGO
cN0 / ycN0	ypN0(sn)	5	D	-
cN0 / ycN0	ypN1mic(sn) / ypN+(sn) (keine ALND erfolgt)	5	D	+[4]
$cN+_{CNB}$ / ycN0	ypN0(sn/TAD)	5	D	+/-[4]
$cN+_{CNB}$/ ycN0	ypN1mic(sn/TAD) / ypN+(sn/TAD) (keine ALND erfolgt)	5	D	+[4]
cN0/cN+	ypN0/+ nach ALND	2b	B	-
	R2-Situation Axilla	5	D	++

[1] Eine inzidentelle Dosisbelastung in Teilen von Level I/II ist technisch nicht zu umgehen. [2]Die Indikation für eine RT der SCG/ICG und der IMC ist separat zu prüfen. [3]Bis 5 mm unterhalb der Vena axillaris. [4] Studienteilnahme empfohlen.

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.

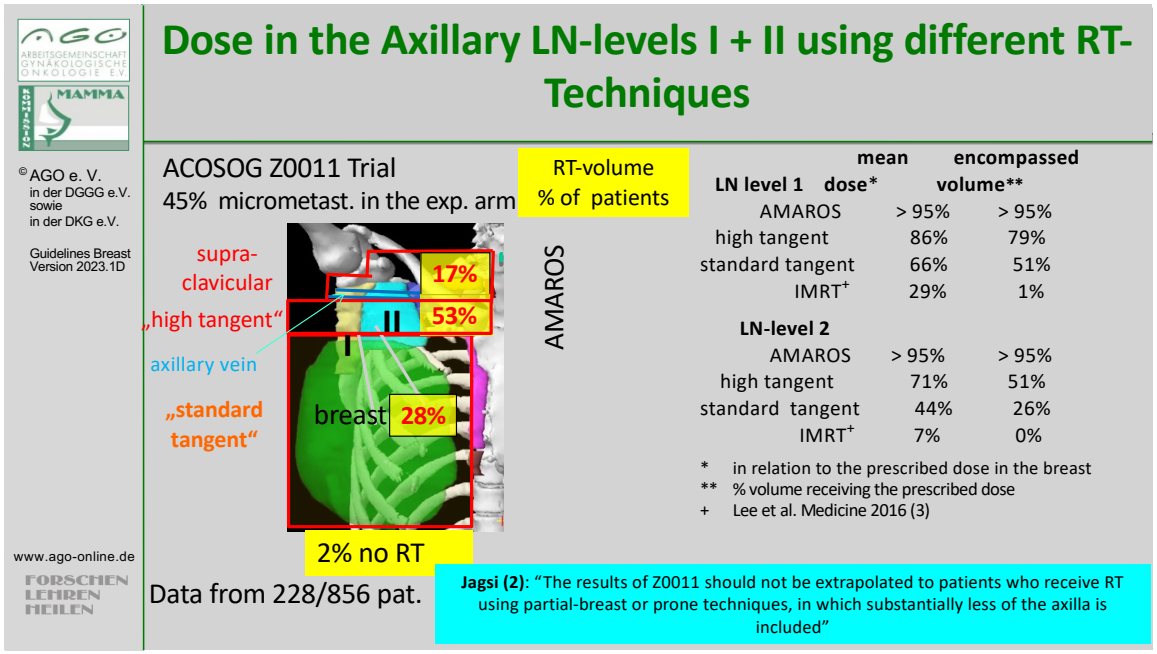
Axillary intervention after PST

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.

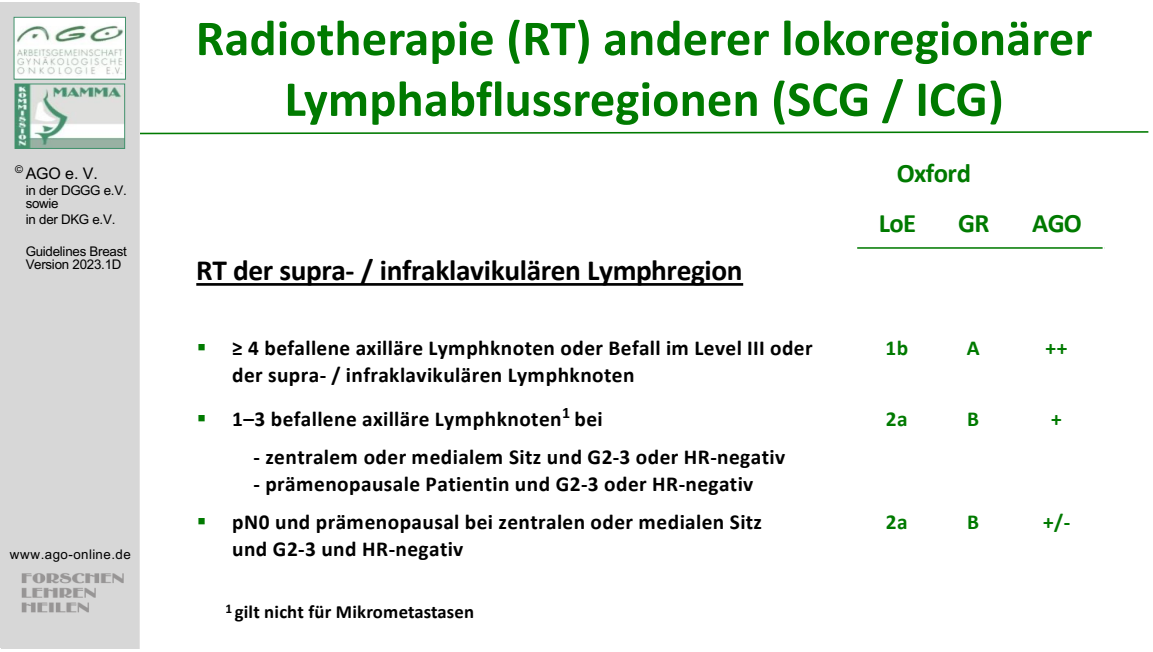
3. Classe JM, Loaec C, Gimbergues P et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019 Jan;173(2):343-352.
4. Moo TA, Edelweiss M, Hajiyeva S, et al. Is Low-Volume Disease in the Sentinel Node After Neoadjuvant Chemotherapy an Indication for Axillary Dissection? [published correction appears in Ann Surg Oncol. 2020 Feb 21;:]. *Ann Surg Oncol*. 2018;25(6):1488–1494.
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.



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)

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, 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.
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

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

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

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

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

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

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

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

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. 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

Radiotherapie (RT) anderer lokoregionärer Lymphabflussregionen (IMC)

	Oxford		
	LoE	GR	AGO
Mammaria interna Lymphknotenregion (IMC)			
▪ pN0 und prämenopausal und zentraler oder medialer Sitz und G2-3 und ER / PR-negativ	1b	B	+/-
▪ 1–3 befallene axilläre Lymphknoten[1] bei - zentralem oder medialem Sitz - HR-negativ	2a	B	+
▪ ≥ 4 befallene axilläre Lymphknoten	2a	B	+
▪ befallene Mammaria interna Lymphknoten	2a	B	+
▪ Bei linksseitigem Tumorsitz und erhöhtem kardialem Risiko oder simultaner Gabe von HER2-zielgerichteter Therapie	2b	A	-

[1] gilt nicht für Mikrometastasen

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.
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

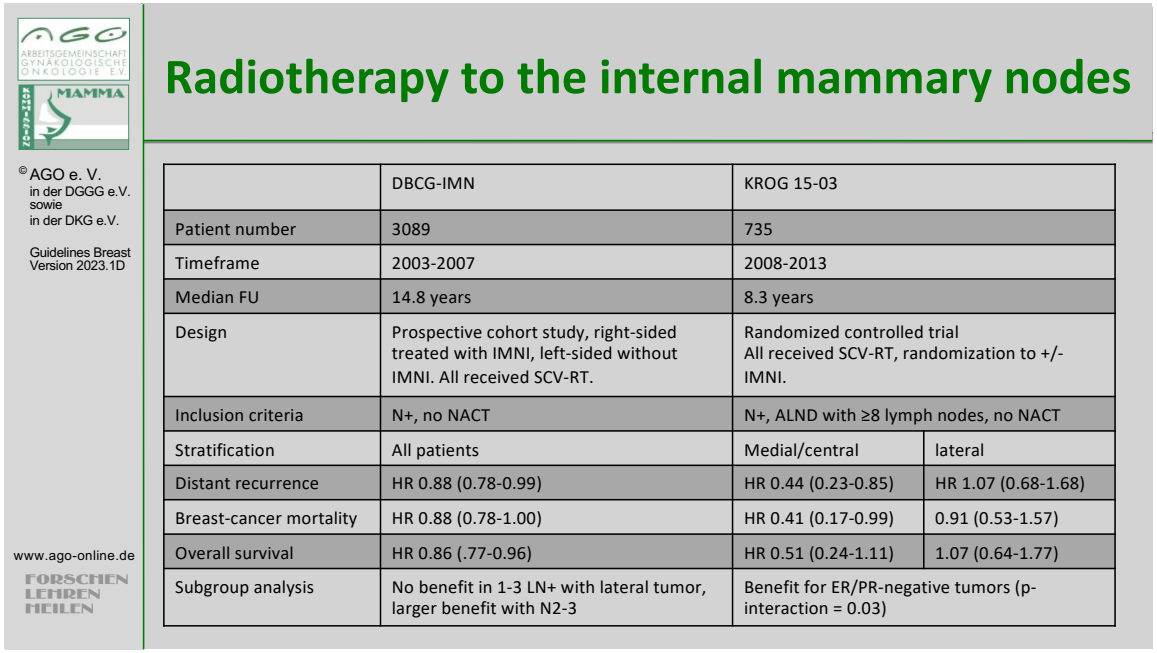
RT to Internal mammaria lymph node region (IMN) if pN1-pN2

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.



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)	

1. 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
2. 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.

Fraktionierung der Radiotherapie lokoregionärer Lymphabflussregionen

	Oxford		
	LoE	GR	AGO
▪ Konventionell fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25–28 Fraktionen in ca. 5–6 Wochen)	1a	A	++
▪ Moderat hypofraktionierte RT (Gesamtdosis ca. 40–43,5 Gy in ca. 15–16 Fraktionen in ca. 3 bis 5 Wochen)	1b[a]	B	+
▪ Ultra-hypofraktionierte RT (Gesamtdosis 26 Gy, d.h. 5 Fraktionen in einer Woche = 1 Fraktion/Tag)	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.
5. Badiyan SN, Shah C, Arthur D et al. Hypofractionated regional nodal irradiation for breast cancer: examining the data and potential for future studies. Radiother Oncol. 2014 Jan;110(1):39-44.
6. Haviland JS, Mannino M, Griffin C et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018 Jan;126(1):155-162.
7. 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

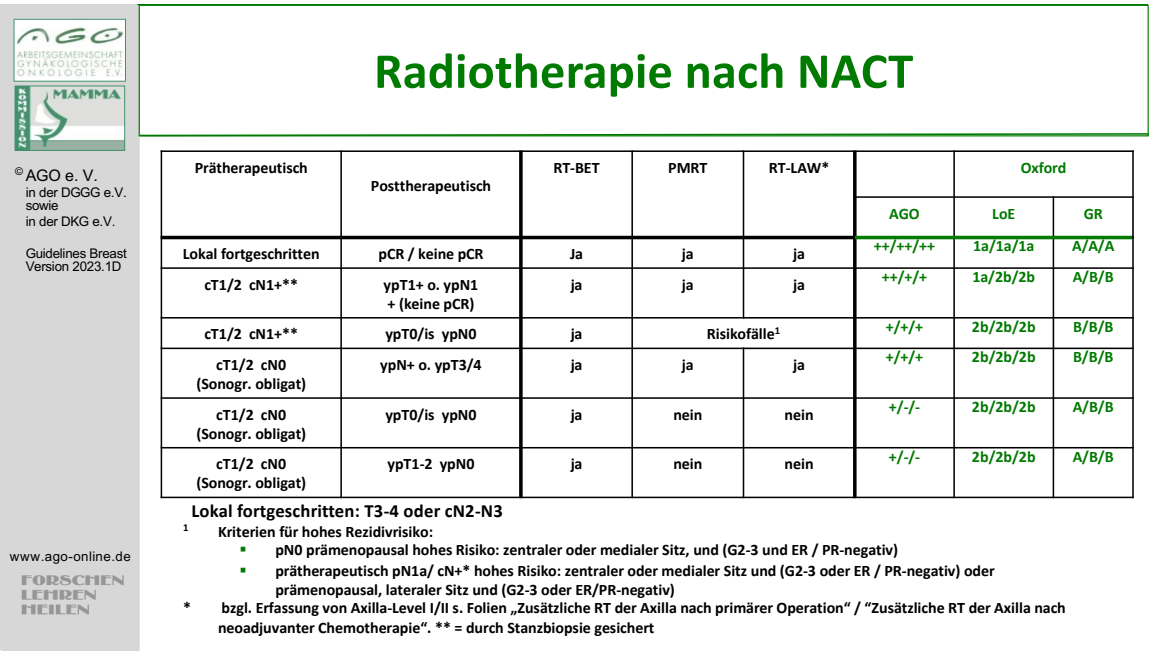
cancer. Lancet Oncol. 2022;23(1):e21-e31.

8. Offersen B, Alsner J, Nielsen HM, et al (2022) OC-0102 DBCG phase III randomized trial of hypo- vs standard fractionated RT in 2879 pN+ breast cancer pts. Radiother Oncol 170:S76–S77.
9. Wheatley D, Haviland J, Patel J, et al (2022) OC-0101 First results of FAST-Forward phase 3 RCT nodal substudy: 3-year normal tissue effects. Radiother Oncol 170:S75–S76.

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)

1. Haviland JS, Mannino M, Griffin C et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018 Jan;126(1):155-162.
2. 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.
3. Offersen B, Alsner J, Nielsen HM, et al (2022) OC-0102 DBCG phase III randomized trial of hypo- vs standard fractionated RT in 2879 pN+ breast cancer pts. Radiother Oncol 170:S76–S77.
4. Wheatley D, Haviland J, Patel J, et al (2022) OC-0101 First results of FAST-Forward phase 3 RCT nodal substudy: 3-year normal tissue effects. Radiother Oncol 170:S75–S76.



Radiotherapie nach NACT

Prätherapeutisch	Posttherapeutisch	RT-BET	PMRT	RT-LAW*	Oxford		
					AGO	LoE	GR
Lokal fortgeschritten	pCR / keine pCR	Ja	ja	ja	++/++/++	1a/1a/1a	A/A/A
cT1/2 cN1+**	ypT1+ o. ypN1 + (keine pCR)	ja	ja	ja	++/+/+	1a/2b/2b	A/B/B
cT1/2 cN1+**	ypT0/is ypN0	ja	Risikofälle[1]		+/+/+	2b/2b/2b	B/B/B
cT1/2 cN0 (Sonogr. obligat)	ypN+ o. ypT3/4	ja	ja	ja	+/+/+	2b/2b/2b	B/B/B
cT1/2 cN0 (Sonogr. obligat)	ypT0/is ypN0	ja	nein	nein	+/-/-	2b/2b/2b	A/B/B
cT1/2 cN0 (Sonogr. obligat)	ypT1-2 ypN0	ja	nein	nein	+/-/-	2b/2b/2b	A/B/B

Lokal fortgeschritten: T3-4 oder cN2-N3

[1] **Kriterien für hohes Rezidivrisiko:**
- **pN0 prämenopausal hohes Risiko: zentraler oder medialer Sitz, und (G2-3 und ER / PR-negativ)**
- **prätherapeutisch pN1a/ cN+* hohes Risiko: zentraler oder medialer Sitz und (G2-3 oder ER / PR-negativ) oder prämenopausal, lateraler Sitz und (G2-3 oder ER/PR-negativ)**

* **bzgl. Erfassung von Axilla-Level I/II s. Folien „Zusätzliche RT der Axilla nach primärer Operation" / "Zusätzliche RT der Axilla nach neoadjuvanter Chemotherapie". ** = durch Stanzbiopsie gesichert**

1. Cortazar P, Zhang L, Untch M, et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384:164–172. doi: 10.1016/S0140-6736(13)62422-8
2. Mamounas EP, Anderson SJ, Dignam JJ, et al (2012) Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 30:3960–3966. doi: 10.1200/JCO.2011.40.8369
3. Recht A, Comen EA, Fine RE, et al (2016) Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. J Clin Oncol 34:4431–4442. doi: 10.1200/JCO.2016.69.1188
4. EBCTCG EBCTCG, McGale P, Taylor C, et al (2014) 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 383:2127–2135. doi: 10.1016/S0140-6736(14)60488-8
5. Poortmans PM, Collette S, Kirkove C, et al (2015) Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med 373:317–327. doi: 10.1056/NEJMoa1415369
6. Whelan TJ, Olivotto IA, Parulekar WR, et al (2015) Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med 373:307–316. doi: 10.1056/NEJMoa1415340
8. Marks LB, Kaidar-Person O, Poortmans P (2017) Regarding Current Recommendations for Postmastectomy Radiation Therapy in

Patients With One to Three Positive Axillary Lymph Nodes. J Clin Oncol 35:1256-1258. doi: 10.1200/JCO.2016.71.0764
9. Poortmans P (2014) Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. Lancet 383:2104–2106. doi: 10.1016/S0140-6736(14)60192-6
10. Fowble BL, Einck JP, Kim DN, et al (2012) Role of postmastectomy radiation after neoadjuvant chemotherapy in stage II-III breast cancer. Int J Radiat Oncol Biol Phys 83:494–503. doi: 10.1016/j.ijrobp.2012.01.068
11. White J, Mamounas E (2014) Locoregional Radiotherapy in Patients With Breast Cancer Responding to Neoadjuvant Chemotherapy: A Paradigm for Treatment Individualization. J Clin Oncol 32:494–495. doi: 10.1200/JCO.2013.53.4974
12. Rusthoven CG, Rabinovitch RA, Jones BL, et al (2016) 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 27:818–827. doi: 10.1093/annonc/mdw046
13. Daveau C, Stevens D, Brain E, et al (2010) Is regional lymph node irradiation necessary in stage II to III breast cancer patients with negative pathologic node status after neoadjuvant chemotherapy? Int J Radiat Oncol Biol Phys 78:337–342. doi: 10.1016/j.ijrobp.2009.08.053
14. Bae SH, Park W, Huh SJ, et al (2012) Radiation Treatment in Pathologic N0-N1 Patients Treated with Neoadjuvant Chemotherapy Followed by Surgery for Locally Advanced Breast Cancer. J Breast Cancer 15:329–8. doi: 10.4048/jbc.2012.15.3.329
15. Noh JM, Park W, Suh C-O, et al (2014) Is elective nodal irradiation beneficial in patients with pathologically negative lymph nodes after neoadjuvant chemotherapy and breast-conserving surgery for clinical stage II-III breast cancer? A multicentre retrospective study (KROG 12-05). Br J Cancer 110:1420–1426. doi: 10.1038/bjc.2014.26
16. Kim KH, Noh JM, Kim YB, et al (2015) Does internal mammary node irradiation affect treatment outcome in clinical stage II–III breast cancer patients receiving neoadjuv ant chemotherapy? Breast Cancer Res Treat 152:589–599. doi: 10.1007/s10549-015-3505-1
17. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al (2007) Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 68:1004–1009. doi: 10.1016/j.ijrobp.2007.01.023
18. Nagar H, Mittendorf EA, Strom EA, et al (2011) Local-regional recurrence with and without radiation therapy after neoadjuvant chemotherapy and mastectomy for clinically staged T3N0 breast cancer. Int J Radiat Oncol Biol Phys 81:782–787. doi: 10.1016/j.ijrobp.2010.06.027
19. Le Scodan R, Selz J, Stevens D, et al (2012) Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 82:e1–7. doi: 10.1016/j.ijrobp.2010.12.054
20. Shim SJ, Park W, Huh SJ, et al (2014) The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage

II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). Int J Radiat Oncol Biol Phys 88:65–72. doi: 10.1016/j.ijrobp.2013.09.021
21. Xin F, Yu Y, Yang Z-J, et al (2016) Number of negative lymph nodes as a prognostic factor for ypN0-N1 breast cancer patients undergoing neoadjuvant chemotherapy. Tumor Biol 37:1–10. doi: 10.1007/s13277-015-4640-3
22. Meattini I, Cecchini S, Di Cataldo V, et al (2014) Postmastectomy radiotherapy for locally advanced breast cancer receiving neoadjuvant chemotherapy. Biomed Res Int 2014:719175. doi: 10.1155/2014/719175
23. Liu J, Mao K, Jiang S, et al (2016) The role of postmastectomy radiotherapy in clinically node-positive, stage II-III breast cancer patients with pathological negative nodes after neoadjuvant chemotherapy: an analysis from the NCDB. Oncotarget 7:24848–24859. doi: 10.18632/oncotarget.6664
24. Kantor O, Pesce C, Singh P, et al (2017) Post-mastectomy radiation therapy and overall survival after neoadjuvant chemotherapy. J Surg Oncol 28:2396–9. doi: 10.1002/jso.24551
25. Mamounas EP, Cortazar P, Zhang L, et al (2014) Locoregional recurrence (LRR) after neoadjuvant chemotherapy (NAC): Pooled-analysis results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). J Clin Oncol 32:61–61. doi: 10.1200/jco.2014.32.26_suppl.61
26. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2018) Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 19:27–39. doi: 10.1016/S1470-2045(17)30777-5
27. Budach W, Bölke E, Kammers K, et al (2015) Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta- analysis of randomized trials- an update. Radiat Oncol 10:1–7. doi: 10.1186/s13014-015-0568-4
28. Krug D, Lederer B, Seither F. et al. Post-Mastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer: A Pooled Retrospective Analysis of Three Prospective Randomized Trials. Ann Surg Oncol. 2019 Nov;26(12):3892-3901.
29. 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.
30. Krug D, Baumann R, Budach W et al. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. Strahlenther Onkol. 2018 Jul;194(7):607-618.
31. Krug D, Vladimirova V, Untch M et al. PD15-06: Pathologic complete response and breast-conserving surgery are associated with improved prognosis in patients with early-stage triple-negative breast cancer treated with neoadjuvant chemotherapy. Presented at

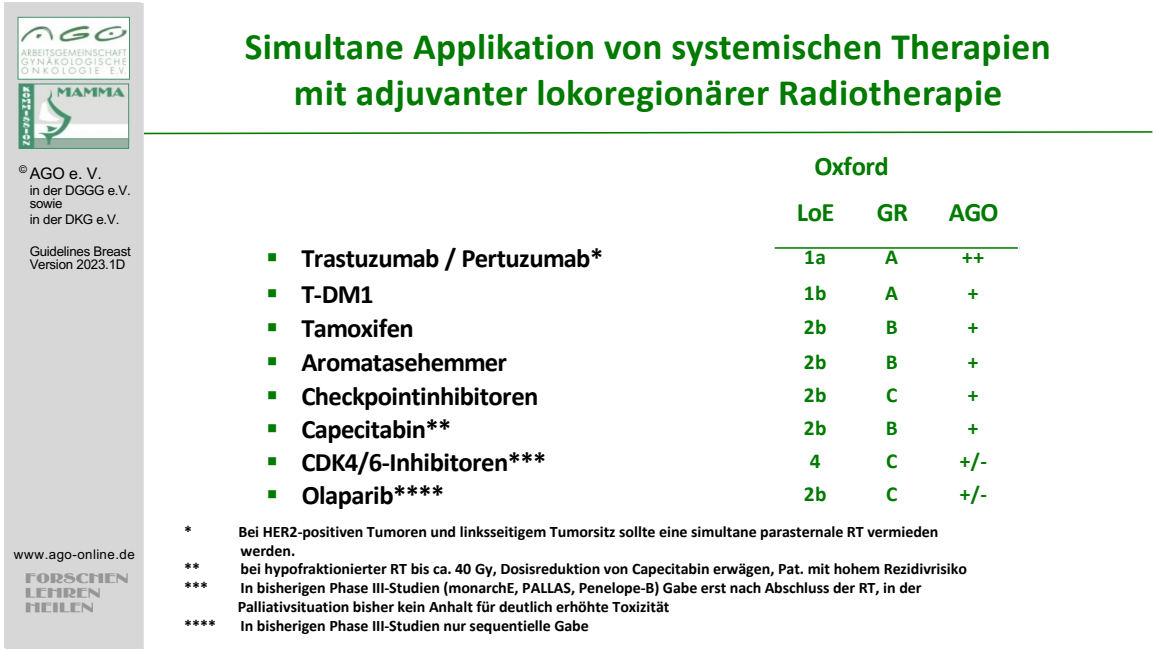
San Antonio Breast Cancer Symposium 2022.

Guidelines Breast
Version 2023.1D

Molekulare Prädiktion für die Radiotherapie

	Oxford		
	LoE	GR	AGO
▪ **Ergebnisse von Genexpressionsprofilen sollen nicht für die Indikationsstellung der Radiotherapie herangezogen werden**	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 (Basel). 2020 Apr;15(2):118-126.
2. Sjöström M, Fyles A, Liu FF et al. Development and Validation of a Genomic Profile for the Omission of Local Adjuvant Radiation in Breast Cancer. 10.1200/JCO.22.00655 Journal of Clinical Oncology. Published online January 04, 2023.



Trastuzumab +/- Pertuzumab concurrent with radiotherapy

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. 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
9. 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.
10. Azambuja E de, Agostinetto E, Procter M, et al (2023) Cardiac safety of dual anti-HER2 blockade with pertuzumab plus trastuzumab in early HER2-positive breast cancer in the APHINITY trial. Esmo Open 8:100772.

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.
2. Karlsson P, Cole BF, Colleoni M, et al.; International Breast Cancer Study Group. Timing of radiotherapy and outcome in patients receiving adjuvant endocrine therapy. Int J Radiat Oncol Biol Phys 2011;80:398-402.
3. Recht A. Radiotherapy, antihormonal therapy, and personalised medicine. Lancet Oncol 2010;11:215-216.
4. Tsoutsou PG, Belkacemi Y, Gligorov J, et al.; on behalf of the Association of Radiotherapy and Oncology in the Mediterranean area (AROME). Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider. Oncologist 2010;15:1169-78
5. Winzer KJ, Sauerbrei W, Braun M, et al.; German Breast Cancer Study Group (GBSG). Radiation therapy and tamoxifen after breast-conserving surgery: updated results of a 2 x 2 randomised clinical trial in patients with low risk of recurrence. Eur J Cancer 2010;46:95-101.

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
3. Valakh V, Trombetta MG, Werts ED, et al. Influence of concurrent anastrozole on acute and late side effects of whole breast radiotherapy. Am J Clin Oncol 2011;34:245-8
4. Ishitobi M, Nakahara S, Komoike Y, et al. Risk of ipsilateral breast tumor recurrence in patients treated with tamoxifen or anastrozole following breast-conserving surgery with or without radiotherapy. Anticancer Res 2011;31:367-371.
5. Azria D, Belkacemi Y, Romieu G, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for

early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. Lancet Oncol 2010;11:258-265.
6. Azria D, Betz M, Bourgier C et al. Identifying patients at risk for late radiation-induced toxicity. Crit Rev Oncol Hematol 2012;84 Suppl 1:e35-41.
7. Cecchini MJ, Yu E, Potvin K et al. Concurrent or Sequential Hormonal and Radiation Therapy in Breast Cancer: A Literature Review. Cureus. 2015 Oct 25;7(10):e364.

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. 2019;380(7):617-628.
2. Bellon JR, Tayob N, Yang DD et al. Local therapy outcomes and toxicity from the ATEMPT trial: A phase II randomized trial of adjuvant trastuzumab emtansine vs. paclitaxel in combination with trastuzumab in women with stage I HER2-positive breast cancer. Int J Radiat Oncol Biol Phys 2022. DOI:https://doi.org/10.1016/j.ijrobp.2021.12.173
3. Piroth MD, Krug D, Sedlmayer F et al. Post-neoadjuvant treatment with capecitabine and trastuzumab emtansine in breast cancer patients-sequentially, or better simultaneously? Strahlenther Onkol. 2021 Jan;197(1):1-7.

Checkpoint-inhibitors concurrent with radiotherapy

1. Schmid P, Cortes J, Pusztai L et al. Pembrolizumab for Early Triple-Negative Breast Cancer. New Engl J Med. 2020. 382(9):810-821.
2. Anscher MS, Arora S, Weinstock C et al. Association of Radiation Therapy With Risk of Adverse Events in Patients Receiving Immunotherapy: A Pooled Analysis of Trials in the US Food and Drug Administration Database. JAMA Oncol. 2022 Jan 6. doi: 10.1001/jamaoncol.2021.6439.
3. McArthur H, Cortes J, Dent R et al. PD3-01 Neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy followed by adjuvant pembrolizumab vs placebo for early TNBC: Post hoc analysis of adjuvant radiation therapy in the phase 3 KEYNOTE-522 study. SABCS 2022.

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
2. Woodward WA, Fang P, Arriaga L, et al. A Phase 2 Study of Preoperative Capecitabine andConcomitant Radiation in Women With Advanced Breast Cancer. Int J Radiat OncolBiol Phys. 2017 Nov 15;99(4):777-783

3. Gaui MF, Amorim G, Arcuri RA, Pereira G, et al. A phase II study of second-line neoadjuvant chemotherapy with capecitabine and radiation therapy for anthracycline-resistant locally advanced breast cancer. Am J Clin Oncol. 2007 Feb;30(1):78-81. Erratum in: Am J Clin Oncol. 2007 Jun;30(3):331.
4. Alhanafy AM HT, El-Fetouh MA, El-Ghany AEA et al. Safety and feasibility of concurrent capecitabine and hypofractionated postmastectomy radiotherapy. Menoufia Medical Journal 2015, 28:325-332
5. Piroth MD, Krug D, Sedlmayer F et al. Post-neoadjuvant treatment with capecitabine and trastuzumab emtansine in breast cancer patients-sequentially, or better simultaneously? Strahlenther Onkol. 2021 Jan;197(1):1-7.

CDK4/6-Inhibitors

1. Gnant M, Dueck AC, Frantal S et al. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). 2021 Dec 7;JCO2102554. doi: 10.1200/JCO.21.02554.
2. Loibl S, Marmé F, Martin M et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-The Penelope-B Trial. J Clin Oncol. 2021;39(14):1518-1530.
3. Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021;32(12):1571-1581.
4. Bosacki C, Bouleftour W, Sotton S et al. CDK 4/6 inhibitors combined with radiotherapy: A review of literature. Clin Transl Radiat Oncol. 2020 Dec 1;26:79-85.
5. Messer JA, Ekinci E, Patel TA, Teh BS. Enhanced dermatologic toxicity following concurrent treatment with palbociclib and radiation therapy: a case report. Rep Pract Oncol Radiother 2019;24(3):276e280.
6. Kawamoto T, Shikama N, Sasai K. Severe acute radiation-induced enterocolitis after combined palbociclib and palliative radiotherapy treatment. Radiother Oncol 2019;131: 240e241.
7. Ippolito E, Greco C, Silipigni S, et al. Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: preliminary assessment of toxicity. Breast 2019;46:70e74.
8. Meattini I, Desideri I, Scotti V et al. Ribociclib plus letrozole and concomitant palliative radiotherapy for metastatic breast cancer. Breast 2018;42:1e2.
9. Chowdhary M, Sen N, Chowdhary A et al. Safety and efficacy of palbociclib and radiation therapy in patients with metastatic breast cancer:initial results of a novel combination.Adv Radiat Oncol 2019;4(3):453e457.

10. Hans S, Cottu P, Kirova YM et al. Preliminary results of the association of palbociclib and radiotherapy in metastatic breast cancer patients. Radiother Oncol. 2018; 126: 181.
11. Figura NB, Potluri TK, Mohammadi H et al. CDK 4/6 inhibitors and stereotactic radiation in the management of hormone receptor positive breast cancer brain metastases. J Neurooncol. 2019
12. David S, Ho G, Day D et al. Enhanced toxicity with CDK 4/6 inhibitors and palliative radiotherapy: Non-consecutive case series and review of the literature. Transl Oncol. 2021 Jan;14(1):100939.

Olaparib

1. Loap P, Loirat D, Berger F et al. Combination of Olaparib with radiotherapy for triple-negative breast cancers: One-year toxicity report of the RADIOPARP Phase I trial. Int J Cancer. 2021;149(10):1828-1832.
2. Loap P, Loirat D, Berger F, et al (2022) Concurrent Olaparib and Radiotherapy in Patients With Triple-Negative Breast Cancer. Jama Oncol 8:1802–1808.
3. Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.

Simultaneous Capecitabine with locoregional radiotherapy

Guidelines Breast
Version 2023.1D

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/m^2 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%

Interaktion zwischen Strahlentherapie und Rauchen

	Oxford		
	LoE	GR	AGO
▪ **Nach einer Strahlentherapie wegen Brustkrebs ist das Risiko für ein Lungenkarzinom für Raucher erhöht**	1a	A	
▪ **Patientinnen sollten über dieses Risiko informiert werden**			++
▪ **Es sollte empfohlen werden, nicht mehr zu rauchen**			++

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.