


Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Adjuvante Strahlentherapie



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Adjuvante Radiotherapie (RT)

- **Versionen 2002 – 2018:**
**Blohmer / Budach / Friedrichs / Göhring / Huober /
Janni / Kühn / Möbus / Scharl / Seegenschmiedt /
Souchon / Thomssen / Untch / Wenz**
- **Version 2019:**
Budach / Rody / Wenz

Search Strategy

Search Terms: Radiotherapy Breast Cancer

Source: Pubmed 1/2010 – 1/2018

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


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

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, et al. Lancet. 2011 Nov 12;378(9804):1707-16.

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

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



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Vorbemerkung

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



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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 AS, Winer EP, Goldhirsch A, 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 JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013 Oct;14(11):1086-94.
2. Whelan TJ, Pignol JP, Levine M et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010 Feb 11;362(6):513-20.
3. Haffty BG¹, Buchholz TA. Hypofractionated breast radiation: preferred standard of care? *Lancet Oncol.* 2013 Oct;14(11):1032-4.
4. Hopwood P, Haviland JS, Sumo G et al; START Trial Management Group. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol.* 2010 Mar;11(3):231-40.
5. Shaitelman SF, 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 AL, Whelan TJ, Pond GR, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. *Ann Oncol.* 2014 May;25(5):992-8.
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



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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 (Brustschumpfung, Teleangiectasien 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 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. 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



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

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

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

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

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

Boost und Teilbrustbestrahlung nach BEO beim invasiven Karzinom			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Boost-RT des Tumorbettes (verbesserte lokale Kontrolle, kein Überlebensvorteil) <ul style="list-style-type: none"> Prämenopausal Postmenopausal, sofern >T1°, G3, HER2-positiv, triple-negativ, EIC (mindestens 1 Faktor) 	1b	B	++
	2b	B	+
<ul style="list-style-type: none"> Intraoperative Radiotherapie (intraop. APBI) <ul style="list-style-type: none"> Als Boost-Bestrahlung vor Ganzbrust-RT Als alleinige Radiotherapie-Maßnahme (IORT 50 kV, IOERT)** 	2a	B	+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> >50 Jahre ** >70 Jahre** 	1a	A	+/-*
	1a	A	+
<ul style="list-style-type: none"> Postoperative Teilbrustbestrahlung als alleinige Radiotherapie-Maßnahme bei ausgewählten Pat. (APBI) <ul style="list-style-type: none"> Interstitielle Brachytherapie <ul style="list-style-type: none"> >70 Jahre** Intrakavitäre Ballontechnik IMRT*** 	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;

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1. Bartelink H, Maingon P, Poortmans P, et al: European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):47-56. Including Supplemantary 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 ISIORT 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 , Bulsar M, Wenz F, et al.: Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *Int J Radiation Oncol Biol Phys*, Vol. 96, No. 2, pp. 259e265, 2016
5. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess* 2016;20(73).
6. Gentilini O, Botteri E, Leonardi MC, et al. Ipsilateral axillary recurrence after breast conservative surgery: The protective effect of whole breast radiotherapy. *Radiother Oncol*. 2017 Jan 4. pii: S0167-8140(16)34462-0. doi: 10.1016/j.radonc.2016.12.021. [Epub ahead of print]

>70 yrs

1. Abbott AM, Dossett LA, Loftus L, et al: Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. *Am J Surg*. 2015 Oct;210(4):624-8.
2. Vaidya JS, Wenz F, Bulsara M, et al: TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77.
4. Vaidya JS , 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 multicatheter highdose rate brachytherapy. *Radiother Oncol* 2013;108:236-241.
2. Strnad V, Ott OJ, Hildebrandt G, et al: Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet*. 2016 Jan 16;387(10015):229-38.

Interstitial brachytherapy >70 yrs


1. Strnad V, Ott OJ, Hildebrandt G, Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO) et al. 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.



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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).
3. 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

	<h2 style="text-align: center;">EORTC 22881-10882: Boost vs no Boost (Endpoint: any first recurrence)</h2>				
<p>© AGO e. V. in der DGOG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p>	<p>@15 yrs/20 yrs (95% C.I.)</p>	<p>Boost (n=2.661)</p>	<p>No boost (n=2.657)</p>	<p>Hazard Ratio (95% C.I.)</p>	
	<p>Overall Survival (Δ= - 1.4%)</p>	<p>59.7% (56.3–63.0)</p>	<p>61.1% (57.6–64.3)</p>	<p>HR 1.05 (0.92–1.19) n.s.</p>	
<p>Cumulative Risk of Any First Recurrence</p>					
<p>All patients (Δ≥4%)</p>	<p>@15y @20y</p>	<p>28.1% 32.8%</p>	<p>32.1% 38.7%</p>	<p>HR=0.92 (0.81-1.04), n.s.</p>	
<p>≤40 years (Δ>6%)</p>	<p>@15y @20y</p>	<p>41.5% 49.5%</p>	<p>48.1% 56.8%</p>	<p>HR=0.80 (0.56-1.15) , n.s.</p>	
<p>41–50 years</p>	<p>@15y @20y</p>	<p>34.0% 38.6%</p>	<p>35.6% 44.2%</p>	<p>HR=0.91 (0.71-1.16), n.s.</p>	
<p>51–60 years</p>	<p>@15y @20y</p>	<p>28.5% 34.7%</p>	<p>28.7% 36.2%</p>	<p>HR=0.96 (0.76-1.21), n.s.</p>	
<p>>60 years</p>	<p>@15y @20y</p>	<p>27.4% 32.1%</p>	<p>29.1% 32.8%</p>	<p>HR=0.94 (0.74-1.19), n.s.</p>	
<p>(Median F/U 17.2 y)</p>					
<p>acc. Bartelink et al. Lancet Oncol 2015; 16: 47–56. Suppl.</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.
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Guidelines Breast
Version 2019.1D

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FORSCHEN
LEHREN
HEILEN

Postmastektomie-Bestrahlung (PMRT)* der Thoraxwand

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

- **>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

* 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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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with T3 / T4 breast cancer

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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. 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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Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment


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	<h2 style="text-align: center;">Indikation zur Brustwandbestrahlung (PMRT) bei 1–3 axillären Lymphknotenmetastasen</h2>		
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p>	<p style="text-align: center;">Auf PMRT kann verzichtet werden LoE 3b B AGO +</p>	<p style="text-align: center;">PMRT zu diskutieren LoE 3b B AGO +/-</p>	<p style="text-align: center;">PMRT empfohlen LoE 3b B AGO +</p>
<p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<p style="border: 2px solid green; padding: 5px; text-align: center;">ER pos, G1, HER2 neg, pT1 (wenn mind. 3 der 4 Kriterien zutreffen)</p> <p style="text-align: center;">Kyndi et al. 2013</p>	<p style="text-align: center;">Patientinnen, für die die genannten Risikokriterien (high-risk / low- risk) nicht zutreffen</p>	<div style="border: 1px solid blue; padding: 5px; margin-bottom: 5px;"> <p>≥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)</p> <p style="text-align: right;">Truong et al. 2005</p> </div> <div style="border: 1px solid blue; padding: 5px; margin-bottom: 5px;"> <p><40 J. ODER HER2 pos. ODER Lymphovaskuläre Invasion</p> <p style="text-align: right;">Shen H et al. 2015</p> </div> <div style="border: 1px solid blue; padding: 5px;"> <p>G3 ODER Lymphovaskuläre Invasion oder triple-negativ</p> <p style="text-align: right;">Verschiedene Publikationen</p> </div>
<p style="text-align: center;">Anmerkung: „Besteht eine Indikation zur Bestrahlung der Lymphabflusswege sollte auch eine Bestrahlung der Brustwand erfolgen.“</p>			

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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
2. Freedman GM, Fowble BL, Hanlon AL, et al: A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. Int J Radiat Oncol Biol Phys. 1998 Jun 1;41(3):599-605.
3. Truong PT, Olivotto IA, Speers CH, et al. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys. 2004 Mar 1;58(3):797-804.
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
5. Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. Breast. 2010 Feb;19(1):14-22.
6. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother

Oncol. 2009 Apr;91(1):23-32.

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

1. Garg AK, Oh JL, Oswald MJ, et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. *Int J Radiat Oncol Biol Phys* 2007; 69: 1478–83.
2. Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77.
3. Dragun AE, Huang B, Gupta S, et al. One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. *Int J Radiat Oncol Biol Phys* 2012;83:e591-6.
4. Mallon PT, McIntosh SA. Post mastectomy radiotherapy in breast cancer: a survey of current United Kingdom practice. *J BUON* 2012;17:245-8.
5. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. *Breast Cancer Res Treat* 2011;127:207-15.

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

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

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

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

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

Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment


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

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

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

DEGRO practical guidelines for radiotherapy of breast cancer 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.



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sowie
in der DGK e. V.

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Boost bei PMRT

	Oxford		
	LoE	GR	AGO
■ Eine boost-Bestrahlung der Thoraxwand hat keinen Einfluss auf das brustkrebspezifische und Gesamtüberleben ¹	2a	B	
■ Eine boost-Bestrahlung der Thoraxwand sollte nur bei nachgewiesener R1/R2-Situation ohne Möglichkeit einer Nachresektion erfolgen ²	5	D	++
■ Reicht der Tumor nach Mastektomie (unter Mitnahme der Pectoralisfaszie) an den pectoralen Absetzungsrand heran und ist ein faszienüberschreitendes Tumorstadium klinisch nicht zu erkennen, ist von einer R0-Situation auszugehen. Eine Boostbestrahlung ist nicht erforderlich ²	5	D	++

² GCP

Boost Thoraxwand und Gesamtüberleben

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



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Radiotherapie der Axilla nach axilläre Dissektion oder negativen SN

	Oxford		
	LoE	GR	AGO
■ Tumorresiduen nach axillärer Dissektion	5	D	++
■ Sentinel-Lymphknoten negativ	1b	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, et al. Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis. A Randomized Clinical Trial. *JAMA*. 2011;305(6):569-575


Extracapsular tumor spread (ECS)

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

Axillary micrometastases or isolated cells found in regional lymph nodes

1. Pernas S1, Gil M, Benítez A, et al: Avoiding axillary treatment in sentinel lymph node micrometastases of breast cancer: a prospective analysis of axillary or distant recurrence. *Ann Surg Oncol*. 2010 Mar;17(3):772-7.

2. Yegiyants S, Romero LM, Haigh PI et al: Completion axillary lymph node dissection not required for regional control in patients with breast cancer who have micrometastases in a sentinel node. Arch Surg. 2010 Jun;145(6):564-9.

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	LoE	GR	AGO
	BET und ACOSOG Z0011-Kriterien⁺ erfüllt		
	<ul style="list-style-type: none"> Radiotherapie der Brust unter Einschluss von Level 1 + 2 bis 5 mm unterhalb der Vena axillaris (PTV) 		
	2b	B	+*
	BET und ACOSOG Z0011-Kriterien⁺ nicht erfüllt		
	<ul style="list-style-type: none"> Radiotherapie der Axilla (analog AMAROS) 		
	1b	B	++*
	Nach ME, RT der Thoraxwand indiziert und ACOSOG Z011-Kriterien⁺ nicht erfüllt oder ME und RT der Thoraxwand nicht geplant		
	<ul style="list-style-type: none"> Radiotherapie der Axilla (analog AMAROS) 		
	1b	B	++
	>=3 pos. SLN		
	<ul style="list-style-type: none"> Radiotherapie der Axilla (analog AMAROS) 		
	1b	B	+
<p>* = Study participation recommended</p> <p>** = Makrometastasen</p> <p>⁺ = <T3, keine palpablen LK, R0, 1-2 befallene SN, kein extrakapsuläres Wachstum, keine NACT</p>			

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, 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.
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

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

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

EXPERT OPINION, extrapolated from:

1. Donker M, Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10.

>=3 positive SLN: Axillary LN dissection

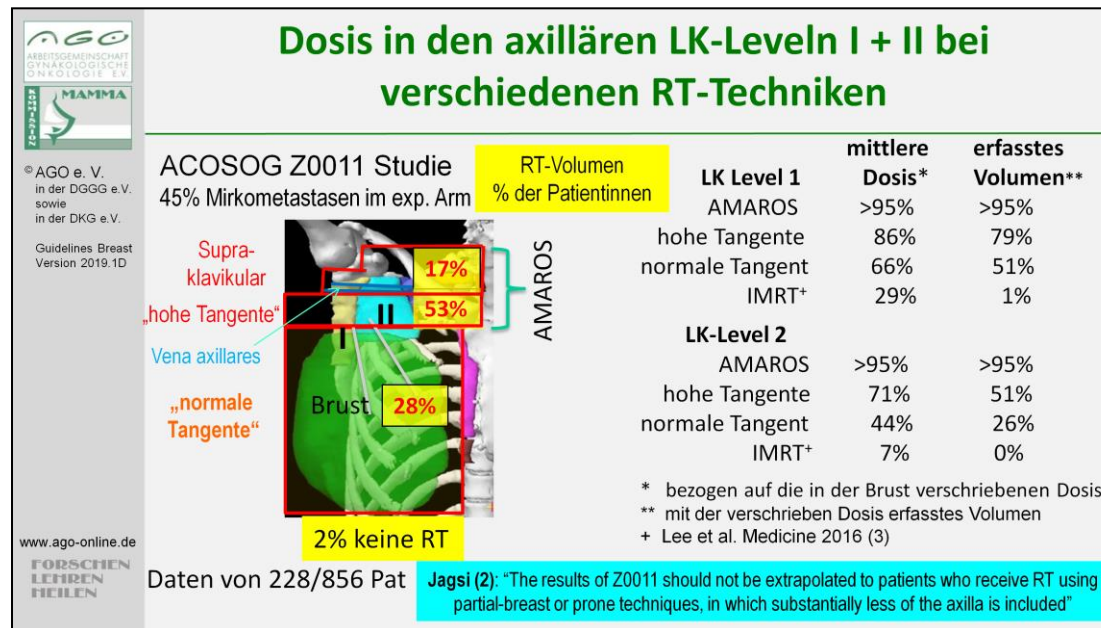
1. Giuliano AE, Hunt KK, Ballmann KV, et al. Axillary dissection vs no axillary dissection in women with breast invasive cancer and

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.



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):e4036

Radiotherapie (RT) anderer locoregionärer Lymphabflussregionen (SCG/ICG)			
	Oxford		
	LoE	GR	AGO
RT der supra-/infraklavikulären Lymphregion			
▪ ≥ 4 befallene axilläre Lymphknoten oder Befall im Level III oder der supra-/infraklavikulären Lymphknoten	1b	A	++
▪ 1–3 befallene axilläre Lymphknoten¹ bei - zentralem oder medialem Sitz und G2-3 oder ER/PgR-negativ - prämenopausale Patientin und G2-3 oder ER/PgR-negativ	2a	B	+
▪ pN0 und prämenopausal bei zentralen oder medialen Sitz und G2-3 und ER/PgR-negativ	2a	B	+/-
¹ = gilt nicht für Mikrometastasen			

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG) (15/20)

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

Supra-/infracavicular lymphatic regions

RT to Supra-/infracavicular lymphatic regions if ≥ pN2a

1. 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.
2. 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.

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

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 et al. MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
3. 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.
4. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, et al. MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
3. 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.
4. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, et al. MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
3. 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.
4. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.

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

1. Whelan TJ, Olivetto IA, Parulekar WR, et al; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
3. Whelan TJ, Ackerman I, Chapman JW, et al: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
4. Budach W, Kammers K, Boelke E, et al. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
5. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.

RT to Supra-/intraclavicular 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, 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, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol 2002;20:17–23.
4. Rusthoven CG, Rabinovitch RA, Jones BL, et al. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant

Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. Ann Oncol. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

	Oxford		
	LoE	GR	AGO
Mammaria interna Lymphknotenregion (IMC)			
▪ pN0 und prämenopausal und zentraler oder medialer Sitz und G2-3 und ER/PgR-negativ	1b	B	+/-
▪ 1–3 befallene axilläre Lymphknoten ¹ bei - zentralem oder medialem Sitz und G2-3 oder ER/PgR-negativ - prämenopausale Patientin und G2-3 oder ER/PgR-negativ	2a	B	+
▪ > = 4 befallene axilläre Lymphknoten bei G2-3 oder ER/PgR-negativ	2a	B	+
▪ befallene mammaria interna Lymphknoten	2a	B	+
▪ bei kardialem Risiko oder bei Gabe von Trastuzumab	2b	A	--

¹ = gilt nicht für Mikrometastasen

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN) - Slide 16/20

Internal mammaia lymph node region (IMN)


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

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Fraktionierung der Radiotherapie lokoregionärer Lymphabflussregionen

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

- Konventionelle fraktionierte RT (Gesamtdosis ca. 50 Gy in ca. 25–28 Fraktionen in ca. 5–6 Wochen)
- Hypofraktionierung RT (Gesamtdosis ca. 40 Gy in ca. 15–16 Fraktionen in ca. 3 bis 5 Wochen)

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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



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Radiotherapie nach NACT

Prätherapeutisch	Posttherapeutisch	RT-BET	PMRT	RT-LAW
Lokal fortgeschritten	pCR / keine pCR	Ja	ja	ja
cT1/2 cN1+*	ypT1+ o. ypN1+ (keine pCR)	ja	ja	ja
cT1/2 cN1+*	ypT0/is ypN0	ja	Risikofälle ¹	
cT1/2 cN0 (Sonogr. obligat)	ypT0/is ypN0	ja	nein	nein

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

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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Molekulare Prädiktion für die Radiotherapie

- Ergebnisse von Genexpressionsprofilen (z.B. TAILOR RT, IDEA) sollen nicht für die Indikationsstellung der Radiotherapie herangezogen werden

Oxford		
LoE	GR	AGO
2b	A	++

1. Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiother Oncol.* 2015 Jan;114(1):56-65
2. Taylor C, Correa C, Anderson S, et al: Late side-effects of breast cancer radiotherapy: Second cancer incidence and non-breast-cancer mortality among 40,000 women in 75 trials. *San Antonio Breast Cancer Symposium 2015; S5-08*

Kombination systemischer Therapien mit simultaner lokoregionärer Radiotherapie			
	Oxford		
	LoE	GR	AGO
▪ Trastuzumab/Pertuzumab* simultan zur Radiotherapie	1a	A	++
▪ T-DM1	1b	A	+
▪ Tamoxifen simultan zur Radiotherapie	2b	B	+
▪ AI (Letrozol) simultan zur Radiotherapie	2b	B	+
▪ Checkpointinhibitoren	3b	C	+
▪ Capecitabin	2b	B	+

* Bei HER2-positiven Tumoren sollte eine simultane 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)

1. Belkacemi and J. Gligorov, Concurrent trastuzumab — internal mammary irradiation for HER2 positive breast cancer: “It hurts to be on the cutting edge”. Radiother Oncol 2010;94:119-20 (Letter to the editor).
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Tamoxifen concurrent with radiotherapy

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

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

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

T-DM1 concurrent with radiotherapy

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

Checkpointinhibitors concurrent with radiotherapy

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

Capecitabine and radiotherapy


1. Masuda N, Lee SJ, Ohtani S et al., Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy, *N Engl J Med*. 2017 Jun 1;376(22):2147-2159
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3. Gauj MF, Amorim G, Arcuri RA, Pereira G, et al. A phase II study of second-line neoadjuvant chemotherapy with capecitabine and radiation therapy for anthracycline-resistant locally advanced breast cancer. Am J Clin Oncol. 2007 Feb;30(1):78-81. Erratum in: Am J Clin Oncol. 2007 Jun;30(3):331.

Other compounds (bevacizumab)

1. Late toxicities and outcomes after one year of adjuvant radiotherapy combined with concurrent bevacizumab in patients with triple negative non-metastatic breast cancer. Pernin V, Belin L, Cottu P, et al. Br J Radiol. 2015 Feb 3;20140800.



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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			++

1. Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. Radiother Oncol. 2015 Jan;114(1):56-65
2. Taylor C, Correa C, Anderson S, et al: Late side-effects of breast cancer radiotherapy: Second cancer incidence and non-breast-cancer mortality among 40,000 women in 75 trials. San Antonio Breast Cancer Symposium 2015; S5-08