

# 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 2023:**  
**Blohmer / Mundhenke**

# DCIS - Pretherapeutic Assessment

## Oxford

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

# DCIS – Upstaging, ipsi- / Contralateral Events und Mortality

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)

**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.**

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# Surgical Treatment for Histologically Proven DCIS I

## Oxford

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

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# Surgical Treatment for Histologically Proven DCIS II

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- **Histologically clear margins (Ris0)**
- **Multifocal DCIS: BCS if feasible**
- **Re-excision required for close margin in case of BCS and radiotherapy ( $\leq 2$  mm in paraffin section)\***
- **Mastectomy\*\***
  - Large lesions confirmed by multiple biopsies; no clear margins after re-excision
- **SLNE**
  - Mastectomy
  - BCS
  - In case of DCIS in the male breast
- **ALND**

	Oxford		
	LoE	GR	AGO
	1a	A	++
	2b	B	+
	2b	C	+
	2a	B	++
	3b	B	+
	3b	B	--
	5	D	+/-
	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>
▪ <b>Resection margins</b>	<b>1a</b>
▪ <b>Age</b>	<b>1a</b>
▪ <b>Size</b>	<b>1a</b>
▪ <b>Grade</b>	<b>1a</b>
▪ <b>Comedo necrosis</b>	<b>1a</b>
▪ <b>Method of diagnosis</b>	<b>1a</b>
▪ <b>Focality</b>	<b>1a</b>
▪ <b>HER2-overexpression</b>	<b>1a</b>
▪ <b>ER / PR (positive vs. negative)</b>	<b>1a</b>

# Prognostic Factors for an Ipsilateral Recurrence after DCIS II

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

LoE

2a

2a

2a

2a

2b

2b

2b

2b

2b

2b

2b

2b

2b

2b

2b

2b

# DCIS 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).**

## Adjuvant Radiotherapy

Oxford

LoE GR AGO

### Radiotherapy after:

- Breast conserving surgery (BCS)
- Mastectomy

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

### Radiotherapy procedure:

- Conventionally fractionated radiotherapy (50 Gy in 25 fract.)
- Hypofractionated radiotherapy (40-42,5 Gy in 15-16 fract.)
- Radiotherapy boost of the tumor bed
  - in case of risk factors\* (absolute benefit 5-y-RFS 4 %, rate of fibrosis significant increased)
  - without risk factors
- Partial breast irradiation [age  $\geq$  50y, DCIS  $\leq$  3 cm, G1-2, R0 ( $\geq$  5 mm), unifocal / unicentric]

1a	A	+
1a	A	+
1b	B	+/-
1b	B	+/-
2b	B	-
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** **LoE 1a**
- **Endocrine treatment may have a small effect on ipsilateral invasive and DCIS recurrences** **LoE 1a**
- **Endocrine treatment for DCIS has an effect on contralateral invasive and non-invasive 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**

# DCIS – Adjuvant Systemic Treatment

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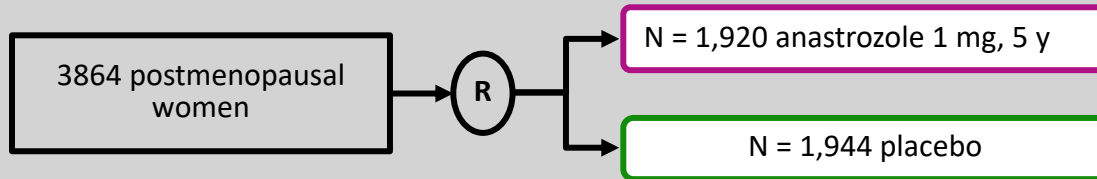
	Oxford		
	LoE	GR	AGO
▪ Tamoxifen (only ER+) 20 mg	1a	A	+/-*
▪ Tamoxifen (only ER+) 5 mg (long-term data missing)	2b <sup>a</sup>	B	+/-*
▪ Aromatase inhibitor (only ER+) in postmenopausal women only	1b	A	+/-**
▪ Trastuzumab (only HER2+)	5	D	--

\* 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).**

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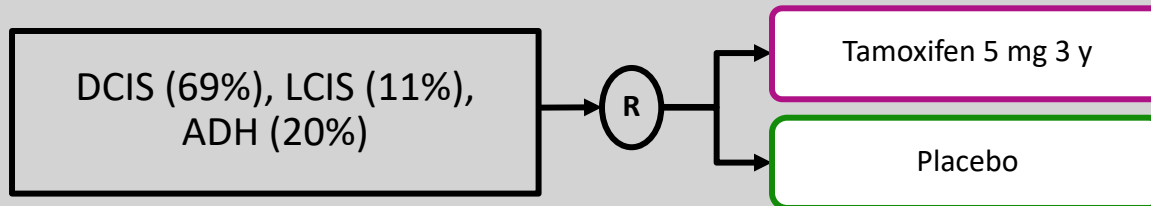
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# Low Dose Tamoxifen (5 mg) in Premalignant Lesions

Lazzeroni M et al: Breast 2019



- **N = 500,**
- **follow-up 5.69 years,**
- **results:**
  - **EFS: Tam 5.5% (14/253) vs. Placebo 11.3% (28/247),**
  - **severe adverse event with same incidence (endometrial cancer Tam 1 vs. PLAC 0, thrombo-embolic event Tam 1 vs. PLAC 1)**
  - **adherence Tam 65% vs. PLAC 61%.**

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# Therapy of Local DCIS Recurrence after Tumorectomy

Oxford		
LoE	GR	AGO

## After Radiation:

- Simple Mastectomy
- + SLNE
- Secondary breast conserving surgery

3a	C	+
5	D	+
4	C	+/-

## Without radiation after first tumorectomy

- Treatment like primary disease

3	C	++
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