Guidelines Breast
Version 2023.1E

Adjuvant Radiotherapy

Guidelines Breast
Version 2023.1E

Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2022:**
  Blohmer / Budach / Friedrich / Friedrichs / Göhring / Huober / Janni / Krug / Kühn / Möbus / Rody / Scharl / Schmidt / Seegenschmiedt / Souchon / Thomssen / Untch / Wenz

- **Version 2023:**
  Budach / Krug / Solbach

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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	+
▪ Ultra-hypofractionated RT (total dose 26 or 28,5 Gy in 5 fractions in 1 or 5 weeks)	1b	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.	1a	B	+

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FAST / FAST-Forward

	FAST	FAST Forward
Timeframe	2004-2007	2011-2014
Sample size	915	4096
Dose / Fractionation	50 Gy / 2 Gy / 5 weeks 30 Gy / 6 Gy / 5 weeks 28,5 Gy / 5,7 Gy / 5 weeks	40 Gy / 2,67 Gy / 3 weeks 27 Gy / 5,4 Gy / 1 weeks 26 Gy / 5,2 Gy / 1 weeks
Median follow-up	119.8 months	71.5 months
Primary endpoint	change in photographic breast appearance	Ipsilateral breast tumor recurrence (non-inferiority margin 1,6%)
Inclusion criteria	pT1-2 (< 3 cm) pN0 Age ≥ 50 years Breast conserving surgery No chemotherapy	pT1-3 pN0-1 Age ≥ 18 years Breast-conserving surgery or mastectomy Approx. 25% adj. chemotherapy
Boost	No	Approx. 25%, 5-8x 2 Gy

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

Guidelines Breast
Version 2023.1E

FAST / FAST-Forward

	FAST (10 year-data)			FAST Forward (5 year-data)		
	Dose	Frequency	Hazard ratio (95%-CI)	Dose	Frequency	Hazard ratio (95%-CI)
Ipsilateral in-breast recurrence	50 Gy	0.7%	-	40 Gy	2.1%	-
	30 Gy	1.4%	HR 1.36 (0.3-6.06)	27 Gy	1.7%	HR 0.86 (0.51-1.44)
	28.5 Gy	1.7%	HR 1.35 (0.3-6.05)	26 Gy	1.4%	HR 0.67 (0.38-1.16)
Moderate / marked normal tissue effects breast / chestwall	50 Gy	33.6%	-	40 Gy	26.8%	-
	30 Gy	50.4%	**HR 1.79 (1.37-2.34)**	27 Gy	35.1%	**HR 1.41 (1.23-1.61)**
	28.5 Gy	47.6%	**HR 1.45 (1.10-1.91)**	26 Gy	28.5%	HR 1.09 (0.95-1.27)

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

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

Trial	N	Time-frame	Inclusion criteria	Follow up	Local recurrence (no RT)	Local recurrence (RT)	Hazard ratio
Toronto-British Columbia	769	1992-2000	≥ 50 years, T1/2 N0 R0 (ink) 80% HR+	5 y 8 y	7.7% 17.6%	0.6% 3.5%	8.3
BASO-II	204	1992-2000	< 70 J., T1, G1 L0	5 y	0.8% p.a.	0.2% p.a.	7.34
CALGB 9343	636	1994-1999	≥ 70 years, T1 (98%) cN0 ER+ (97%), R0 (ink)	5 y 10 y	4% 8%	1% 2%	5.55
ABCSG-8A	831	1996-2004	Postmenopausal T ≤ 3 cm N0, G1/2, ER+ and/or PR+	5 y 10 y	5.1% 7.5%	0.4% 2.5%	10.2
PRIME II	1326	2003-2009	≥ 65 years, T ≤ 3 cm N0, ER+ and/or PR+, R0 (≥1 mm)	5 y 10 y	4.3% 9.8%	1.3% 0.9%	5.2

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

Guidelines Breast
Version 2023.1E

	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[a]	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 (ESTRO 2021)
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

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

Guidelines Breast
Version 2023.1E

	Oxford LoE	Oxford GR	Oxford AGO
Intraoperative Radiotherapy (low-risk)*			
As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT)			
> 50 years	1b	A	+/-
> 70 years	1b	A	+
Postoperative partial breast irradiation (low-risk)*			
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 3.8-4 Gy in 2 weeks)	2b	B	+/-
3D-conformal radiotherapy (10 x 3.85 Gy in 1 week)	1b	A	+/-
Intraoperative clip placement at the tumor bed if partial breasst irradiation is indicated	2b	B	+

For definition of target volume and practical conduct see DEGRO practical guidelines

* only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS

Meta-analyses on partial-breast irradiation

Guidelines Breast
Version 2023.1E

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

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	2b	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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Version 2023.1E

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	++

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

	Oxford		
	LoE	GR	AGO
BCS and ACOSOG Z0011-criteria+ met	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	++
R2-situation in the axilla	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

Guidelines Breast
Version 2023.1E

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(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	-
	R2-situation in the axilla	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.

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

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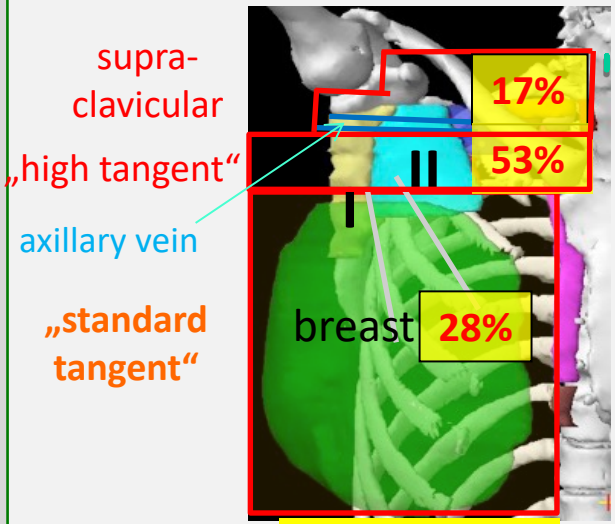
ACOSOG Z0011 Trial

45% micrometast. in the exp. arm



RT-volume
% of patients

AMAROS

LN level 1	mean dose*	encompassed volume**
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)

Data from 228/856 pat.

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”

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

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	Oxford		
	LoE	GR	AGO
RT to supra- / infraclavicular lymphatic regions			
▪ ≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in supra- / infraclavicular LN	1b	A	++
▪ 1–3 positive axillary lymph nodes[1] in case of - central or medial tumor and G2-3 or HR-negative - premenopausal patient and G2-3 or HR-negative	2a	B	+
▪ pN0 with central or medial tumors, if premenopausal and G2-3 and HR-negative	2a	B	+/-

[1] not applicable for micrometastases

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)

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	Oxford		
	LoE	GR	AGO
Internal mammary lymph node region (IMN)			
▪ pN0 high-risk with central or medial tumor and premenopausal and G2-3 and ER/PR-negative	1b	B	+/-
▪ 1–3 positive axillary lymph nodes[1] in case of - central or medial tumor - HR-negative	2a	B	+
▪ ≥ 4 positive axillary lymph nodes	2a	B	+
▪ involved internal mammary lymph nodes	2a	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

Radiotherapy to the internal mammary nodes

	DBCG-IMN	KROG 15-03	
Patient number	3089	735	
Timeframe	2003-2007	2008-2013	
Median FU	14.8 years	8.3 years	
Design	Prospective cohort study, right-sided treated with IMNI, left-sided without IMNI. All received SCV-RT.	Randomized controlled trial All received SCV-RT, randomization to +/- IMNI.	
Inclusion criteria	N+, no NACT	N+, ALND with ≥8 lymph nodes, no NACT	
Stratification	All patients	Medial/central	lateral
Distant recurrence	HR 0.88 (0.78-0.99)	HR 0.44 (0.23-0.85)	HR 1.07 (0.68-1.68)
Breast-cancer mortality	HR 0.88 (0.78-1.00)	HR 0.41 (0.17-0.99)	0.91 (0.53-1.57)
Overall survival	HR 0.86 (.77-0.96)	HR 0.51 (0.24-1.11)	1.07 (0.64-1.77)
Subgroup analysis	No benefit in 1-3 LN+ with lateral tumor, larger benefit with N2-3	Benefit for ER/PR-negative tumors (p-interaction = 0.03)	

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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[a]	B	+
▪ Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)	2b	B	-

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Hypofractionated regional nodal irradiation

	START-P/A/B subgroups	Wang et al.	DBCG Skagen 1 (Abstract)	FAST-Forward Nodal substudy (Abstract)
Patient number	864	820	2963	469
Fractionation	39-42.9 Gy in 13-15 fx	43.5 Gy in 15 Fx	40 Gy in 15 Fx	26 Gy / 27 Gy in 5 Fx
Median FU	10 years	58.5 months	3 years	?
Primary endpoint	Late normal tissue effects	Locoregional recurrence	Lymphedema at 3 years	Arm/hand swelling at 5 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)	No increased risk of late normal tissue effects (preliminary data at 2-3 years)

Radiotherapy following NACT

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Pretreatment	Post-treatment	RT-BCS	PMRT	RNI*	Oxford		
					AGO	LoE	GR
Locally advanced	pCR / no pCR	yes	yes	yes	++/++/++	1a/1a/1a	A/A/A
cT1/2 cN1+*	ypT1+ or ypN1 + (no pCR)	yes	yes	yes	++/+/+	1a/2b/2b	A/B/B
cT1/2 cN1+*	ypT0/is ypN0	yes	Increased risk of relapse[1]		+/+/+	2b/2b/2b	B/B/B
cT1/2 cN0 (Sonogr. obligatory)	ypN+ or ypT3/4	yes	yes	yes	+/+/+	2b/2b/2b	B/B/B
cT1/2 cN0 (Sonogr. obligatory)	ypT0/is ypN0	yes	no	no	+/-/-	2b/2b/2b	A/B/B
cT1/2 cN0 (Sonogr. obligatory)	ypT1-2 ypN0	yes	no	no	+/-/-	2b/2b/2b	A/B/B

Locally advanced: T3-4 or cN2-N3

[1] Criteria for increased risk of relapse:
- pN0 premenopausal high risk: central or medium tumor localization, and (G2-3 and ER/PR-neg.)
- pretreatment pN1a/ cN+* high risk: central or medium tumor localization and (G2-3 or ER/PR-neg.) or premenopausal, lateral tumor localization and (G2-3 or ER/PR-neg.)

* 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

Guidelines Breast
Version 2023.1E

Molecular Predictors and Use of Radiotherapy

- **Results of gene expression profiling should not be used for indication of radiotherapy**

Oxford		
LoE	GR	AGO
2b	B	++

Guidelines Breast
Version 2023.1E

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.

Simultaneous Capecitabine with Locoregional Radiotherapy

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Woodward et al. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):777-783

- Prospective phase trial, 32 pat. with LABC, sim. def. / neoadj. chemoradiotherapy, median total dose 66 Gy
- "The first 9 patients analyzed […] received CAP 825 mg/m^2 twice daily continuously beginning on the first day of RT. **Because of observed excess grade 3 toxicity the protocol was amended,** and subsequent patients received CAP only on RT days (5 days per week)."
- "Noncontinuous CAP dosing was much better tolerated than continuous dosing. **Thirteen of 26 patients (50%) had grade ≥ 3 and higher treatment-related dermatologic toxicity**. "

Alhanafy et al. Menoufia Medical Journal 2015, 28:325-332

- Randomised phase II-trial, 100 pat., adj. Radiotherapy 40 Gy / 15 fr. +/- CAP 825 mg/m2 Mo-Fr, LABC
- " […] **concurrent capecitabine was feasible with a high percent of patients (96%),** […] only two out of 50 (4%) patients had capecitabine dose modification …".
- "**All early toxicities were GI/GII.** Radiation dermatitis had a peak incidence in the last few fractions of the radiation therapy and the week after radiotherapy; no treatment interruption was needed and the incidence was close in both groups".
- Radiation dermatitis grade I 14% vs. 18%; grade 2 4% vs. 4%

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Smoking and Risk of Secondary Lung Cancer

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