

Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Ductal Carcinoma in Situ (DCIS)

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Version 2024:

Budach / Gerber

DCIS - Pretherapeutic Assessment

Oxford

	LoE	GR	AGO
Mammography	1b	B	++
Magnification view of microcalcifications	4	C	++
Increased detection rate of G1 / G2 DCIS by full-field digital mammography (versus screen-film)	2b	B	+
Ultrasound (to rule out an accompanying invasive component)	4	C	++
For tumors with a solid part	4	C	++
MRI to determine the extension and planning of surgery	1a	B	+/-
Clinical examination	5	D	++
Stereotactic core needle / vacuum biopsy (VAB)	2b	B	++
Specimen radiography	2b	B	++
Marker (clip) left at biopsy site for localization if lesion is completely removed	5	D	++
Interdisciplinary board presentation	5	D	++

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DCIS – Upstaging, ipsi- / Contralateral Events und Mortality



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Upstaging to BC %	Ipsilateral events (cum. incidence) %	Contralateral events (cum. incidence) %	BC-specific mortality % (95% CI)
5-25.9	<p><i>10 years:</i> BCS: 24.6 BCS and radiotherapy: 9.6</p> <p><i>20 years:</i> BCS: 30.6 BCS and radiotherapy: 18.2</p>	<p><i>10 years:</i> 4.8-6.4</p> <p><i>15 years:</i> 6.4-~11</p>	<p><i>10 years:</i> 0.9 (0.7-1.1) (BCS) 0.8 (0.7-1.0) (BCS and radiotherapy) 1.3 (1.1-1.5) (unilateral mastectomy)</p>

~ 50% of all ipsilateral events are invasive.

Breast cancer specific mortality is 3,3%.

Women with DCIS have a 1.8-3-fold increased risk of death compared to normal population/women without DCIS. Risk is greater for young and black women.

Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer

Giannakeas V, Sopik V, Narod SA. JAMA Netw Open. 2020 Sep 1;3(9):e2017124

144,524 women treated for DCIS, 1,540 women died of breast cancer, cohort study included data for women who had first primary DCIS diagnosed between 1995 and 2014 from the SEER registries database (use of ET is not reported), retrospective analysis, results:

standardized mortality ratio for death from breast cancer among women with DCIS was 3.36 (95% CI, 3.20-3.53), risk is greater for young and black women, 4,502 (3.1%) ipsilateral invasive recurrences, resulting in a 20-year actuarial risk of 13.9%, 5,527 (3.8%) contralateral invasive breast cancers, resulting in a 20-year actuarial risk of 11.3%, women with DCIS had a 3-fold increased risk of death from breast cancer compared to women without DCIS.



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Risk Factors for Upstaging from DCIS to Invasive Cancer in Final Surgical Specimen

Oxford

LoE

Higher risk

- **DCIS without microcalcification in core needle or vaccum biopsy** 3b
- **Microcalcification $\geq 11,5$ mm** 3b
- **Presentation as tumor in MRI** 3b
- **Increased Ki-67 ($\geq 20\%$)** 3b
- **PR negative** 3b
- **High peak contrast enhancement on MRI** 3b
- **Irregularly shaped, non-circumscribed, heterogeneous or margin-enhancing tumors with intratumoral high signal intensity or peritumoral edema on MRI** 3b
- **Biopsy technique: diagnosis by core needle biopsy versus vacuum biopsy (smaller sampling volume)** 3b
- **High platelet-lymphocyte ratio** 3b

Lower risk

- **Removal $\geq 90\%$ of the microcalcifications by vacuum biopsy** 3b

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Good Clinical Practice (GCP)

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Surgical excision (BCS or mastectomy) is the standard treatment for DCIS.

Adjuvant treatment (radiotherapy, endocrine treatment) must be discussed with the patient individually. Adverse effects should be weighted against risk reduction.

Surgical Treatment for Histologically Proven DCIS I

Oxford

	LoE	GR	AGO
Excisional biopsy (wire guided)	2b	B	++
Localization with wire-free procedure	3b	C	+/-
Bracketing wire localization in large lesions	3a	C	+
Specimen radiography	2b	B	++
Intraoperative ultrasound (pre-op visible lesion)	3a	C	+/-
Immediate re-excision in case of incomplete resection (specimen radiography)	1c	B	++
Intraoperative frozen section (in individual cases for margin assessment)	3a	D	+/-
Interdisciplinary board presentation	2b	C	++
Open biopsy in suspicious lesions (mammographic microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided			

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Surgical Treatment for Histologically Proven DCIS II

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	Oxford		
	LoE	GR	AGO
Histologically clear margins (Ris0)	1a	A	++
Multifocal DCIS: BCS if feasible	2b	B	+
Re-excision required for close margin in case of BCS and radiotherapy (≤ 2 mm in paraffin section)*	2b	C	+
Mastectomy**			
Large lesions confirmed by multiple biopsies; no clear margins after re-excision	2a	B	++
SLNE			
Mastectomy	3b	B	+
BCS	3b	B	--
In case of DCIS in the male breast	5	D	+/-
ALND	2b	B	--

* Individual approach taking into account age, tumor size, grading and implementation of radiation, especially in case of no subsequent radiation

** Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence

Prognostic Factors for an Ipsilateral Recurrence after DCIS I

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	<u>LoE</u>
Resection margins	1a
Age	1a
Size	1a
Grade	1a
Comedo necrosis	1a
Method of diagnosis	1a
Focality	1a
HER2-overexpression	1a
ER / PR (positive vs. negative)	1a

See also chapter “Prognostic Faktors“

Prognostic Factors for an Ipsilateral Recurrence after DCIS II

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	LoE
Hereditary breast cancer risk	2a
Premenopausal at time of DCIS diagnosis	2a
High BMI	2a
High breast density	2a
Growth pattern (cribriform / solid versus „clinging“ / micro-papillary)	2b
Residual tumor-associated microcalcifications	2b
Architecture	2b
(modified) Van Nuys Prognostic Index/ mitotic rate	2b
Palpable DCIS	2b
ER-, HER2+, Ki-67+	2b
Scores: DCIS, Oncotype DX Breast DCIS Score (12 genes); CCP (23 genes)	2b
MSKCC Nomogram	2b
▪ DCISionRT	2b
Intrinsic subtypes (luminal A, B, HER2+, triple negative)	2b
DCIS compared to invasive carcinoma with higher risk of contralateral BC	2b
High number of TILs	2b

See also chapter “Prognostic Faktoren“

Radiotherapy Statements

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Radiotherapy has no impact on survival

LoE 1a

Radiotherapy reduces the risk of ipsilateral (invasive and non invasive) recurrences by 50 %

LoE 1a

The number needed to treat (for ipsilateral breast recurrence) is 9 (over all risk groups).

DCIS –

Adjuvant Radiotherapy

Oxford

LoE GR AGO

Radiotherapy after:

Breast conserving surgery (BCS)

1a A ++

Mastectomy

2b B --

Radiotherapy procedure:

Conventionally fractionated radiotherapy (50 Gy in 25 fract.)

1a A +

Hypofractionated radiotherapy (40-42,5 Gy in 15-16 fract.)

1a A +

Radiotherapy boost of the tumor bed

1b B +/-

in case of risk factors* (absolute benefit 5-y-RFS 4 %, rate of fibrosis significant increased)

1b B +/-

without risk factors

2b B -

Partial breast irradiation [age \geq 50y, DCIS \leq 3 cm, G1-2, R0 (\geq 5 mm), unifocal / unicentric]

1b B +

Side effects and disadvantages must be weighed against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of „good risk“ patients. Lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 2.5 cm, low and intermediate nuclear grade, mammographically detected.

* < 50 years or \geq 50 years and diagnosis based on symptoms, \geq 15 mm, multifocality, palpable tumor, resection margins < 10 mm, G2 / 3, central necrosis, comedo type

Adjuvant Systemic Treatment

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Adjuvant endocrine treatment has no impact on survival (RR 1.11; 95% CI 0.89-1.39) LoE 1a

Endocrine treatment may have a small effect on ipsilateral invasive (HR 0.79; 95% CI 0.62-1.01) and DCIS (HR 0.75; 95% CI 0.61-0.92) recurrences LoE 1a

Endocrine treatment for DCIS has an effect on contralateral invasive (RR 0.57; 95% CI 0.39-0.83) and non-invasive (RR 0.50; 95% CI 0.28-0.87) cancer LoE 1a

The number needed to treat for any ipsilateral breast event is 15 LoE 1a

The number needed to treat to prevent invasive breast cancer is 29 for anastrozole vs. 59 for tamoxifen* LoE 1b

* within 12 years; according to IBIS II-trial

DCIS – Adjuvant Systemic Treatment

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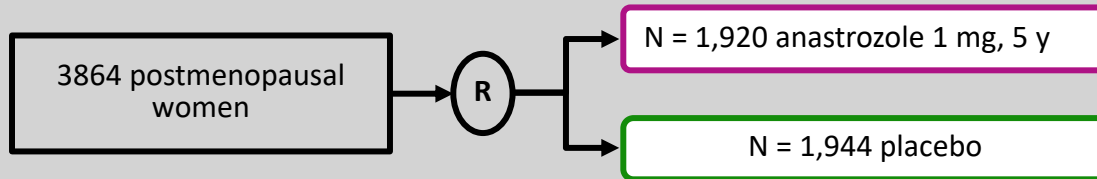
	Oxford		
	LoE	GR	AGO
Tamoxifen (only ER+) 20 mg	1a	A	+/-*
Tamoxifen (only ER+) 5 mg for 3 years	2b	B	+/-*
Aromatase inhibitor (only ER+) in postmenopausal women only	1b	A	+/-**
Trastuzumab (only HER2+)	5	D	--

* Indication for treatment depends on risk factors, side effects and patient preference

Anastrozole versus Tamoxifen: Anastrozole higher fracture rate (OR 1.34), Tamoxifen higher rate of stroke (OR 3.10) and TIA (OR 3.10)

Use of Anastrozole for Breast Cancer Prevention (IBIS-II): Long-Term Results of a Randomised Controlled Trial

Cuzick J et al, Lancet 2020



**N = 3,864 postmenopausal women at increased risk for breast cancer,
median follow-up of 131 months,
results:**

**49% reduction of all breast cancers with anastrozole (HR 0.51, 95% CI 0.39–0.66,
p < 0.0001),**

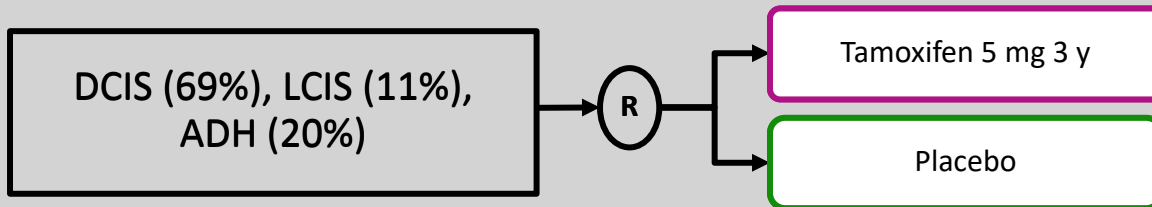
**significant reduction in incidence for anastrozole for ductal carcinoma in situ (HR 0.41,
0.22–0.79, p = 0.0081), especially for oestrogen-positive (HR 0.22, 0.07–0.65, p = 0.0062),
5-year adherence anastrozole 74.6% vs. 77.0% for placebo,**

**no difference in major side effects (fractures, myocardial infarctions, deep vein thrombosis,
pulmonary embolism),**

NNT to prevent one breast cancer during 12 years: 29 (anastrozole) vs. 59 (tamoxifen).

Low Dose Tamoxifen (5 mg) in Premalignant Lesions

Lazzeroni M et al: J Clin Oncol 2023



- **N = 500,**
- **follow-up 9.7 years,**
- **results:**
 - Events: 66 breast cancers (15 in situ; 51 invasive) were diagnosed: Tam 25 and Placebo 41; hazard ratio: 0.58; 95% CI, 0.35 to 0.95; log-rank $P = .03$).
 - Contralateral BC incidence: Tam 6 vs. Plac 16 (HR, 0.36; 95% CI, 0.14 - 0.92; $P = .025$)
 - NNT to prevent one case of breast event with tam 22 in 5 and 14 in 10 years.
 - Severe adverse event: no significant differences
 - Adherence Tam 65% vs. PLAC 61%.

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Therapy of Local DCIS Recurrence after Tumorectomy



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LoE	GR	AGO

After Radiation:

Simple mastectomy	3a	C	+
+ SLNE	5	D	+
Secondary breast conserving surgery	4	C	+/-

Without radiation after first tumorectomy

Treatment like primary disease	3	C	++
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