

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Version 2025.1E

Adjuvant Radiotherapy

Adjuvant Radiotherapy (RT)

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- **Versions 2002 – 2024:**
Blohmer / Budach / Friedrich / Friedrichs / Göhring / Huober / Janni / Krug / Kühn / Möbus / Rody / Scharl / Schmidt / Seegenschmiedt / Solbach / Souchon / Thomssen / Untch / Wenz
- **Version 2025:**
Budach / Krug / Thomssen

Preliminary Note

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

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

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

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

Randomized controlled trials of radiotherapy omission after breast-conserving surgery in early breast cancer

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

Prospective observational studies of radiotherapy omission incorporating tumor biology and MRI

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

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

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



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LoE GR AGO

| | LoE | GR | AGO |
|--|-----|----|-----|
| <ul style="list-style-type: none"> Boost-RT (improves local control, no survival benefit) <ul style="list-style-type: none"> Premenopausal Postmenopausal, if > T1* G3, HER2-positive, triple negative, EIC (at least 1 factor) | 1b | B | ++ |
| | 2b | B | + |
| <ul style="list-style-type: none"> Techniques <ul style="list-style-type: none"> Percutaneous boost (photons, electrons) as sequential boost Multicatheter brachytherapy-boost Percutaneous boost as simultaneous integrated boost (with conventionally fractionated whole-breast irradiation) Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation) Intraoperative boost irradiation (followed by whole-breast irradiation) | 1a | A | ++ |
| | 1a | A | ++ |
| | 1b | B | + |
| | 1b | B | ++ |
| | 2b | B | + |
| <ul style="list-style-type: none"> Intraoperative clip placement at the tumor bed if boost irradiation is indicated | 2b | B | + |

* continuous parameter with regard to risk of relapse

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

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

(Median F/U 17.2 y)

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

EORTC 22881-10882: Boost vs. no Boost (Endpoint: Any First Recurrence)

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

(Median F/U 17.2 y)

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

Moderate hypofractionation with simultaneous-integrated boost

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| | RTOG 1005 (ASTRO 2022) | IMPORT-HIGH (Lancet 2023) | HYPOSIB (ASTRO 2024) |
|------------------|--|--|--|
| Patient number | 2262 | 2617 | 2179 |
| Schedule Breast | 40 Gy in 15 fx | 36 Gy in 15 fx 40 Gy in 15 fx | 40 Gy in 16 fx |
| Schedule Boost | 48 Gy in 15 fx | 48 Gy in 15 fx | 48 Gy in 16 fx |
| Primary endpoint | Ipsilateral in-breast recurrence HR 1.32 (0.8-2.1) → Non-inferiority for SIB | Ipsilateral in-breast recurrence HR 1.04 (0.56-1.92) → Non-inferiority for SIB | Disease-free survival HR 1.10 (0.78-1.54) → Non-inferiority for SIB |
| Toxicity | Toxicity grade ≥ 3 (ROTG) p = 0.79 | Any moderate / marked breast AE p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB) | No significant difference for grade ≥ 2 skin toxicity, fibrosis, teleangiectasia, nausea, hot flashes, pain |

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

Oxford

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- | | | | |
|--|----|---|-----|
| <ul style="list-style-type: none"> ■ Eligible patients: Age ≥ 50 years, Tumor < 3 cm, pN0, ER/PgR pos.**, HER2 neg., G1-2**, L0 R0, non-lobular histology, no BRCA-mutation known | | | |
| <ul style="list-style-type: none"> ■ Postoperative partial breast irradiation <ul style="list-style-type: none"> ■ Interstitial Multicatheter-Brachytherapy ■ Intracavitary balloon-technique ■ Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 1.5 weeks) ■ 3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks) ■ 3D-conformal radiotherapy (10 x 3.85 Gy in 1 week) ■ Intraoperative Radiotherapy (IORT 50 kV, IOERT) <ul style="list-style-type: none"> ■ As sole radiotherapy, during first breast surgery ■ Intraoperative clip placement at the tumor bed if partial breast irradiation is indicated | 1b | A | + |
| | 2b | B | - |
| | 1b | A | + |
| | 1b | A | ++ |
| | 1b | A | - |
| | 1b | A | +/- |
| | 2b | B | + |

*Definition of the target volume and practical procedures see the related DEGRO practical guidelines.

**Individual decision for PBI is possible, if one of the criteria is not met.

Meta-analyses on partial-breast irradiation

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

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

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

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

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

Comparison of different techniques for partial breast irradiation

| | Intraoperative radiotherapy | Multicatheter interstitial brachytherapy | External-beam radiotherapy |
|---------------|---|---|--|
| Advantages | <ul style="list-style-type: none"> • Shortest possible treatment time • Direct visualization of the tumor bed | <ul style="list-style-type: none"> • High conformality • Longest available follow-up | <ul style="list-style-type: none"> • Broad availability • Reproducibility |
| Disadvantages | <ul style="list-style-type: none"> • Lack of complete knowledge of risk factors (e.g. margin status, lympho-vascular invasion) • Potentially increased risk of fibrosis with additional whole-breast irradiation • Availability limited to specialized centers • Prolongation of anesthesia | <ul style="list-style-type: none"> • Availability limited to specialized centers with high expertise • Additional invasive procedure • Additional hospital stay • Risk of target miss due to visualization of the tumor bed | <ul style="list-style-type: none"> • Risk of target miss due to visualization of the tumor bed • Larger irradiated volume due to intra- and interfractional motion |

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

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- **≥4 tumor infiltrated lymph nodes (LN)**
- **1–3 tumor infiltrated LN (high-risk)**
- **1–3 tumor infiltrated LN (low-risk*, with ALND)**
- **1–3 tumor infiltrated LN (low-risk*, no ALND)**
- **T3 / T4**
 - **pT3 pN0 R0 (and no additional risk factors)**
- **If R0 is impossible to reach (for invasive tumor)**

The indications for PMRT and regional RT are independent of adjuvant systemic treatment

Inflammatory breast cancer: PMRT and regional nodal irradiation

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

*See slide Radiotherapy of the Chest Wall After Mastectomy (PMRT). Low risk: pT1-2, involved 1-2 LN, ER/PR pos., HER2 neg.

SUPREMO: Post-mastectomy radiotherapy in intermediate risk breast cancer patients

Kunkler et al. SABCS 2024

- Prospective randomized controlled trial, n = 1607
- Inclusion criteria:
 - T1-2 N1, T3 N0, T2 N0 if G3 and/or L1
 - Simple mastectomy, reconstruction allowed. If N1, ALND with ≥ 8 removed nodes was required. NACT was allowed (26 patients).
- Randomization to Post-Mastectomy Radiotherapy or no RT.
- Primary endpoint: overall survival (powered to demonstrate improvement by 7%, 609 events)
- Patient characteristics:
 - Median 55 years, 24% T2N0, 29% T1N1, 45% T2N1, <1% T3N0, 63% 1-2 LK, 21% HER2 pos., 11% TNBC
 - No data on systemic therapy and type of surgery.
- Results:
 - No improvement in OS (HR 1.04, 95%-CI 0.82-1.30, 295 events)
 - Significant reduction in Chest wall recurrence (HR 0.45, 95%-CI 0.2-0.99; 2.5 vs. 1.1%)
 - Trend towards reduced regional recurrence (HR 0.61, 95%-CI 0.36-1.03, 4.5 vs. 2.7%)
 - No improvement in metastasis-free survival or disease-free survival
- Limitations:
 - No subgroup analyses were presented.
 - Regional nodal irradiation was not prespecified.

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

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PMRT
not recommended
LoE 1b B AGO +

pT1-2, 1-2 involved lymph nodes,
axillary dissection, ER/PR pos.,
HER2 neg.

According to Kunkler et al. 2024

PMRT
to be discussed
LoE 3b B AGO +/-

Patients, who
don't fulfill
the mentioned
criteria for
high or low
risk

PMRT
recommended
LoE 3b B AGO +

≥ 45 y. AND > 25% pos. ax. Lnn in case of
axillary dissection OR
<45 y. AND (ER neg. OR >25% pos. ax. Lnn in case
of axillary dissection OR medial tumor location)

Truong et al. 2005

< 40 y. OR
HER2 pos. OR
lymphovascular invasion

Shen H et al. 2015

G3 OR
lymphovascular invasion OR
triple negative

Different publications

**Comment: In case of an indication for radiotherapy of regional lymph nodes,
radiotherapy of the chest wall should also be administered**

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

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|---|-----------|----------|-----------|
| | LoE | GR | AGO |
| <ul style="list-style-type: none"> Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks) <ul style="list-style-type: none"> After breast reconstruction | 1a | A | ++ |
| <ul style="list-style-type: none"> Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week) | 1b | B | ++ |
| <ul style="list-style-type: none"> Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 5-6 weeks) | 1a | B | + |

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

RT-CHARM: Moderate hypofractionation in patients with breast reconstruction

Poppe et al. RT CHARM-trial (Alliance A221505), ASTRO 2024

- Prospective randomized controlled non-inferiority trial, n = 825
- Inclusion criteria: T1-3 N1-2, T3 N0, planned reconstruction within 18 months of radiotherapy
- Randomization to 25x2 Gy or 16x2.66 Gy.
- Primary endpoint: Reconstruction-associated complications at 2 years - non-inferiority was shown.
- Type of reconstruction was the most important predictor of complications (autologous vs. implant: OR 0.49; expander vs. immediate reconstruction OR 2.06)
- Locoregional recurrence 1.9 vs. 1.5% at 3 years.

Reconstruction-associated complications at 2 years

| | 25x2 Gy | 16x2.66 Gy | Absolute difference |
|--------------|---------|------------|---------------------|
| All patients | 12.2% | 14.2% | +2.1% |
| Immediate | 11.9% | 10.3% | -1.6% |
| Delayed | 12.3% | 15.6% | +3.3% |
| Autologous | 8.9% | 8.5% | -0.4% |
| Implant | 13.8% | 17.1% | +3.3% |

Boost in PMRT

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

Oxford

| LoE | GR | AGO |
|-----|----|-----|
|-----|----|-----|

| | | |
|----|---|--|
| 2a | B | |
|----|---|--|

| | | |
|---|---|----|
| 5 | D | ++ |
|---|---|----|

| | | |
|---|---|----|
| 5 | D | ++ |
|---|---|----|

Radiotherapy of the axilla in patients with positive sentinel lymph nodes*, who did not undergo axillary dissection

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| | Oxford | | |
|--|-----------|----------|------------|
| | LoE | GR | AGO |
| BCS or mastectomy and SENOMAC-criteria** met | | | |
| ▪ Radiotherapy to the breast/chest wall and axilla (Level I-IV) | 1b | B | + |
| ▪ Radiotherapy to the breast/chest wall including LN level I+II to 5 mm below the axillary vein (PTV)*** | 2b | B | + |
| BCS or mastectomy and SENOMAC-Kriterien** <u>not</u> met | 5 | D | ++ |
| ▪ Radiotherapy to the breast/chest wall and axilla (Level I-IV) | | | |
| Mastectomy and SENOMAC-criteria met, radiotherapy to the chest wall not planned | | | |
| ▪ Exclusive radiotherapy to the axilla | 5 | D | +/- |
| ≥ 3 pos. SLN | | | |
| ▪ Radiotherapy to the axilla (Level I-IV analog AMAROS) | 1b | B | + |

*Macrometastases ** T1-T3, no suspicious nodes on ultrasound (or FNP/CNB neg.), 1-2 involved SLN, no NACT

***only if there is otherwise no indication for regional nodal irradiation (see slide „Regional nodal irradiation“)

Radiotherapy target volumes in the SENOMAC-trial

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- Collection of radiotherapy target volumes for patients in the ITT population (n = 2624 patients)
- Collection of dosimetric data for patients receiving radiotherapy in Denmark and Sweden (n = 1229, data available for 96% of those patients)

| ITT population (N = 2624) | SLNB (n = 1371) | ALND (n = 1253) |
|------------------------------|--------------------|--------------------|
| No RT | 3.8% | 5.3% |
| Breast/CW only | 6.2% | 5.8% |
| Breast/CW + RNI | 88.8% | 87.4% |
| RNI only | 1.1% | 0.9% |
| Missing | 0.1% | 0.4% |

| RTQA population (N = 1176) | SLNB (n = 611) | ALND (n = 565) |
|-------------------------------|-------------------|-------------------|
| Breast/CW | 100% | 100% |
| Level I (complete) | 55% | 31% |
| Level II-IV | 97% | 97% |

Additional radiotherapy of the axilla after primary surgery

(in case of an indication for RT of the breast/chest wall¹ +/- supra-/infraclavicular and internal mammary node RT²)

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|---|--|----|---|----|
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| pN-Status | | | | |
| cN0 / pNx analog SOUND/INSEMA | No intentional Rt to the axilla ¹ | 1b | B | - |
| pN0(sn) / pN1mic(sn) | No intentional Rt to the axilla ¹ | 1b | B | -- |
| pN0/+ after ALND | No intentional Rt to the axilla ¹ | 1a | A | -- |
| pN+(sn) analog SENOMAC/AMAROS ³ (no ALND) | Level I-IV | 1b | B | + |
| pN+(sn) analog SENOMAC/AMAROS ³ (no ALND) | Level I-II ⁴ | 2b | B | + |
| pN+(sn) not analog SENOMAC/AMAROS ³ (no ALND) | Level I-IV | 5 | D | ++ |
| Extensive perinodal soft tissue involvement in the axilla | Level I-IV | 2b | B | + |
| Residual tumor in the axilla after ALND | Level I-IV | 5 | D | ++ |

¹Incidental dose to parts of level I/II is inevitable. ²The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately ³T1-T3, no suspicious nodes on ultrasound (or FNP/CNB neg.), 1-2 involved SLN, no NACT ⁴Cranial border 5 mm below the axillary vein. Only if there is otherwise no indication for regional nodal irradiation, see slide „Regional nodal irradiation“

Additional RT of the Axilla after Neoadjuvant Therapy

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(in case of an indication for RT of the breast/chest wall¹ +/- supra- / infraclavicular and internal mammary node RT²)

Expansion of the PTV (planning target volume) to level I-II³

| N-status pre/post NACT | pN-status | | | |
|---------------------------------------|--|-----------|----------|------------------------|
| cN0 / ycN0 | ypN0(sn) | 5 | D | - |
| cN0 / ycN0 | ypN1mi(sn) / ypN+(sn) (no ALND) | 5 | D | +⁴ |
| cN+_{CNB} / ycN0 | ypN0 / ypN0(i+) (sn/TAD) | 5 | D | +/-⁴ |
| cN+_{CNB}/ ycN0 | ypN1mi(sn/TAD) / ypN+(sn/TAD) (no ALND) | 5 | D | +⁴ |
| cN0/cN+ | ypN0/+ after ALND | 2b | B | - |
| cN0/cN+ | Extensive perinodal soft tissue involvement in the axilla | 2b | B | + |
| cN0/cN+ | Residual tumor in the axilla after ALND | 5 | D | ++ |

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

Impact of axillary soft tissue involvement on regional recurrence

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Naoum et al. J Clin Oncol 2023 Nov 15;JCO2301009. doi: 10.1200/JCO.23.01009.

- Retrospective single center analysis, 2162 pat. with node-positive breast cancer treated 2000-2020.
- Analysis according to extracapsular extension (ECE) and axillary soft tissue involvement (AXT).
 - No ECE or AXT in 57.7%
 - ECE only in 24.9%
 - AXT only in 2.6%
 - ECE and AXT in 13.9%
- On multivariate analysis, AXT was significantly associated with distant failure (HR 1.61, $p < 0.001$), locoregional failure (HR 2.31, $p < 0.001$) and axillary failure (HR 3.33, $p = 0.003$).
- Regional nodal irradiation improved locoregional control in patients with ECT and/or AXT (HR 0.5, $p = 0.03$). Delivering a dose of < 50 Gy with conventional fractionation was associated with a higher risk of axillary failure.
- AXT was also associated with distant failure, locoregional failure and axillary failure in patients that underwent neoadjuvant chemotherapy.

Regional nodal irradiation

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RT to the supra-/ infraclavicular and internal mammary region

| | Oxford | | |
|--|--------|----|-----|
| | LoE | GR | AGO |
| ▪ ≥ 4 involved axillary lymph nodes ¹ | 1a | A | ++ |
| ▪ 1–3 involved axillary lymph nodes ¹ <ul style="list-style-type: none"> • Central or medial tumor or • HR-negative | 1a | A | + |
| ▪ pN0 and premenopausal with central or medial tumor and G3 and HR-negative | 1a | B | + |
| ▪ Clinical involvement of the above mentioned regions | 2b | B | + |
| ▪ In case of left-sided breast cancer with elevated cardiac risk or if simultaneous HER2-targeted therapy is given | 2b | A | - |

¹ not applicable for micrometastases

Regional nodal irradiation: EBCTCG-metaanalysis 2023

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

Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

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- **Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)**
- **Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)**
- **Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)**

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

Hypofractionated regional nodal irradiation



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| | START-P/A/B subgroups | Wang et al. | DBCG Skagen 1 (Abstract) | HypoG-01 (Abstract) |
|--------------------|--|--|---|---|
| Patient number | 864 | 820 | 2963 | 1265 |
| Fractionation | 39-42.9 Gy in 13-15 fx | 43.5 Gy in 15 Fx | 40 Gy in 15 Fx | 40 Gy in 15 Fx |
| Median FU | 10 years | 58.5 months | 3 years | 5 years |
| Primary endpoint | Late normal tissue effects | Locoregional recurrence | Lymphedema at 3 years | Lymphedema at 3 years |
| Statistical design | Retrospective analysis | Non-inferiority | Non-inferiority | Non-inferiority |
| Results | No statistically significant differences for LRR or late normal tissue effects | Non-inferiority for LRR (primary analysis) | No increased risk of lymphedema or LRR (primary analysis) | Non-inferiority for lymphedema Superiority for LRR, DDFS, OS |

Radiotherapy after NACT

| Pretherapeutic | Posttherapeutic | RT-BCS | PMRT | RNI* | Oxford | |
|---|--------------------------|--------|------------------|------------------|----------|-------|
| | | AGO | AGO | AGO | LoE | GR |
| Locally advanced | pCR / no pCR | ++ | ++ | ++ | 1a/1a/1a | A/A/A |
| cT1-3 cN1** | ypT+ ypN0 | ++ | + | +/- ¹ | 1a/1b/1b | A/B/B |
| cT1-3 cN1** | ypT0/is ypN0 | ++ | +/- ¹ | +/- ¹ | 1a/1b/1b | A/B/B |
| cT1-3 cN0 / cN1** (Sonogr. obligatory) | ypN+/ypN1mi o. ypT3/4 | ++ | + | + | 1a/2b/2b | A/B/B |
| cT1-3 cN0 (Sonogr. obligatory) | ypT0/is ypN0 | ++ | - | - | 1a/2b/2b | A/B/B |
| cT1-3 cN0 (Sonogr. obligatory) | ypT1-2 ypN0 | ++ | - | - | 1a/2b/2b | A/B/B |

Locally advanced: T4 or cN2-N3

- Criteria for increased risk of relapse / benefit of locoregional radiotherapy:
 - Central/medial tumor, HR-negative, premenopausal, non-pCR in the breast, residual micrometastases in the axillary nodes, cT3
- Regarding coverage of axilla level I/II please also see slides „Additional RT of the axilla after primary surgery“ and „Additional RT of the axilla after neoadjuvant therapy“. ** = confirmed by core biopsy
- In the case of residual isolated tumor cells, an individual decision is made as there are no data on RT

Role of locoregional radiotherapy after neoadjuvant chemotherapy

Mamounas et al. SABCS 2023 – GS02-07 (NSABP B-51/RTOG 1304)

- Prospective randomized controlled trial, 1641 pts., 2013-2020, median follow-up 59.5 months
- cT1-3 cN1 (FNA/CNB) → ypN0 (SLNB/ALND) after standard neoadjuvant chemotherapy
- Randomization:
 - BCS: RT breast vs. RT breast + regional nodal irradiation
 - Mastectomy: No RT vs. Post-mastectomy RT + regional nodal irradiation
- Primary endpoint: Invasive breast cancer recurrence-free interval
 - 80% power to detect 4.6% absolute reduction (HR 0.65) – superiority trial, 172 events
- Patient characteristics: 80% cT1-2, 58% BCS, 55% SLNB, 78% pCR in breast, 20% TNBC, 20% Lum
- Results:
 - No improvement in BCRFI (HR 0.88), isolated locoregional recurrence-free interval (HR 0.37), distant recurrence-free interval (HR 1.00), DFS (1.06) and OS (HR 1.12)
- Discussion:
 - Short follow-up (benefit of RNI appeared in EBCTCG-metaanalysis after 10-15 years)
 - Underpowered for primary analysis (109/172 planned events)
 - Trial should have been designed as a non-inferiority trial
 - Underrepresented subgroups: cT3, ypT+
 - Not applicable to: cT4 cN2-3

Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy



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| | Oxford | | |
|--|--------|----|-----|
| | LoE | GR | AGO |
| ▪ Trastuzumab / Pertuzumab* | 1a | A | ++ |
| ▪ T-DM1 | 1b | A | + |
| ▪ Tamoxifen | 2b | B | + |
| ▪ Aromatase inhibitors | 2b | B | + |
| ▪ Checkpoint inhibitors | 2b | C | + |
| ▪ Capecitabine** | 2b | B | + |
| ▪ CDK4/6-inhibitors*** | 4 | C | +/- |
| ▪ Olaparib**** | 2b | C | +/- |
| * Simultaneous parasternal RT should be avoided in patients with HER2-positive tumors and tumor-localisation on the left side | | | |
| ** With hypofractionated RT approx. 40 Gy, consider dose reduction of Capecitabine, Pat. with high risk for locoregional recurrence | | | |
| *** In currently available phase III-trials (monarchE, PALLAS, Penelope-B) RT was given before initiation of CDK4/6-inhibitors. No definitive signs of significantly increased toxicity with concomitant RT in the palliative setting. | | | |
| **** In currently available phase III-trials, RT was given before initiation of Olaparib. | | | |

Smoking and Risk of Secondary Lung Cancer

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

| Oxford | | |
|--------|----|-----|
| LoE | GR | AGO |
| 1a | A | |
| | | ++ |
| | | ++ |