Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

FORSCHEN
LEHREN
HEILEN

Adjuvant Radiotherapy

Adjuvant Radiotherapy (RT)

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

- **Version 2024:**
  Blohmer / Budach / Krug

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

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

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

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials
1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, et al. Lancet. 2011 Nov 12;378(9804):1707-16.

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

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

Preliminary Note

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

1. Sedlmayer F, Sautter-Bihl ML, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol. 2013 Oct;189(10):825-33.
2. Sautter-Bihl ML, Sedlmayer F, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer III--radiotherapy of the lymphatic pathways. Strahlenther Onkol. 2014 Apr;190(4):342-51.
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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.
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10. Krug D, Baumann R, Combs SE et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. Strahlenther Onkol 2021 https://doi.org/10.1007/s00066-020-01744-3

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

	Oxford		
	LoE	GR	AGO
▪ **Radiotherapy of the affected breast**	1a	A	++
▪ **Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks**	1a	A	++
▪ **Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week)**	1b	B	+/-
▪ **Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 5-6 weeks)**	1a	B	+
▪ **In case of life expectancy < 10 years and pT1, pN0, R0, ER / PR-positive, HER2-negative, endocrine therapy (all criteria), radiotherapy can be omitted after individual counseling, resulting in an increased risk for in-breast recurrence without imparing survival.**	1a	B	+

Moderate Hypofractionation

1. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
2. Whelan TJ, Pignol JP, Levine M et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010 Feb 11;362(6):513-20.
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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.
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12. Meattini I, Becherini C, Boersma L et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 2022;23(1):e21-e31.

Ultra-Hypofractionation

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.
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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.
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9. Jagsi R, Griffith KA, Harris EE et al. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol. 2023 Dec 7:JCO2302270. doi: 10.1200/JCO.23.02270.
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Randomized controlled trials of radiotherapy omission after breast-conserving surgery in early breast cancer

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

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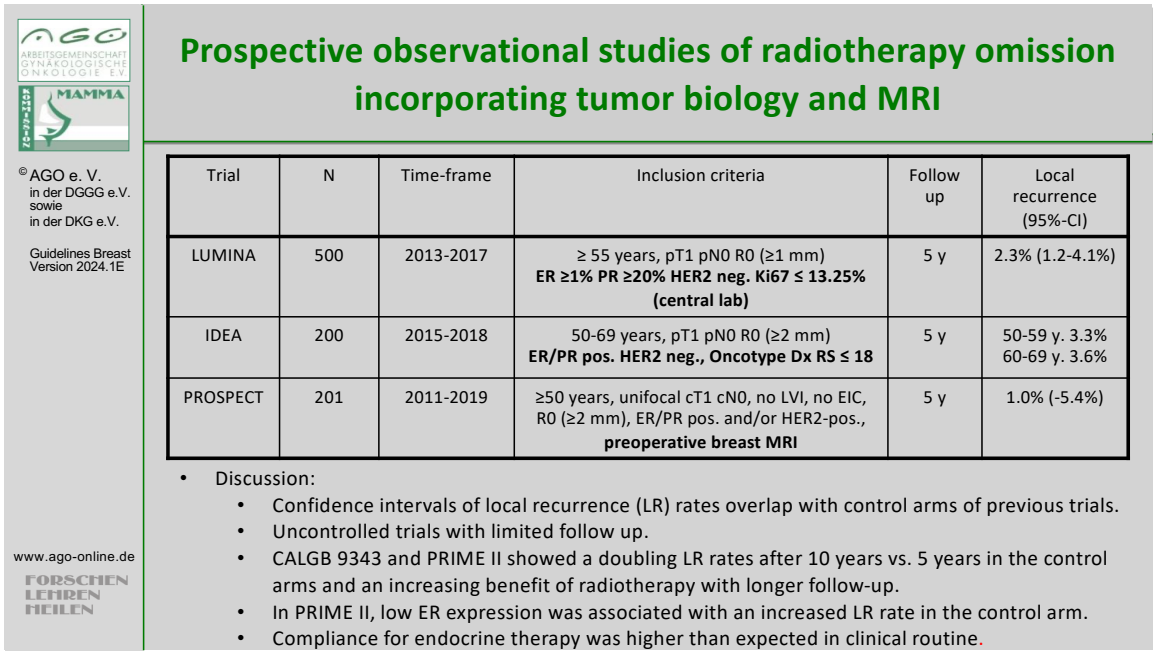

Prospective observational studies of radiotherapy omission incorporating tumor biology and MRI

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

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

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2. Jagsi R, Griffith KA, Harris EE et al. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol. 2023 Dec 7:JCO2302270. doi: 10.1200/JCO.23.02270.
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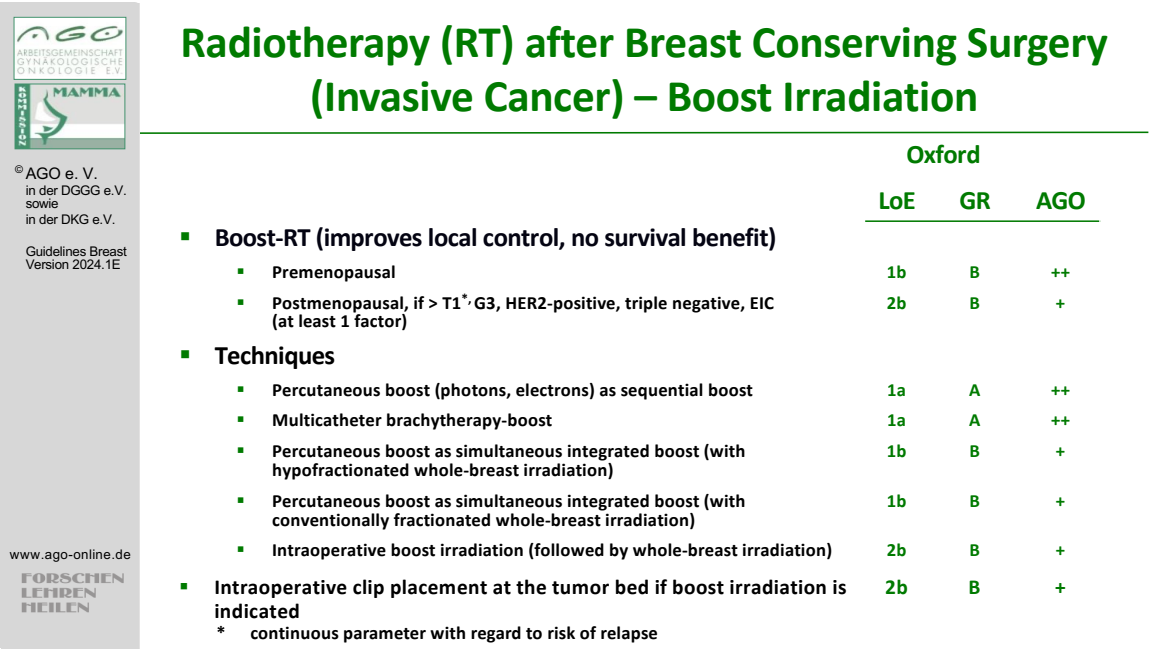

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Boost Irradiation

	Oxford		
	LoE	GR	AGO
Boost-RT (improves local control, no survival benefit)			
Premenopausal	1b	B	++
Postmenopausal, if > T1*, G3, HER2-positive, triple negative, EIC (at least 1 factor)	2b	B	+
Techniques			
Percutaneous boost (photons, electrons) as sequential boost	1a	A	++
Multicatheter brachytherapy-boost	1a	A	++
Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation)	1b	B	+
Percutaneous boost as simultaneous integrated boost (with conventionally fractionated whole-breast irradiation)	1b	B	+
Intraoperative boost irradiation (followed by whole-breast irradiation)	2b	B	+
Intraoperative clip placement at the tumor bed if boost irradiation is indicated	2b	B	+

* continuous parameter with regard to risk of relapse

Boost in general (EBRT/Brachytherapy, sequential)

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

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Simultaneous-integrated boost (conventionally fractionated RT)

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

Simultaneous-integrated boost (hypofractionated RT)

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

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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.

<u>Intraoperative irradiation (IORT/IOERT)</u>
<u>As boost-irradiation followed by WBI</u>

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.
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(HIOB): First Clinical Results of a Prospective Multicenter Trial (NCT01343459). Cancers (Basel). 2022 Mar 9;14(6):1396.
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<u>Clip placement</u>

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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.
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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.
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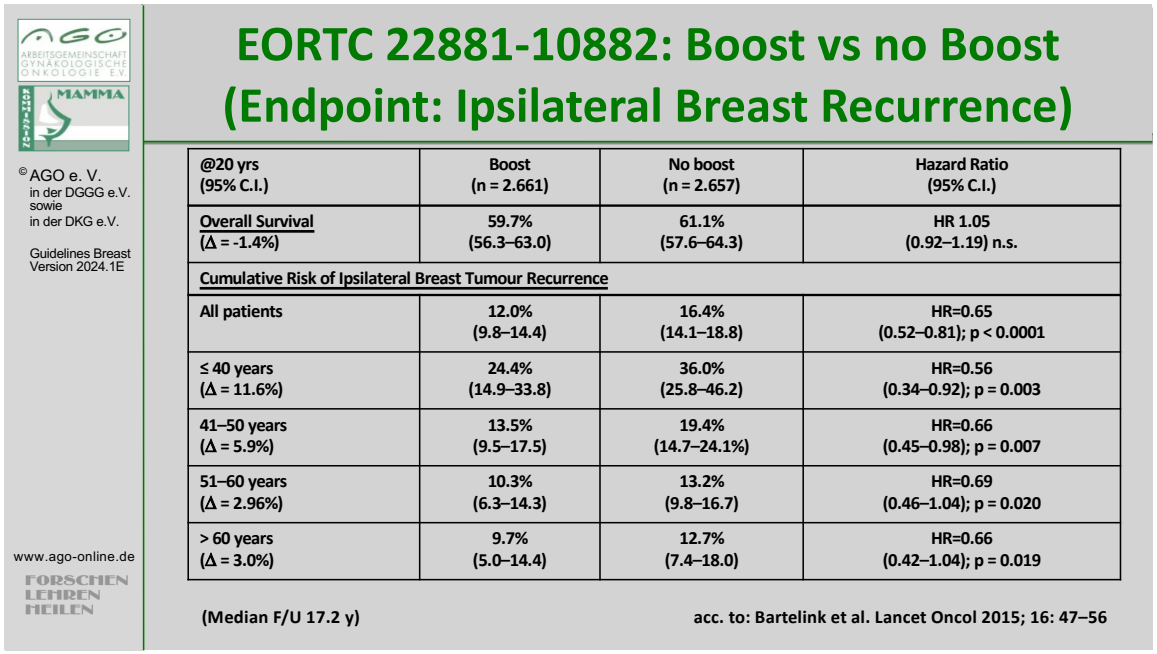


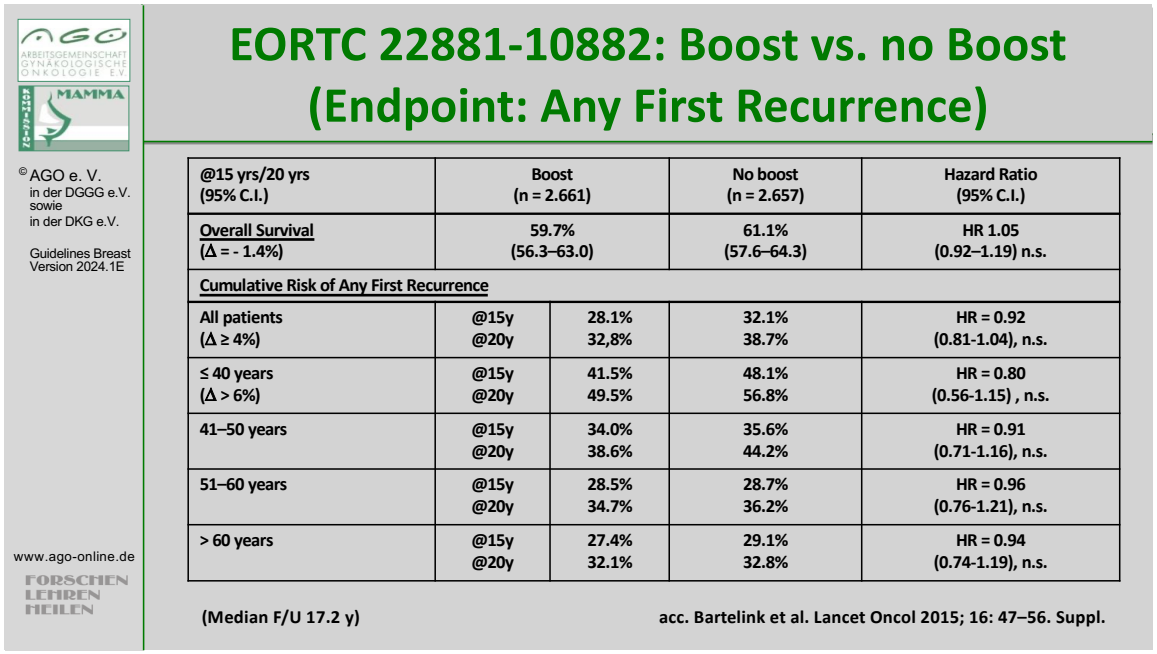
EORTC 22881-10882: Boost vs no Boost (Endpoint: Ipsilateral Breast Recurrence)

@20 yrs (95% C.I.)	Boost (n = 2.661)	No boost (n = 2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ = -1.4%)	59.7% (56.3–63.0)	61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Ipsilateral Breast Tumour Recurrence			
All patients	12.0% (9.8–14.4)	16.4% (14.1–18.8)	HR=0.65 (0.52–0.81); p < 0.0001
≤ 40 years (Δ = 11.6%)	24.4% (14.9–33.8)	36.0% (25.8–46.2)	HR=0.56 (0.34–0.92); p = 0.003
41–50 years (Δ = 5.9%)	13.5% (9.5–17.5)	19.4% (14.7–24.1%)	HR=0.66 (0.45–0.98); p = 0.007
51–60 years (Δ = 2.96%)	10.3% (6.3–14.3)	13.2% (9.8–16.7)	HR=0.69 (0.46–1.04); p = 0.020
> 60 years (Δ = 3.0%)	9.7% (5.0–14.4)	12.7% (7.4–18.0)	HR=0.66 (0.42–1.04); p = 0.019

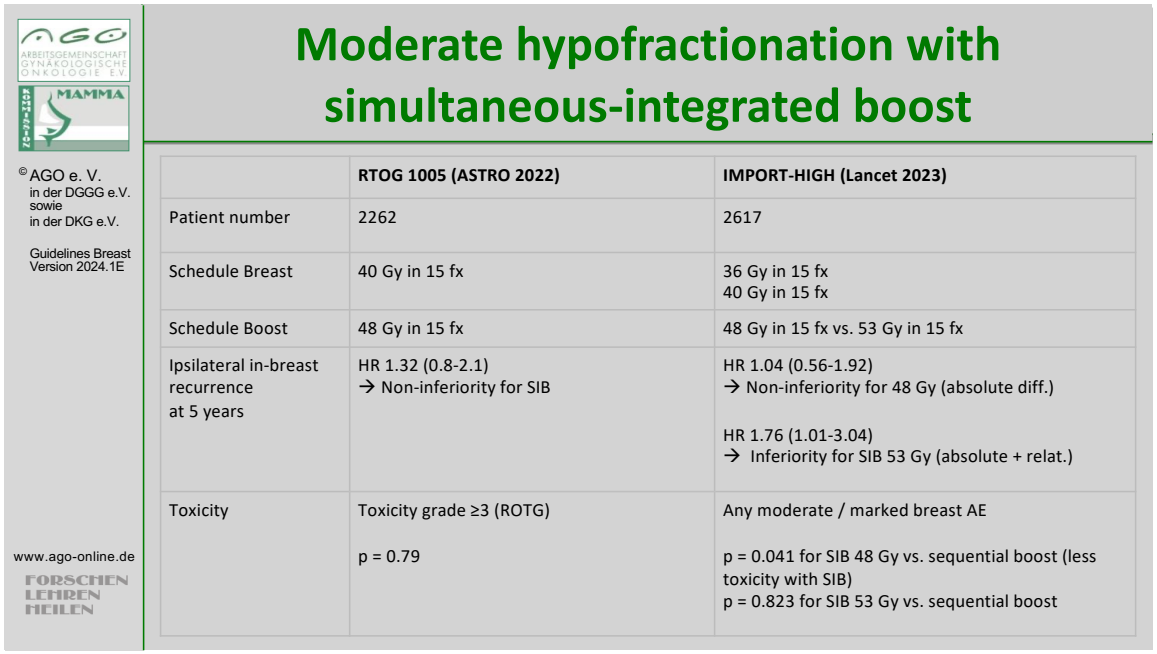
(Median F/U 17.2 y)

acc. to: Bartelink et al. Lancet Oncol 2015; 16: 47–56

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



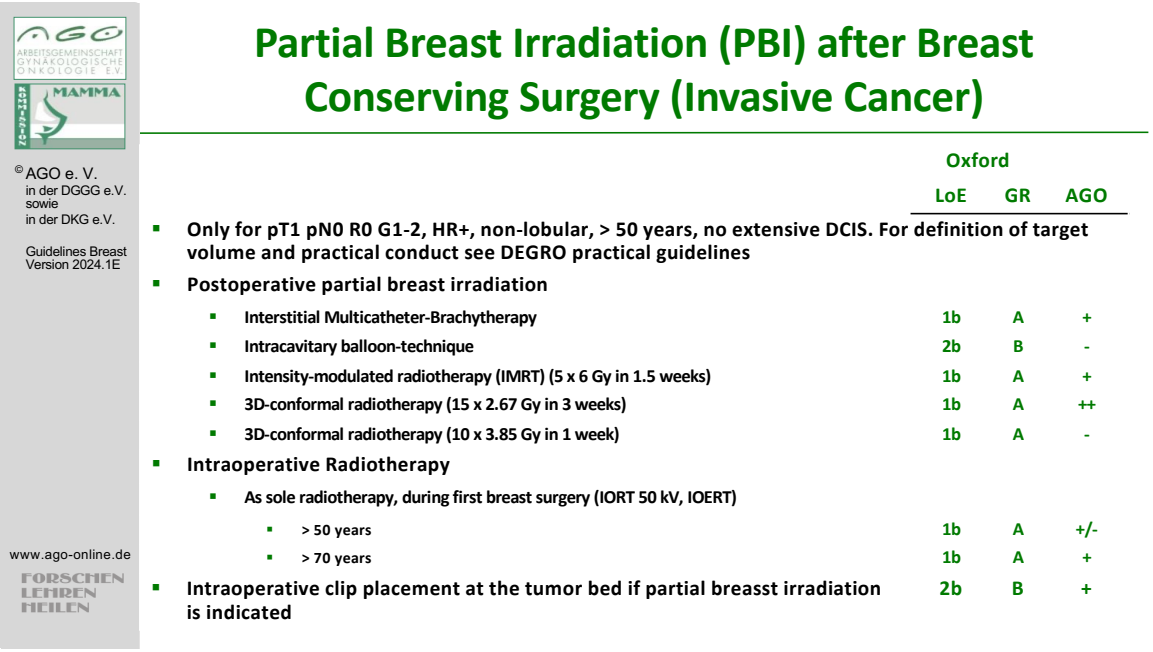
1. Bartelink H, Maingon P, Poortmans P, et al; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised 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 (Lancet 2023)
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. Coles CE, Haviland JS, Kirby AM et al. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. Lancet. 2023 Jun 24;401(10394):2124-2137.



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

	Oxford LoE	GR	AGO
▪ **Only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS. For definition of target volume and practical conduct see DEGRO practical guidelines**			
▪ **Postoperative partial breast irradiation**			
▪ **Interstitial Multicatheter-Brachytherapy**	1b	A	+
▪ **Intracavitary balloon-technique**	2b	B	-
▪ **Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 1.5 weeks)**	1b	A	+
▪ **3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks)**	1b	A	++
▪ **3D-conformal radiotherapy (10 x 3.85 Gy in 1 week)**	1b	A	-
▪ **Intraoperative Radiotherapy**			
▪ **As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT)**			
▪ **> 50 years**	1b	A	+/-
▪ **> 70 years**	1b	A	+
▪ **Intraoperative clip placement at the tumor bed if partial breasst irradiation is indicated**	2b	B	+

General guidelines

1. Shaitelman SF, Anderson BM, Arthur DW et al. Partial Breast Irradiation for Patients With Early-Stage Invasive Breast Cancer or Ductal Carcinoma In Situ: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2023 Nov 14:S1879-8500(23)00296-5. doi: 10.1016/j.prro.2023.11.001.
2. Anderson B, Arthur D, Hannoun-Levi JM et al. Partial breast irradiation: An updated consensus statement from the American brachytherapy society. Brachytherapy. 2022 Nov-Dec;21(6):726-747.
3. Strnad V, Krug D, Sedlmayer F et al. DEGRO practical guideline for partial-breast irradiation. Strahlenther Onkol. 2020 Sep;196(9):749-763.
4. 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.
5. 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.

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.
7. Strnad V, Polgár C, Ott OJ et al. Accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy compared with whole-breast irradiation with boost for early breast cancer: 10-year results of a GEC-ESTRO randomised, phase 3, non-inferiority trial. Lancet Oncol. 2023 Mar;24(3):262-272.

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.
5. Kirby AM, Griffin C, Finneran L et al. Partial Breast Radiotherapy for Women with Early Breast Cancer: 10-Year Outcomes from IMPORT LOW (CRUK/06/003). Presented at ASTRO Annual Meeting 2023 (LBA 10). https://doi.org/10.1016/j.ijrobp.2023.08.034

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.

3D-conformal RT (10x3.85 Gy over one week)

1. Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol. 2013 Nov 10;31(32):4038-45.
2. Whelan TJ, Julian JA, Berrang TS et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet. 2019 Dec 14;394(10215):2165-2172.
3. Vicini FA, Cecchini RS, White JR et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet. 2019 Dec 14;394(10215):2155-2164.
4. Ganz PA, Cecchini RS, White JR et al. Patient-reported outcomes (PROs) in NRG oncology/NSABP B-39/RTOG 0413: A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) in stage 0, I, or II breast cancer. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 508-508. Presented at ASCO Annual Meeting 2019.
5. Meduri B, Baldissera A, Iotti C et al. Cosmetic Results and Side Effects of Accelerated Partial-Breast Irradiation Versus Whole-Breast Irradiation for Low-Risk Invasive Carcinoma of the Breast: The Randomized Phase III IRMA Trial. J Clin Oncol. 2023 Apr 20;41(12):2201-2210.

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.

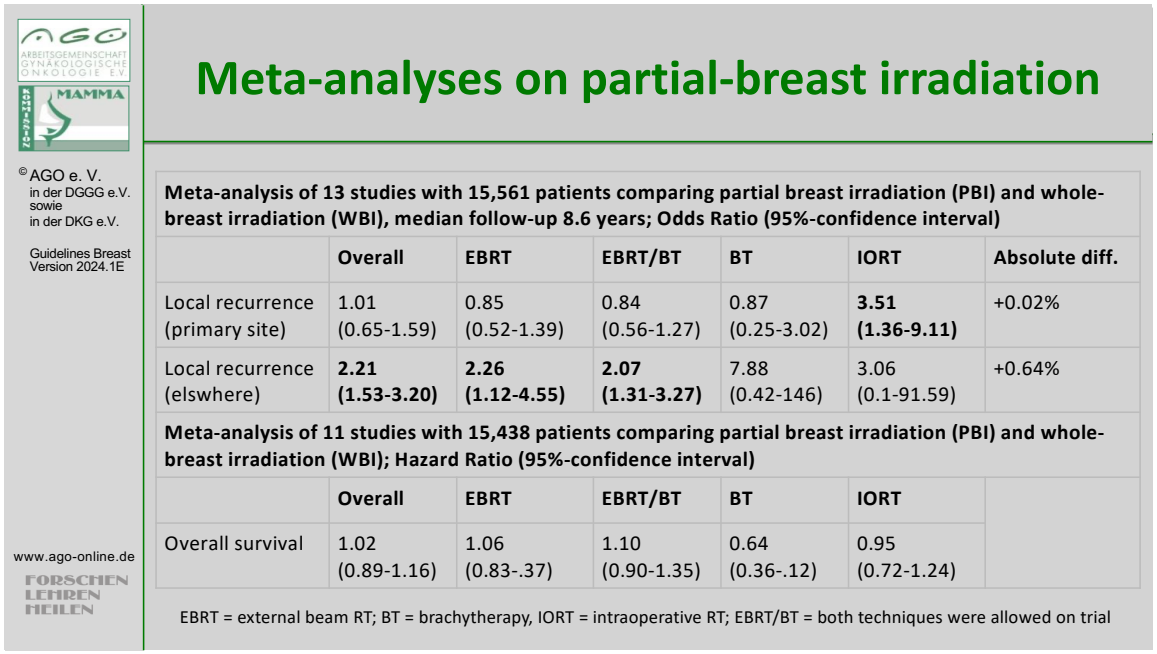
<u>>70 yrs</u>

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).

<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-analyses on partial-breast irradiation

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

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

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

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

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

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.

Guidelines Breast
Version 2024.1E

Comparison of different techniques for partial breast irradiation

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

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

	Oxford		
	LoE	GR	AGO
▪ > 3 tumor infiltrated lymph nodes (LN)	1a	A	++
▪ 1–3 tumor infiltrated LN (high-risk)	1a	A	+
▪ 1–3 tumor infiltrated LN (low-risk*)	5	D	+/-
▪ T3 / T4	1a	A	++
▪ pT3 pN0 R0 (and no additional risk factors)	2b	B	+/-
▪ If R0 is impossible to reach (for invasive tumor)	1a	A	++
▪ In young pts with high-risk features	2b	B	++
The indications for PMRT and regional RT are independent of adjuvant systemic treatment	1a	A	
Inflammatory breast cancer: PMRT and regional nodal irradiation	2c	B	++

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

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
2. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997 Oct 2;337(14):949-55.
3. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999 May 15;353(9165):1641-8.
4. Truong PT, Olivotto IA, Kader HA, et al. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys. 2005 Apr 1;61(5):1337-47.
5. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
6. Kyndi M, Overgaard M, Nielsen HM, et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009 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.
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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.
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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.

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

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

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

Moderate Hypofractionation

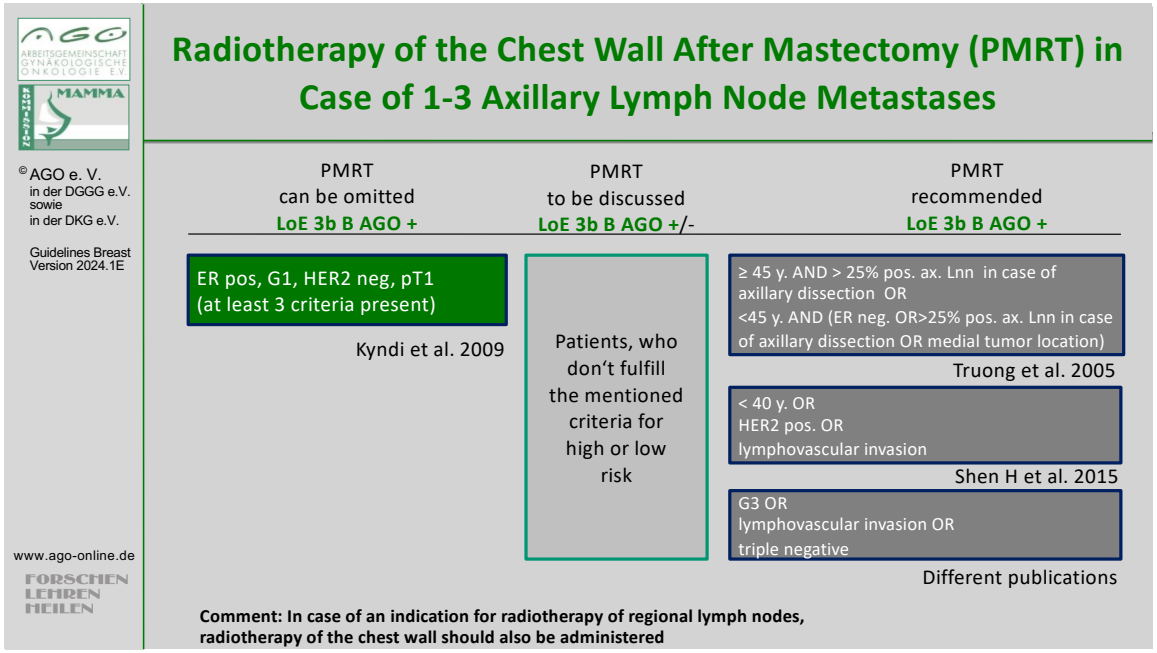
1. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
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.
5. Wong JS, Uno H, Tramontano A et al. Patient-Reported and Toxicity Results from the FABREC Study: A Multicenter Randomized Trial of Hypofractionated vs. Conventionally-Fractionated Postmastectomy Radiation Therapy after Implant-Based Reconstruction. Presented at ASTRO Annual Meeting 2023 (LBA 5) https://doi.org/10.1016/j.ijrobp.2023.08.029

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.
4. Wong JS, Uno H, Tramontano A et al. Patient-Reported and Toxicity Results from the FABREC Study: A Multicenter Randomized Trial of Hypofractionated vs. Conventionally-Fractionated Postmastectomy Radiation Therapy after Implant-Based Reconstruction. Presented at ASTRO Annual Meeting 2023 (LBA 5) https://doi.org/10.1016/j.ijrobp.2023.08.029

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.
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5. Kyndi M, Overgaard M, Nielsen HM, et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009 Jan;90(1):74-9.
6. NCCN Guidelines for Treatment of Cancer by Site "http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf" 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)

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2. Freedman GM, Fowble BL, Hanlon AL, et al: A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. Int J Radiat Oncol Biol Phys. 1998 Jun 1;41(3):599-605.
3. Truong PT, Olivotto IA, Speers CH, et al. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys. 2004 Mar 1;58(3):797-804.
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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

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mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

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

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

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

1. Wenz F, Sperk E, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Strahlenther Onkol. 2014 Aug;190(8):705-14.
2. Hehr T, Baumann R, Budach W et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Radiotherapy after skin-sparing mastectomy with immediate breast reconstruction in intermediate-risk breast cancer : Indication and technical considerations. Strahlenther Onkol. 2019 Nov;195(11):949-963.

Boost in PMRT

	Oxford		
	LoE	GR	AGO
▪ An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival	2a	B	
▪ An additional boost irradiation to a part of the chest wall should be given in case of of R1 / R2-resection, if secondary resection is not feasible	5	D	++
▪ In case of tumor extention to the pectoral resection margin, but no clinical signs of extention beyond the fascia, the resection margin should be regarded as R0 (provided, that the pectoral fascia was resected). A boost radiotherapy is not required in this situation	5	D	++

Thoracic wall boost irradiation

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

Radiotherapy of Axillary Lymph Nodes in Patients with Positive Sentinel-Lymph Nodes**, Who Did not Undergo Axillary Dissection

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

* Study participation recommended
** Macrometastases
+ < T3, no palpable LN, R0, 1-2 positive SN, no NACT

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

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Additional RT of the Axilla after Primary Surgery (in case of an indication for RT of the breast/chest wall[1] +/- supra-/infraclavicular and internal mammary node RT[2]) Expansion of the PTV (planning target volume) to level I-II[3]	Oxford		
	LoE	GR	AGO
pN-status			
pN0(sn) / pN1mic(sn)	1b	B	--
pN0/+ after ALND	1a	A	--
pN+(sn) in analogy to ACOSOG Z0011 (no ALND)	2b	B	+
pN+(sn) not fitting ACOSOG Z0011-criteria → RT in analogy to AMAROS[4] (no ALND)	1b	B	++
Extensive perinodal soft tissue involvement in the axilla	2b	B	+
Residual tumor in the axilla after ALND	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. [3]Cranial border 5 mm below the axillary vein. [4] < T3, no palpable LN, R0, 1-2 positive SN, no NACT, always in conjunction with supra-/infraclavicular RT

Sentinel node negative

1. Krag DN, Anderson SJ, Julian TB, et al: Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival 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

Axillary soft tissue involvement

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

Tumor residuals after axillary dissection

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

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Additional RT of the Axilla after Neoadjuvant Therapy

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

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

N-status pre/post NACT	pN-status	Oxford LoE	Oxford GR	AGO
cN0 / ycN0	ypN0(sn)	5	D	-
cN0 / ycN0	ypN1mic(sn) / ypN+(sn) (no ALND)	5	D	+[4]
$cN+_{CNB}$ / ycN0	ypN0 / ypN0(i+) (sn/TAD)	5	D	+/-[4]
$cN+_{CNB}$/ ycN0	ypN1mic(sn/TAD) / ypN+(sn/TAD) (no ALND)	5	D	+[4]
cN0/cN+	ypN0/+ after ALND	2b	B	-
cN0/cN+	Extensive perinodal soft tissue involvement in the axilla	2b	B	+
cN0/cN+	Residual tumor in the axilla after ALND	5	D	++

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

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.

Axillary soft tissue involvement

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

Tumor residuals after axillary dissection

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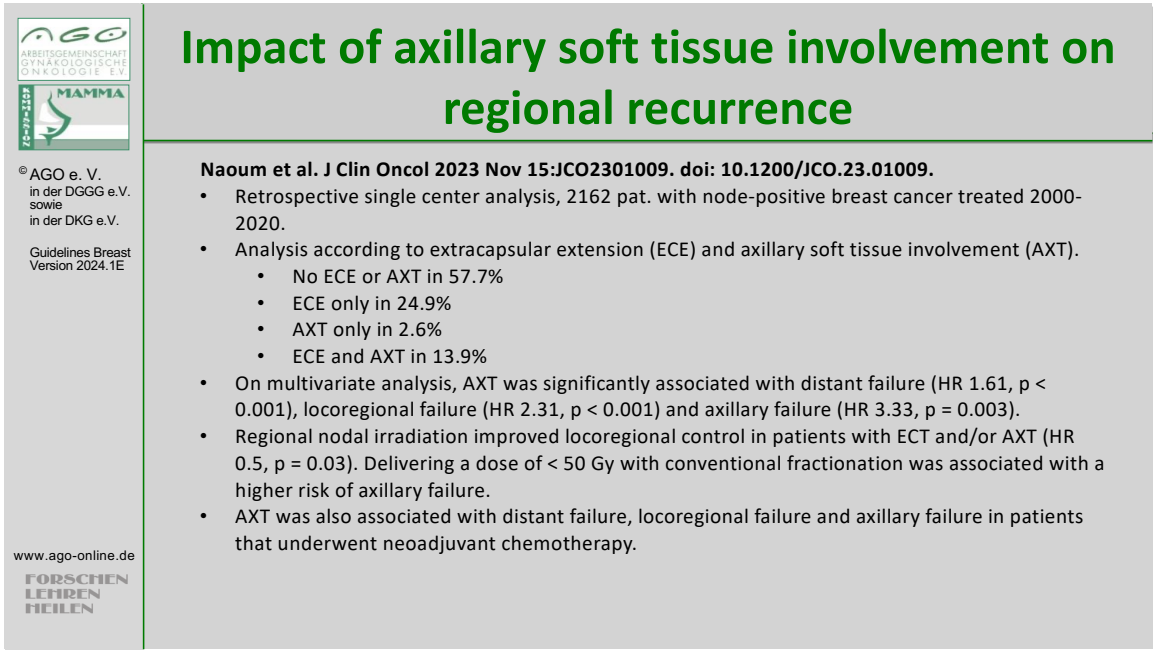
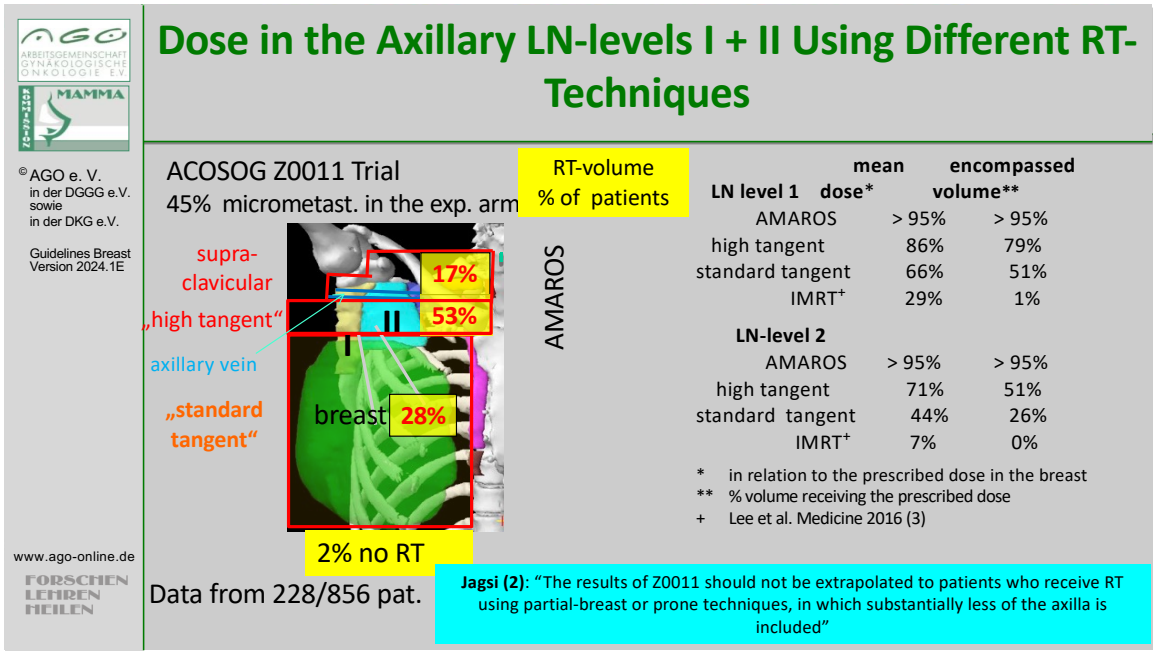


Naoum GE, Oladeru O, Ababneh H et al. Pathological Exploration of the Axillary Soft Tissue Microenvironment and Its Impact on Axillary Management and Breast Cancer Outcomes. J Clin Oncol 2023 Nov 15:JCO2301009. doi: 10.1200/JCO.23.01009.



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

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Regional nodal irradiation

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

[1] not applicable for micrometastases

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

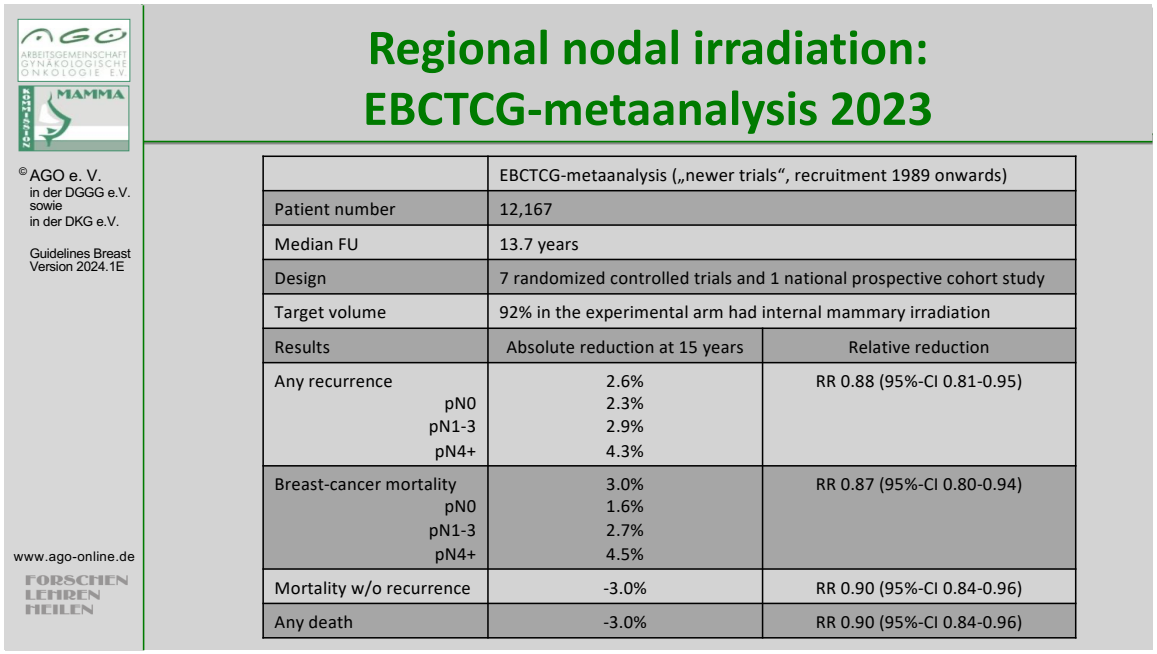
8. Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. Int J Radiation Oncol Biol Phys 2013; 86 (5): 860-866.

RT plus concurrent Trastuzumab +/- Pertuzumab

1. Bachir B, Anouti S, Jaoude JA et al. Evaluation of Cardiotoxicity in HER-2 Positive Breast Cancer Patients Treated with Radiation Therapy and Trastuzumab. Int J Radiat Oncol Biol Phys. 2022;S0360-3016(21)03432-5.
2. Belkacemi and J. Gligorov, Concurrent trastuzumab — internal mammary irradiation for HER2 positive breast cancer: “It hurts to be on the cutting edge”. Radiother Oncol 2010;94:119-20 (Letter to the editor).
3. Belkacémi Y, Gligorov J, Ozsahin M, et al. Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study. Ann Oncol 2008;19:1110-6.
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.

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

1. Please check slide on radiotherapy after NACT



Regional nodal irradiation: EBCTCG-metaanalysis 2023

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

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

Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

	Oxford		
	LoE	GR	AGO
▪ **Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)**	1a	A	++
▪ **Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)**	1b	B	+
▪ **Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)**	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.
10. Rivera S, Karamouza E, Kirova Y et al. HypoG01:UNICANCER phase 3 trial of locoregional hypo vs normo fractionated RT in early breast cancer. Presented at ESTRO Annual Meeting 2023 (OC-0758). DOI: 10.1016/S0167-8140(23)08699-1

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Hypofractionated regional nodal irradiation

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

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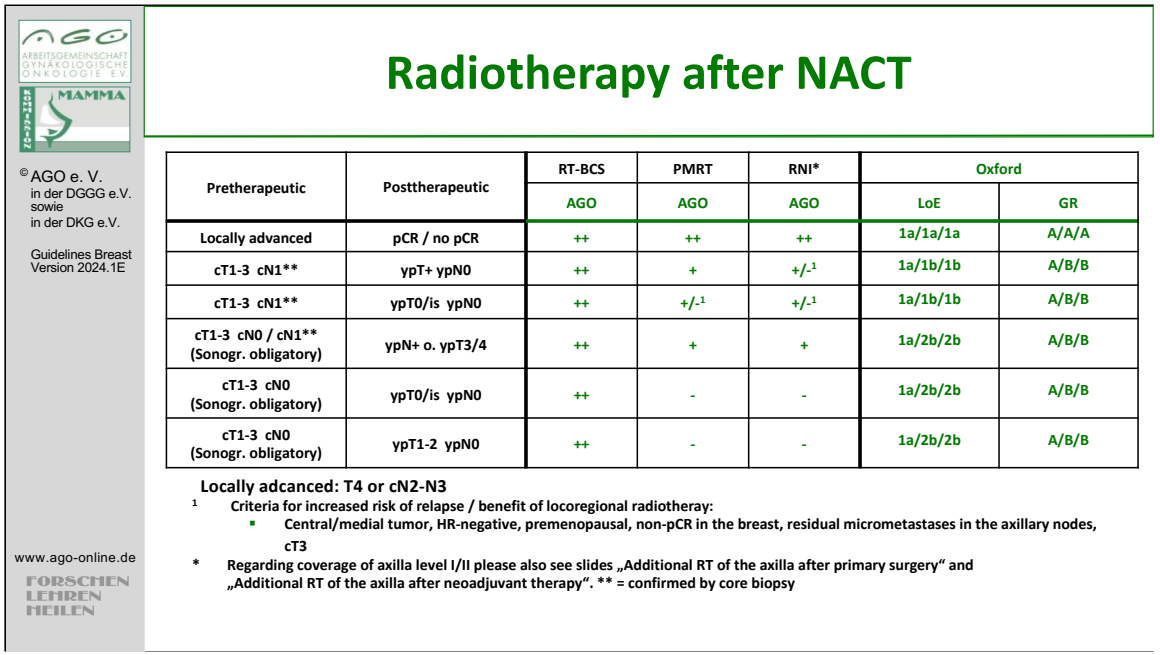
1. Haviland JS, Mannino M, Griffin C et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018 Jan;126(1):155-162.
2. Wang SL, Fang H, Song YW et al.
Hypofractionated versus 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. Rivera S, Karamouza E, Kirova Y et al. HypoG01:UNICANCER phase 3 trial of locoregional hypo vs normo fractionated RT in early breast cancer. Presented at ESTRO Annual Meeting 2023 (OC-0758). DOI: 10.1016/S0167-8140(23)08699-1



Radiotherapy after NACT

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

Locally adcanced: T4 or cN2-N3

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

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

1. Mamounas EP, Bandos H, White J et al. Loco-Regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304. Presented at SABCS 2023 (GS02-07)
2. 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
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4. 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
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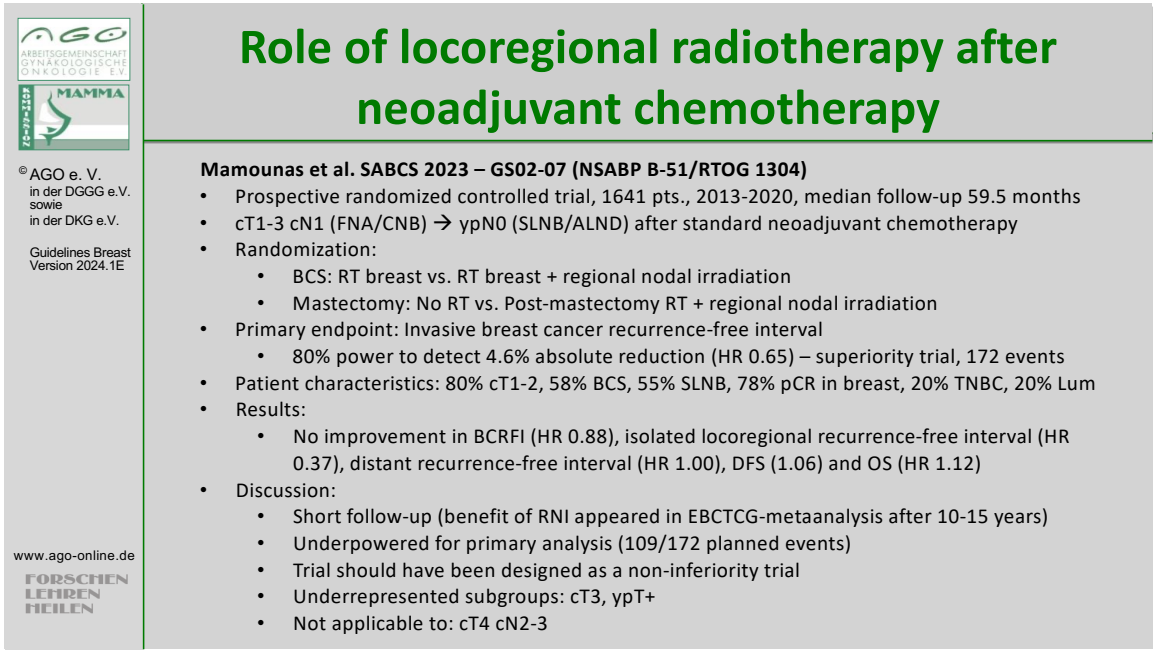

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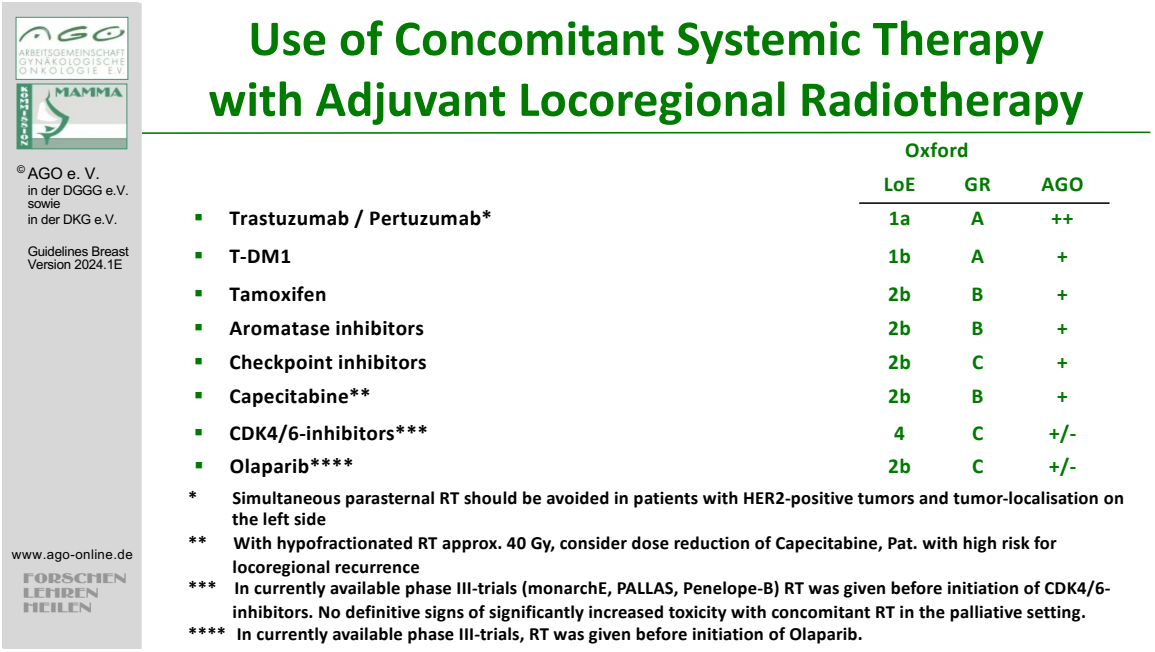

Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

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

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

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

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

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

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Smoking and Risk of Secondary Lung Cancer

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

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