Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Adjuvant Radiotherapy

Guidelines Breast
Version 2024.1E

Adjuvant Radiotherapy (RT)

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

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

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Preliminary Note

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

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

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

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

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

* continuous parameter with regard to risk of relapse

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

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

(Median F/U 17.2 y)

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

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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.)
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 (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.

Moderate hypofractionation with simultaneous-integrated boost

	RTOG 1005 (ASTRO 2022)	**IMPORT-HIGH (Lancet 2023)**
Patient number	2262	2617
Schedule Breast	40 Gy in 15 fx	36 Gy in 15 fx 40 Gy in 15 fx
Schedule Boost	48 Gy in 15 fx	48 Gy in 15 fx vs. 53 Gy in 15 fx
Ipsilateral in-breast recurrence at 5 years	HR 1.32 (0.8-2.1) → Non-inferiority for SIB	HR 1.04 (0.56-1.92) → Non-inferiority for 48 Gy (absolute diff.) HR 1.76 (1.01-3.04) → Inferiority for SIB 53 Gy (absolute + relat.)
Toxicity	Toxicity grade ≥3 (ROTG) p = 0.79	Any moderate / marked breast AE p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB) p = 0.823 for SIB 53 Gy vs. sequential boost

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

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

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 (elswhere)	**2.21 (1.53-3.20)**	**2.26 (1.12-4.55)**	**2.07 (1.31-3.27)**	7.88 (0.42-146)	3.06 (0.1-91.59)	+0.64%

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

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

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

Comparison of different techniques for partial breast irradiation

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

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

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

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

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

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

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

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

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PMRT can be omitted **LoE 3b B AGO +**	PMRT to be discussed **LoE 3b B AGO +/-**	PMRT recommended **LoE 3b B AGO +**
ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)	Patients, who don't fulfill the mentioned criteria for high or low risk	≥ 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)
Kyndi et al. 2009		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

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Boost in PMRT

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

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

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

* Study participation recommended

** Macrometastases

⁺ < T3, no palpable LN, R0, 1-2 positive SN, no NACT

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Additional RT of the Axilla after Primary Surgery

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

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

	Oxford		
	LoE	GR	AGO
pN-status			
pN0(sn) / pN1mic(sn)	1b	B	--
pN0/+ after ALND	1a	A	--
pN+(sn) in analogy to ACOSOG Z0011 (no ALND)	2b	B	+
pN+(sn) not fitting ACOSOG Z0011-criteria → RT in analogy to AMAROS[4] (no ALND)	1b	B	++
Extensive perinodal soft tissue involvement in the axilla	2b	B	+
Residual tumor in the axilla after ALND	5	D	++

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

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Additional RT of the Axilla after Neoadjuvant Therapy

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

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

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

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

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.

Dose in the Axillary LN-levels I + II Using Different RT-Techniques

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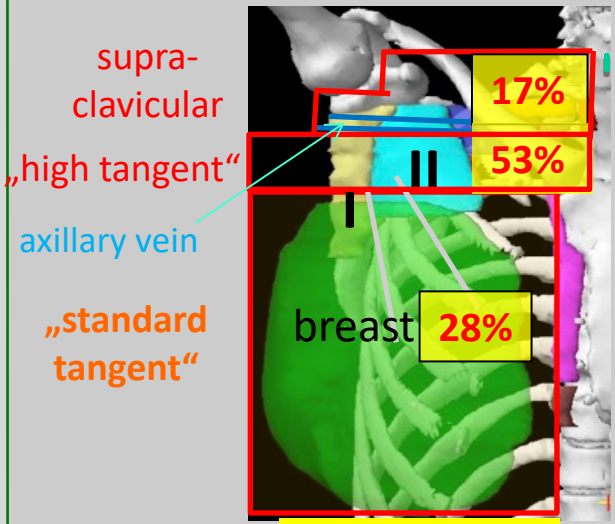
ACOSOG Z0011 Trial

45% micrometast. in the exp. arm



AMAROS

RT-volume
% of patients

Data from 228/856 pat.

	mean dose*	encompassed volume**
LN level 1		
AMAROS	> 95%	> 95%
high tangent	86%	79%
standard tangent	66%	51%
IMRT+	29%	1%
LN-level 2		
AMAROS	> 95%	> 95%
high tangent	71%	51%
standard tangent	44%	26%
IMRT+	7%	0%

* in relation to the prescribed dose in the breast

** % volume receiving the prescribed dose

\+ Lee et al. Medicine 2016 (3)

Jagsi (2): “The results of Z0011 should not be extrapolated to patients who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included”

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Regional nodal irradiation

RT to the supra-/ infraclavicular and internal mammary region

	Oxford LoE	Oxford GR	AGO
≥ 4 involved axillary lymph nodes[1]	1a	A	++
1–3 involved axillary lymph nodes[1] • Central or medial tumor • 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

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

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Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

	Oxford		
	LoE	GR	AGO
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)	1a	A	++
▪ Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)	1b	B	+
▪ Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)	2b	B	-

Hypofractionated regional nodal irradiation

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

Radiotherapy after NACT

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

Locally adcanced: T4 or cN2-N3

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

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

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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

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Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

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

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

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

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

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

Guidelines Breast
Version 2024.1E

Smoking and Risk of Secondary Lung Cancer

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