

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Adjuvante Strahlentherapie

Adjuvante Radiotherapie (RT)

- **Versionen 2002 – 2017:**
Blohmer / Budach / Friedrichs / Göhring / Janni / Kühn /
Möbus / Scharl / Seegenschmiedt / Souchon / Thomssen /
Untch / Wenz
- **Version 2018:**
Budach / Huober / Kühn / Wenz

Search Strategy

Search Terms: Radiotherapy Breast Cancer

Source: Pubmed 1/2010 – 1/2017

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.

Vorbemerkung

- **Diese Empfehlungen zur adjuvanten Strahlentherapie bei Brustkrebs basieren auf einer Konsensdiskussion 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 2014**

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

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.

DEGRO practical guidelines: radiotherapy of breast cancer III--radiotherapy of the lymphatic pathways

1. Sautter-Bihl ML, Sedlmayer F, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Strahlenther Onkol. 2014 Apr;190(4):342-51.

DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer

1. Sedlmayer F, Sautter-Bihl ML, Budach W, et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Strahlenther Onkol. 2013 Oct;189(10):825-33.

Guidelines and Opinions

St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:

Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. **Hypofractionated regimens involving 15 or 16 fractions are now widely accepted as standard of care.**

St. Gallen 2015: Gnant M, Breast Care 2015;10:124:

With respect to **hypofractionated** breast irradiation after breast conserving surgery, the panel felt that this is **appropriate for patients aged 50+** without chemotherapy or axillary involvement (89% Yes, 2% No, 9% Abstain), but **also for patients younger than 50 years** (71% Yes, 2% No, 27% Abstain), with uncertainty about patients with prior chemotherapy or axillary lymph node involvement (51% Yes, 18% No, 31% Abstain).

Statement J Harris, Dana Farber, Boston, SABCS 2015, PL1-01:

With regard to **hypofractionated whole breast irradiation**, cosmetic results are clearly better, patient satisfaction is improved, uncertainty about use in nodal RT. **We are using it just in about all (266 cGy x 15 with boost in about ½).**

1. Coates AS¹, Winer EP², Goldhirsch A³, et al; Panel Members. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
2. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A Brief Summary of the Consensus Discussion. Breast Care (Basel). 2015 Apr;10(2):124-30.
3. Harris JR. Critical Decision-Making in Radiation Therapy for Breast Cancer. Presentation at the San Antonio Breast Cancer Symposium 2016. PL1-01

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

	Oxford		
	LoE	GR	AGO
■ Bestrahlung der operierten Brust	1a	A	++
■ Hypofraktionierung RT (Gesamtdosis ca. 40 Gy in ca. 15-16 Fraktionen in ca. 3 bis 5 Wochen)	1a	A	++
■ Konventionelle 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, HR/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	+

1. Haviland JS¹, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
2. Whelan TJ, Pignol JP, Levine M et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010 Feb 11;362(6):513-20.
3. Haffty BG¹, Buchholz TA. Hypofractionated breast radiation: preferred standard of care? Lancet Oncol. 2013 Oct;14(11):1032-4.
4. Hopwood P¹, Haviland JS, Sumo G et al; START Trial Management Group. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. Lancet Oncol. 2010 Mar;11(3):231-40.
5. Shaitelman SF¹, Khan AJ, Woodward WA, et al. Shortened radiation therapy schedules for early-stage breast cancer: a review of hypofractionated whole-breast irradiation and accelerated partial breast irradiation. Breast J. 2014 Mar-Apr;20(2):131-46.
6. Bane AL¹, Whelan TJ, Pond GR, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. Ann Oncol. 2014 May;25(5):992-8.
7. Chan EK¹, Woods R², McBride ML², et al. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-stage breast cancer: long-term hospital-related morbidity from cardiac causes. Int J Radiat Oncol Biol Phys. 2014 Mar 15;88(4):786-92.
8. 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.

9. Budach W, Bölke E, Matuschek C. Hypofractionated Radiotherapy as Adjuvant Treatment in Early Breast Cancer. A Review and Meta-Analysis of Randomized Controlled Trials. *Breast Care (Basel)*. 2015 Aug;10(4):240-5.
10. Dellas K, Vonthein R, Zimmer J, et al; ARO Study Group. Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01). *Strahlenther Onkol*. 2014 Jul;190(7):646-53.
11. Coates AS1, Winer EP2, Goldhirsch A3, et al. Panel Members. Tailoring therapies- improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015 Aug;26(8):1533-46.
12. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A Brief Summary of the Consensus Discussion. *Breast Care (Basel)*. 2015 Apr;10(2):124-30.
13. Harris JR. Critical Decision-Making in Radiation Therapy for Breast Cancer. Presentation at the San Antonio Breast Cancer Symposium 2016. PL1-01
14. 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.
15. Kunkler IH, Williams LJ, Jack WJ, et al: On behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015 Jan 27.
16. Hughes KS, Schnaper LA. Can older women with early breast cancer avoid radiation? *The Lancet Oncology*, Available online 28 January 2015
17. Paelinck L, Gulyban A, Lakosi F, et al Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation? A randomized controlled trial. *Radiother Oncol*. 2017 Jan 3. pii: S0167-8140(16)34464-4. doi: 10.1016/j.radonc.2016.12.023. [Epub ahead of print]
18. 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
19. J.S. Haviland , P. Hopwood, J. Millset al: On behalf of the START Trialists' Group. Do Patient-reported Outcome Measures Agree with Clinical and Photographic Assessments of Normal Tissue Effects after Breast Radiotherapy? The Experience of the Standardisation of Breast Radiotherapy (START) Trials in Early Breast Cancer. *Clinical Oncology* 28 (2016) 345e353

Zusätzliche Informationen hinsichtlich der Effekte der Radiotherapie der Brust (BET)

▪ Hypofraktionierung:

- Einige Effekte auf das normale Gewebe waren in einem Teil der Studien zur hypofraktionierten Strahlentherapie (15-16 Fraktionen) geringer ausgeprägt als nach einer konventionell fraktionierten Strahlentherapie (Brustschrumpfung, Teleangiektasien und Brustödem).
- Die lokoregionäre Rückfallrate war in keiner der 5 randomisierten Studien statistisch signifikant unterschiedlich. In einer von 5 Studien wurde im hypofraktionierten Arm eine geringere Rate von Fernmetastasen ($HR_{DFS} 0,74$; 95% CI 0,59–0,94) verbunden mit einem besserem Überleben ($HR_{OS}=0,8$; $p=0,042$) beobachtet. (START B: Haviland JS et al. Lancet Oncol 2013; 14: 108)

▪ Ältere Patientinnen sollten über Folgendes beraten werden:

- Die lokale Rückfallrate wird durch eine Brustbestrahlung bei älteren Pat. mit pT1-2 (bis zu 3 cm) pN0, HR-positiven Mammakarzinomen nach brusterhaltender Operation und mit adjuvanter endokriner Therapie um absolut ca. 8% nach 10 Jahren gesenkt. Es findet sich kein Vorteil hinsichtlich des metastasenfreien Überlebens und des Gesamtüberlebens.

1. Haviland JS¹, 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. Hughes KS, Schnaper LA, Bellon JR, 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.
3. Kunkler IH, Williams LJ, Jack WJ, et al: on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.
4. Hughes KS, Schnaper LA. Can older women with early breast cancer avoid radiation? The Lancet Oncology, Available online 28 January 2015

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

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

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

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

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

Boost und Teilbrustbestrahlung nach BEO beim invasiven Karzinom

■ Boost-RT des Tumorbettes (verbesserte lokale Kontrolle, kein Überlebensvorteil)

- Prämenopausal
- Postmenopausal, sofern >T1°, G3, HER2-positiv, triple-negativ, EIC (mindestens 1 Faktor)

■ Intraoperative Radiotherapie (intraop. APBI)

- Als Boost-Bestrahlung vor Ganzbrust-RT
- Als alleinige Radiotherapie-Maßnahme (IORT 50 kV, IOERT)**
 - >50 Jahre **
 - >70 Jahre**

■ Postoperative Teilbrustbestrahlung als alleinige Radiotherapie-Maßnahme bei ausgewählten Pat. (APBI)

- Interstitielle Brachytherapie
 - >70 Jahre**
- Intrakavitäre Ballontechnik
- IMRT***

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

° kontinuierliche Variable bzgl Rezidiv, *Studienteilnahme empfohlen; **nur bei pT1 pN0 R0 G1-2, HR+, nicht-lobulär, >50 J., kein extensives DCIS, IORT während des ersten Eingriffs; ***keine Langzeitdaten;

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. 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.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Partial Breast Irradiation - Boost-RT (improves local control, no survival benefit)

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.

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

Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI

1. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: long term results of an ISORT pooled analysis. Fastner G, Sedlmayer F, Merz F, et al. 2013 Aug;108(2):279-86.
2. 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. Fastner G, Reitsamer R, Ziegler I, et al. *Int J Cancer*. 2015 Mar 1;136(5):1193-201.
3. *Ann Surg Oncol*. 2010 Oct;17 Suppl 3:352-8. doi: 10.1245/s10434-010-1265-z. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. Blank E¹, Kraus-Tiefenbacher U, Welzel G, Keller A, et al.

As sole radiotherapy modality

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

1. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet*. 2010 Jul 10;376(9735):91-102.
2. Vaidya JS, Wenz F, Bulsara M, et al; TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77. #
4. Vaidya JS, Bulsara M, Wenz F, et al.: Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *Int J Radiation Oncol Biol Phys*, Vol. 96, No. 2, pp. 259e265, 2016
5. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare TARGITed Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess* 2016;20(73).
6. Gentilini O, Botteri E, Leonardi MC, et al. Ipsilateral axillary recurrence after breast conservative surgery: The protective effect of whole breast radiotherapy. *Radiother Oncol*. 2017 Jan 4. pii: S0167-8140(16)34462-0. doi: 10.1016/j.radonc.2016.12.021. [Epub ahead of print]

>70 yrs

1. Abbott AM, Dossett LA, Loftus L, et al: Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. *Am J Surg*. 2015 Oct;210(4):624-8.
2. Vaidya JS, Wenz F, Bulsara M, et al: TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77.
4. Vaidya JS , Bulsar M, Wenz F, et al: Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *Int J Radiation Oncol Biol Phys*, Vol. 96, No. 2, pp. 259e265, 2016
5. Vaidya JS, Wenz F, Bulsara M et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess* 2016;20(73).
6. Gentilini O, Botteri E, Leonardi M et al. Ipsilateral axillary recurrence after breast conservative surgery: The protective effect of whole breast radiotherapy. *Radiother Oncol*. 2017 Jan 4. pii: S0167-8140(16)34462-0. doi: 10.1016/j.radonc.2016.12.021. [Epub ahead of print]

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.

Interstitial brachytherapy >70 yrs

1. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Gutierrez Miguelez C, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fishedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Malzer M, Uter W, Polgár C; 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.

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

1. Lehman M, Hickey BE, Francis DP, 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. 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.

Boost vs no Boost: EORTC 22881-10882 Trial

@20 yrs (95% C.I.)	Boost (n=2.661)	No boost (n=2.657)	Hazard Ratio (95% C.I.)
<u>Overall Survival</u> (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)

nach: 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. Bartelink et al. 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. Supplementary appendix. Lancet Oncol 2014; published online Dec 9.
[http://dx.doi.org/10.1016/S1470-2045\(14\)71156-8](http://dx.doi.org/10.1016/S1470-2045(14)71156-8).

EORTC 22881-10882: Boost vs no Boost (Endpoint: any first recurrence)

@15 yrs/20 yrs (95% C.I.)	Boost (n=2.661)		No boost (n=2.657)	Hazard Ratio (95% C.I.)
<u>Overall Survival</u> (Δ= - 1.4%)	59.7% (56.3–63.0)		61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Any First Recurrence				
All patients (Δ≥4%)	@15y @20y	28.1% 32,8%	32.1% 38.7%	HR=0.92 (0.81-1.04), n.s.
≤40 years (Δ>6%)	@15y @20y	41.5% 49.5%	48.1% 56.8%	HR=0.80 (0.56-1.15) , n.s.
41–50 years	@15y @20y	34.0% 38.6%	35.6% 44.2%	HR=0.91 (0.71-1.16), n.s.
51–60 years	@15y @20y	28.5% 34.7%	28.7% 36.2%	HR=0.96 (0.76-1.21), n.s.
>60 years	@15y @20y	27.4% 32.1%	29.1% 32.8%	HR=0.94 (0.74-1.19), n.s.

(Median F/U 17.2 y)

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

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. Bartelink et al. 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. Supplementary appendix. Lancet Oncol 2014; published online Dec 9. [http://dx.doi.org/10.1016/S1470-2045\(14\)71156-8](http://dx.doi.org/10.1016/S1470-2045(14)71156-8).

Postmastektomie-Bestrahlung (PMRT)* der Thoraxwand

- **>3 positive Lymphknoten**
 - **1-3 positive Lymphknoten (hohes Risiko)**
 - **1-3 positive Lymphknoten (niedriges Risiko*)**
 - **T3 / T4**
 - pT3 pN0 R0 (ohne zusätzliche Risikofaktoren)
 - **R0-Resektion nicht erreichbar (bei invasiven Tumoren)**
 - **Bei jungen Patientinnen mit hohem Rückfallrisiko**
- Die Indikationen zur PMRT und regionalen RT sind unabhängig von der adjuvanten systemischen Therapie**

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

* Zur Definition „niedriges Risiko“ siehe nächste Folie Indikation zur Brustwandbestrahlung (PMRT)

1. PEBCTCG (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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Guidelines Breast
Version 2018.1D

Indikation zur Brustwandbestrahlung (PMRT) bei 1–3 axillären Lymphknotenmetastasen

Auf PMRT
kann verzichtet werden
LoE 3b B AGO +

PMRT
zu diskutieren
LoE 3b B AGO +/-

PMRT
empfohlen
LoE 3b B AGO +

ER pos, G1, HER2 neg, pT1 (wenn
mind. 3 der 4 Kriterien zutreffen)

Kyndi et al. 2013

Patientinnen,
für die die
genannten
Risikokriterien
(high-risk / low-
risk) nicht
zutreffen

≥45 J. UND >25% pos. ax. Lnn bei axillärer
Dissektion ODER
<45 J. UND (ER neg. ODER >25% pos. ax.
Lnn bei axillärer Dissektion ODER
medialer Tumorsitz)

Truong et al. 2005

<40 J. ODER
HER2 pos. ODER
Lymphovaskuläre Invasion

Shen H et al. 2015

G3 ODER
Lymphovaskuläre Invasion oder
triple-negativ

Verschiedene Publikationen

Anmerkung: „Besteht eine Indikation zur Bestrahlung der Lymphabflusswege
sollte auch eine Bestrahlung der Brustwand erfolgen.“

www.ago-online.de

**FORSCHEN
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HEILEN**

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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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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 IV: 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.

Radiotherapie der Axilla

	Oxford		
	LoE	GR	AGO
▪ Tumorresiduen nach axillärer Dissektion	5	D	++
▪ Sentinel-Lymphknoten negativ	1b	B	--
▪ Axilladissektion nicht indiziert (z.B. cN0 mit pos. SLN; s. operat. Therapie)	2a	B	-
▪ Extrakapsuläres Tumorwachstum (ECS)	2b	B	-
▪ Axilläre Mikrometastasen oder isolierte Tumorzellen in regionalen Lymphknoten	1b	B	--

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

Tumor residuals after axillary dissection

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 045OL Leitlinie. Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.

Sentinel node negative

1. Krag DN, Anderson SJ, Julian TB, et al: Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABPB-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927–33.
2. Helms G, Kuhn T, Moser L, et al. Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection: data from a prospective randomised trial. Eur J Surg Oncol 2009; 35: 697–701.
3. Kuehn T, Bembenek A, Decker T, et al, for the Consensus Committee of the German Society of Senology. A concept for the clinical implementation of sentinel lymph node biopsy (SLNB) in breast cancer patients with special regard to quality assurance. Cancer 2005; 103: 451–61.
4. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline

recommendations for sentinel lymph node biopsy in early stage breast cancer. J Clin Oncol 2005; 23: 7703–20.

5. Galimberti V, Manika A, Maisonneuve P, et al. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. Eur J Surg Oncol. 2014 Oct;40(10):1203-8.

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

1. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis. A Randomized Clinical Trial. JAMA. 2011;305(6):569-575

Extracapsular tumor spread (ECS)

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

Axillary micrometastases or isolated cells found in regional lymph nodes

1. Pernas S1, Gil M, Benítez A, et al: Avoiding axillary treatment in sentinel lymph node micrometastases of breast cancer: a prospective analysis of axillary or distant recurrence. Ann Surg Oncol. 2010 Mar;17(3):772-7.
2. Yegiyants S, Romero LM, Haigh PI et al: Completion axillary lymph node dissection not required for regional control in patients with breast cancer who have micrometastases in a sentinel node. Arch Surg. 2010 Jun;145(6):564-9.

Axilläre Interventionen bei Patientinnen mit positiven Sentinel-Lymphknoten

Axilläre Dissektion oder RT der Axilla bei 1-2 pos. SLN:

- BET und ACOSOG Z0011-Kriterien erfüllt
 - Keine weitere axilläre Intervention
- Mastektomie (ME), RT der Thoraxwand indiziert und ACOSOG Z0011-Kriterien erfüllt
 - Keine weitere axilläre Intervention
- BET und ACOSOG Z0011-Kriterien nicht erfüllt
- Nach ME, RT der Thoraxwand indiziert und ACOSOG Z0011-Kriterien nicht erfüllt oder ME und RT der Thoraxwand nicht geplant

>=3 pos. SLN

- Axilläre Dissektion
- Radiotherapie der Axilla

Oxford		
LoE	GR	AGO
1b	B	+/-*
1b	B	+/-
5	D	+/-*
5	D	+/-
1b	B	++*
1b	B	++
1b	B	++
1b	B	+

* Study participation recommended

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

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

- 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.
- 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

- 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

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.

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.

≥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. 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. 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.

Radiotherapie (RT) anderer locoregionärer Lymphabflussregionen (SCG/ICG)

RT der supra-/infraklavikulären Lymphregion

- **≥ pN2a oder Level III befallen**
- **pN1a hohes Risiko***
 - *zentraler oder medialer Sitz und (G2-3 oder ER/PgR-negativ)
 - *prämenopausal, lateraler Sitz und (G2-3 oder ER/PgR-negativ)
- **pN0 prämenopausal, hohes Risiko****
 - **zentraler oder medialer Sitz, und G2-3 und ER/PgR-negativ

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

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 PSH, Kirkove C, Budach V, et al: Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC radiation oncology and breast cancer groups phase III trial 22922/10925. EJC 2013, 47(Suppl 2).
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
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. 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.

RT to Internal mammaria lymph node region (IMN) if pN1-pN2 and HR positive in patients who had systemic chemotherapy

1. Hennequin C, Bossard N, Servagi-Vernat S, et al: Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. *Int J Radiation Oncol Biol Phys* 2013; 86 (5): 860-866.
2. Chang JS, Park W, YB Kim, et al. Long-term Survival Outcomes Following Internal Mammary Node Irradiation in Stage II-III Breast Cancer: Results of a Large Retrospective Study With 12-Year Follow-up. *Int J Radiation Oncol Biol Phys*, 2013; 86 (5): 867-872.
3. Poortmans PSH, Kirkove C, Budach V, et al: Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC radiation oncology and breast cancer groups phase III trial 22922/10925. *EJC* 2013, 47(Suppl 2).
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg.* 2013 Sep 11;2013:212979.
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. 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.

Radiotherapie (RT) anderer Lokoregionärer Lymphabflussregionen (IMC)

Mammaria interna Lymphknotenregion (IMC)

- **pN0 prämenopausal, hohes Risiko*****
***zentraler oder medialer Sitz und G2-3 und ER/PgR-negativ
- **pN1a hohes Risiko***
* zentraler oder medialer Sitz, und (G2-3 oder ER/PgR-negativ)
* lateraler Sitz, prämenopausal und (G2-3 oder ER/PgR-negativ)
- **pN2a hohes Risiko****
**G2-3 oder ER/PgR-negativ
- **pN1b-c, pN2c, pN3b**
- **IMC-RT, bei kardialem Risiko oder bei Gabe von Trastuzumab**

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

- Yates L, Kirby A, Crichton S, Gillett C, Cane P, Fentiman I, Sawyer E. 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.
- 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 \geq pN2a

- Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: 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.
- Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
- 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.
- Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20

Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.

5. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. 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.
6. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W; 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.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. 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.
3. Whelan TJ, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W; 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.
4. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. *Radiat Oncol*. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W; 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.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. 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.
3. Whelan TJ, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau

P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: 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.

4. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W; 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.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. 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.
3. Whelan TJ, Olivotto IA, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: 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.
4. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W; 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.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. 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.

3. Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: 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.
4. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. *Radiat Oncol*. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W; 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.

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

1. Bernier J. Post-mastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer patients: A review. *Crit Rev Oncol Hematol*. 2015 Mar;93(3):180-189.
2. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer Jr CE, et al. 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* 2012;30:3960–6.
3. Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol* 2002;20:17–23.
4. Rusthoven CG1, Rabinovitch RA1, Jones BL1, Koshy M2, Amini A1, Yeh N1, Jackson MW1, Fisher CM1. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. *Ann Oncol*. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

Fraktionierung der Radiotherapie lokoregionärer Lymphabflussregionen

	Oxford		
	LoE	GR	AGO
▪ Konventionelle fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25–28 Fraktionen in ca. 5–6 Wochen)	1a	A	++
▪ Hypofraktionierung RT (Gesamtdosis ca. 40 Gy in ca. 15–16 Fraktionen in ca. 3 bis 5 Wochen)	2b	B	+/-

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



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Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

(median follow-up 10.9 yrs)

Adjuvant treatment	n*	Hazard ratio (95%CI)
No adjuvant reported	625	0.91 (0.59 - 1.39)
Chemotherapy	954	1.05 (0.84 - 1.32)
Endocrine therapy	1185	0.82 (0.63 - 1.06)
Both (endocrine th. and chemotherapy)	1200	0.72 (0.55 – 0.94)
Total	4004	0.88 (0.76 – 1.01)

* missing data on 40 patients

Poortmans et al. ECCO Amsterdam 2013

Radiotherapie nach NACT

Prätherapeutisch	Posttherapeutisch	RT-BET	PMRT	RT-LAW	Oxford		
					LoE	GR	AGO
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)	ypT0/is 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/PgR-negativ)
 - prätherapeutisch pN1a/ cN+* hohes Risiko: zentraler oder medialer Sitz und (G2-3 oder ER/PgR-negativ) oder prämenopausal, lateraler Sitz und (G2-3 oder ER/PgR-negativ)
- * = durch Stanzbiopsie gesichert

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Kombination systemischer Therapien mit simultaner Radiotherapie

- **Trastuzumab* simultan zur Radiotherapie**
- **Tamoxifen simultan zur Radiotherapie**
- **AI (Letrozol) simultan zur Radiotherapie**

Oxford		
LoE	GR	AGO
2b	B	+
2b	B	+
2b	B	+

* Bei HER2-positiven Tumoren sollte eine parasternale RT generell vermieden werden;
keine simultane Trastuzumabtherapie bei parasternaler RT.

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

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Tamoxifen concurrent with radiotherapy

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AI (letrozole, anastrozole) concurrent with radiotherapy

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Other compounds (bevacizumab)

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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			++
■ Das Rauchen sollte beendet werden.			++

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