

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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## Breast Cancer: Specific Situations

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# Breast Cancer: Specific Situations

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- **Versions 2005–2020:**

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- **Version 2021:**

**Gluz / Sinn**



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- **Young patients**
- **Pregnancy- and breast-feeding-associated BC**
- **Elderly patients**
- **Male patients**
- **Inflammatory BC**
- **Occult Breast Cancer (Cancer of unknown primary – axillary CUP)**
- **Paget's disease**
- **Malignant and Borderline Phyllodes Tumor**
- **Angiosarcoma**
- **Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)**
- **Metaplastic breast cancer**

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# Breast Cancer in Young Women $\leq$ 40 Years

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	Oxford		
	LoE	GR	AGO
▪ <b>Aggressive biological behavior with worse prognosis</b>	<b>2a</b>	<b>B</b>	
▪ <b>Local therapy independent of young age</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Guidelines adapted (neo-)adjuvant systemic treatment (see respective chapters)</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>GnRHa as ovarian protection (see chapter gynecological problems)</b>	<b>1a</b>	<b>B</b>	<b>+</b>
▪ <b>Genetic and fertility counseling</b>	<b>2b</b>	<b>B</b>	<b>++</b>
▪ <b>Contraception counseling</b>	<b>2b</b>	<b>B</b>	<b>++</b>

# Breast Cancer During Pregnancy\* or Breast Feeding – Diagnostics and Surgery

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- Breast imaging and biopsy like in non-pregnant
- Staging if indicated (bone scan after delivery)
- Full body MRI (without contrast agent)
- Surgery like in non-pregnant patients
- Sentinel node excision (technetium only)
- SLNE during 1<sup>st</sup> trimester
  - Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs
  - Blue dye (not tested in pregnant animals or humans)

Oxford		
LoE	GR	AGO
4	C	++
5	D	+
4	C	+/-
4	C	++
2b	B	+
5	D	+/-
4	C	++
4	C	--

# Breast Cancer During Pregnancy - (Neo-)adjuvant Therapy -

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- Radiation therapy during pregnancy
- (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)
  - Anthracyclines: AC, EC
  - Taxanes
  - Platinum salts (carboplatin, cisplatin)
  - MTX (e.g. CMF)
- Endocrine treatment
- HER2-targeted treatment
- Bisphosphonates, denosumab

	Oxford		
	LoE	GR	AGO
	4	C	-
			++
	2b	B	++
	2b	B	+
	4	C	+/-
	4	D	--
	4	D	--
	3a	C	--
	4	D	-

Treatment (Chemotherapy, surgical procedure and radiotherapy) of patients with breast cancer during pregnancy should be as similar as possible to standard treatment of young, not pregnant patients with breast cancer.

# Breast Cancer During Pregnancy\*

## – Delivery and Breast-Feeding –



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- **Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)**
- **Termination of pregnancy does not improve maternal outcome**
- **Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir**
- **If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities**

	Oxford		
	LoE	GR	AGO
	2b	C	++
	3b	C	
	4	C	++
	5	D	++

\* Participation in register study recommended

# Breast Cancer and Pregnancy

## – Family Planning –

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- **After breast cancer diagnosis, reproductive techniques can be used to induce pregnancy**
- **Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients**
- **Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment**
- **Breast cancer patients should not be advised against getting pregnant independent of their tumor's hormone receptor status**

	Oxford		
	LoE	GR	AGO
After breast cancer diagnosis, reproductive techniques can be used to induce pregnancy	5	D	++
Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients	5	D	++
Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
Breast cancer patients should not be advised against getting pregnant independent of their tumor's hormone receptor status	5	D	++

# Pregnancy Associated Breast Cancer\*: Outcome

**Oxford  
LoE**

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- **BC during pregnancy / lactation**
  - Adequate treatment is essential
- **Pregnancy and lactation after BC**
  - Outcome not compromised

**3a**

**3a**

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# Geriatric Assessment

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- **No specific algorithm is available**
- **Ability to tolerate treatment varies greatly („functional reserve“)**
- **Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals**
  - Physical, mental, and psycho-social health
  - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
  - Living arrangements, social network, access to support services
- **Assessment tools:**
  - **Charlson Comorbidity Index (widely used; good predictor over a 10-year period)**
  - **12 prognostic indicators to estimate 4-year mortality risk**
  - **Short screening tests (more qualitative evaluation)**
  - **IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8**
  - **Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)**

# Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

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- **Clinical geriatric assessment**
- **Treatment according to guidelines**
  - **Surgery similar to „younger“ age**
  - **Endocrine treatment (endocrine responsive)**
  - **Chemotherapy (standard regimens)**
    - < 70 years
    - > 70 years (especially N+, ER/PR-)
  - **Radiotherapy**
  - **Omit radiotherapy after BCS if low-risk and endocrine treatment**
  - **Trastuzumab**

	Oxford		
	LoE	GR	AGO
	<b>2b</b>	<b>B</b>	<b>++</b>
	<b>2a</b>	<b>C</b>	<b>++</b>
	<b>2b</b>	<b>B</b>	<b>++</b>
	<b>1a</b>	<b>A</b>	<b>++</b>
	<b>1a</b>	<b>A</b>	<b>+</b>
	<b>2a</b>	<b>C</b>	<b>+*</b>
	<b>1a</b>	<b>A</b>	<b>+</b>
	<b>1b</b>	<b>B</b>	<b>+</b>
	<b>2b</b>	<b>C</b>	<b>+</b>

\* Study participation recommended

# Treatment for Frail Patients

(Life Expectancy <5 yrs, Substantial Comorbidities)

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- **Reduced standard treatment**
- **Options extrapolated from trials in elderly:**
  - **No breast surgery (consider endocrine options)**
  - **No axillary clearing (≥ 60 y, cN0, HR-pos)**
  - **No radiotherapy (Tumor size <3 cm, pN0, HR-pos)**
  - **Hypofractionated radiotherapy**
  - **No chemotherapy if >70y and negative risk-benefit analysis**

	<b>Oxford</b>		
	<b>LoE</b>	<b>GR</b>	<b>AGO</b>
	<b>2b</b>	<b>C</b>	<b>++</b>
	<b>2b</b>	<b>C</b>	<b>+</b>
	<b>2b</b>	<b>B</b>	<b>+</b>
	<b>1b</b>	<b>B</b>	<b>++</b>
	<b>2b</b>	<b>B</b>	<b>+</b>
	<b>2b</b>	<b>C</b>	<b>+</b>

# Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

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	Oxford		
	LoE	GR	AGO
■ <b>Diagnostic work-up as in women</b>	4	C	+
	3b	C	+/-
■ Mammography	2b	B	++
■ Ultrasound	4	C	++*
■ <b>Standard-surgery: Mastectomy</b>	4	C	+*
	2b	B	+
■ BCT is an option (tumor/breast relation)			
■ Sentinel-node excision (SLNE)			
■ <b>Radiotherapy as in women (consider tumor/breast relation!)</b>	4	C	+
■ <b>Genetic counseling if one additional relative affected (breast/ovarian cancer)</b>	2b	B	++
■ <b>Screening for 2<sup>nd</sup> malignancies according to guidelines</b>	GCP		++

\* Participation in register study recommended

# Male breast cancer-prognostic factors

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- **Nodal status**
- **Age**
- **Tumor size**
- **ER/PR Expression**
- **Ki-67 Expression**
- **Grade**
- **Genomic signatures (e.g. OncotypeDx)**

<b>Oxford</b>		
<b>LoE</b>	<b>GR</b>	<b>AGO</b>
<b>2b</b>	<b>A</b>	<b>++</b>
<b>2b</b>	<b>B</b>	<b>+</b>
<b>2b</b>	<b>A</b>	<b>++</b>
<b>2b</b>	<b>A</b>	<b>++</b>
<b>2b</b>	<b>C</b>	<b>+/-</b>
<b>2b</b>	<b>C</b>	<b>+/-</b>
<b>2b</b>	<b>B</b>	<b>+</b>

# Male Breast Cancer: Systemic Therapy

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- **Adjuvant chemotherapy as in women**
- **HER2-targeted therapy (if HER2-positive)**
- **Endocrine therapy**
  - Tamoxifen
  - Aromatase inhibitors (adjuvant)
  - Aromatase inhibitors (metastatic BC)
  - GnRHa and AI (metastatic BC)
  - Fulvestrant (metastatic BC)
  - CDK4/6i (in combination) \*
- **Palliative chemotherapy as in women**

	Oxford		
	LoE	GR	AGO
2a	B	++	
5	D	++	
4	D	++	
2b	B	++	
2b	B	.*	
4	C	+/-	
4	C	+*	
4	C	+/-	
2b	B	+	
4	C	++	

\* Study participation recommended

# Benefit from Trimodal Treatment in Inflammatory Breast Cancer

<b>Median survival probability</b>		
<b>Trimodal therapy</b>	72 months	p<0.05
<b>Surgery alone</b>	26 months	

<b>Overall survival-probability (OS)</b>	<b>10 years-OS</b>	<b>5 years-OS</b>
<b>Trimodal therapy</b>	55.4%	37.3%
<b>Surgery &amp; chemotherapy</b>	42.9%	28.5%
<b>Surgery &amp; radiotherapy</b>	40.7%	23.5%
<b>Surgery alone</b>		16.5%

<b>Multivariate analysis of OS</b>	<b>Hazard Ratio</b>	<b>95% CI</b>
Surgery & chemotherapy & RT (trimodal therapy)	1.00	-
Surgery & chemotherapy	1.64	1.46 to 1.84
Surgery & radiotherapy	1.47	0.96 to 2.24
Surgery alone	2.28	1.80 to 2.89

Rueth et al. J Clin Oncol 2014; 32:2018–2024

# Primary inflammatory breast cancer

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	5yr- OS	
<b>pCR</b>	77%	p<0.0001
<b>Non-pCR</b>	54%	
<b>TN-IBC</b>	37%	p<0.0001
<b>other biologic subtypes (HR+/HER2-, HR+/HER2+, HR-/HER2+)</b>	60%	

- **N=8.550**
- **On multivariable analysis, TNBC, positive margins, and not receiving either chemotherapy, hormonal therapy or radiotherapy were independently associated with poor 5-year survival (p < 0.0001).**

# Inflammatory Breast Cancer (IBC, cT4d)

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- Invasive BC and clinical signs of inflammation (e.g.  $\geq 1/3$  of the breast affected) determine stage cT4d
- Staging
- Skin punch biopsy (at least 2; detection rate < 75%)
- Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)
- Mastectomy after chemotherapy
  - Breast conserving therapy in case of pCR (individual)
  - Sentinel excision only
- Radiotherapy (PMRT)

Oxford		
LoE	GR	AGO
		++
2c	B	++
2c	B	+
2c	B	++
2c	B	+
2b	C	+/-
3b	C	-
2c	B	++

# Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary – Axillary CUP)

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- **Incidence: < 1% of metastatic axillary disease**
- **In > 95% occult breast cancer, < 5% other primary**
- **Immunohistology**
  - ER-positive: 55%**
  - HER2 3+: 35%**
  - Triple-negative: 38%**
- **Nodal status:**
  - 1 - 3 Ln-Met. in 48%**
  - > 3 Ln-Met in 52%**
- **Outcome similar compared to breast cancer with similar tumor biology and tumor stage**

# Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Imaging Diagnostics

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- **Breast imaging incl. Breast-MRI**
- **Exclude contralateral cancer**
- **Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)**
- **Staging** (CT thorax / abdomen, pelvis, in certain circumstances also thyroid sonography, HNT-exam)
- **PET / PET-CT**

Oxford		
LoE	GR	AGO
3	B	++
3	B	++
5	D	++
3	B	++
3b	B	+

# Axillary Metastasis in Occult Breast Cancer (ex. CUP)

## Pathology, molecular pathology

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>ER, PR, HER2, GATA3 (in some cases Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, and others)</li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.</li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, Theros CTID)</li> </ul>	2c	B	+/-
<ul style="list-style-type: none"> <li>NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)</li> </ul>	2c	B	+/-
<ul style="list-style-type: none"> <li>Prognostic gene expression tests</li> </ul>	5	D	--

# Axillary Metastasis in Occult Breast Cancer (Axillary CUP): Therapy

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- **Axillary dissection**
- **Mastectomy if breast MRI is negative**
- **(Neo-) adjuvant systemic therapy according to breast cancer guidelines (AGO)**
- **Breast irradiation if breast MRI is negative**
- **Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)**

Oxford		
LoE	GR	AGO
3a	C	++
3a	C	--
5	D	++
2c	B	+
3b	B	+

# Paget's Disease of the Breast

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- **Definition:** Paget's disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer.
- **Clinical presentation:** skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin

Feature	Frequency
Presentation	Paget's disease with invasive Ca. (37 - 58%) Paget's disease mit DCIS (30 - 63%) Isolated Paget's disease (4 - 7%) Isolated Paget's disease with invasion (rare)
IHC	HER2-positive (83 - 97%) ER-positive (10 - 14%) AR-positive (71 - 88%)
Prognosis and tumor biology	Better in isolated Paget's disease Worse if in combination with invasive breast cancer or DCIS compared to isolated Paget's disease

# Paget's Disease of the Breast Diagnosis

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- **Histological verification by skin biopsy**
- **Mammography, sonography**
- **MRI of the breast if other imaging negative**
- **Immunohistochemistry (ER, PR, HER2, Ck7)  
to detect benign and HER2-negative cases**

Oxford		
LoE	GR	AGO
		++
4	D	++
4	C	+
5	D	++

# Paget's Disease of the Breast - Therapy

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- **Paget's disease with underlying disease (invasive breast cancer, DCIS)**

- Therapy according to standard of underlying disease
- Surgery must achieve R0

- **Isolated Paget's disease of the NAC:**

- Surgery must achieve R0
- Surgical resection only, no adjuvant radiotherapy
- Sentinel-node excision (SLNE)

Oxford		
LoE	GR	AGO

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

1c	B	++
----	---	----

1c	B	++
----	---	----

4	D	++
---	---	----

2b	B	--
----	---	----

# Borderline and Malignant Phyllodes Tumor

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- Name derived from greek term of “Phyllon” (leaf) due to its lobulated histological aspect
- Differential diagnosis may be problematic on core biopsy
- Resection margin is independent prognostic parameter
- Comparable rates of recurrence in association with BCT or mastectomy
- In-Breast recurrence relatively frequently seen (10 - 30%)
- Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.
- Adverse pathological criteria: marked stromal cellularity and overgrowth, increased nuclear atypia, presence of large necrohemorrhagic areas, and high mitotic activity associated with increased risk of distant recurrence

# Phyllodes tumor

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- **Fibroepithelial tumors of the breast: frequency 0.3 – 1% of all primary breast tumors**

parameter	frequencies
<b>Grading (3-STEP histological grading system)</b>	<b>Benign (75%) Borderline (16%) Malignant (9%)</b>
<b>Median age at time of diagnosis</b>	<b>Benign PT: 39 y Borderline PT: 45 y Malignant PT: 47 y</b>
<b>Local recurrence</b>	<b>Benign PT: 4 – 17% Borderline PT: 14 – 25% Malignant PT: 23 – 30%</b>
<b>Metastasis</b>	<b>Benign PT: &lt;1% Borderline PT: 1.6% Malignant PT: 16-22%</b>

**10y OS: 86–90% (range: 57–100%) depending on subtype and unfavorable histological criteria**



# Borderline and Malignant Phyllodes Tumor Surgery



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- **Borderline /malignant phyllodes tumor: Complete resection with adequate margins, min. > 1 mm**
- **SLNE / Axillary dissection**
- **Treatment of local recurrence**
  - **R0 resection or simple mastectomy**

Oxford		
LoE	GR	AGO
2b	B	++
4	C	--
4	C	++

# Systematic Reviews (2016 – 2021)



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<p>Rosenberger LH, et al. J Clin Oncol 39: 178-189, 2021. PMID 33301374</p>	<p>Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines.</p>	<p>Local recurrence (all PT grades) was not reduced with wider negative margin width (<math>\leq 2</math> mm v. <math>&gt; 2</math> mm); or final margin status (positive v negative).</p>
<p>Thind A, et al. Ann R Coll Surg Engl. 102(3):165-173, 2020. PMID 31918563</p>	<p>Surgical margins for borderline and malignant phyllodes tumours. (10 studies, 456 cases, 1990 – 2019).</p>	<p>No statistically significant difference between <math>&lt;1</math>cm and <math>\geq 1</math>cm margins in terms of local recurrence rates or distant metastasis.</p>
<p>Lu Y, et al. Ann Surg Oncol. 90:342–13, 2019. PMID 30617873.</p>	<p>Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. (54 studies, 9234 cases, 1995 – 2018).</p>	<p>A positive margin and BCS both were significantly correlated with a higher LR risk for malignant PTs but not for benign and borderline PTs.</p>
<p>Tan BY, et al. Histo-pathology. 2016;68(1):5-21. PMID: 26768026</p>	<p>Phyllodes tumours of the breast: a consensus review.</p>	<p>Tumour on ink, or <math>&lt;1</math> mm, should be considered as a positive margin. Excision with negative margins should be achieved for recurrent and malignant phyllodes tumours.</p>

# Borderline and Malignant Phyllodes Tumor

## Adjuvant Therapy



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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Adjuvant radiotherapy (younger age, increased tumor volume &gt; 5 cm, close resection margin)                             <ul style="list-style-type: none"> <li>Local control</li> <li>Effect on disease-free survival</li> </ul> </li> </ul>	2b	B	+
<ul style="list-style-type: none"> <li>Systemic adjuvant therapy (chemo, endocrine)</li> </ul>	4	C	--
<ul style="list-style-type: none"> <li>Adjuvant Treatment of local recurrence                             <ul style="list-style-type: none"> <li>Radiotherapy, chemotherapy after R1 resection</li> </ul> </li> </ul>	4	C	+/-
<ul style="list-style-type: none"> <li>Distant metastasis (very rare)                             <ul style="list-style-type: none"> <li>Treatment like soft tissue sarcomas</li> </ul> </li> </ul>	4	C	++

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# Sarcomas of the Breast

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- **Not infrequently associated with familial syndromes (Li-Fraumeni, familial adenomatous polyposis, neurofibromatosis type 1)**
- **Primary sarcomas: angiosarcoma, undifferentiated sarcoma, leiomyosarcoma, liposarcoma, osteosarcoma**
- **Secondary malignancies of the breast:**
  - Radiotherapy-Associated Angiosarcoma
  - Breast Implant Associated Large-Cell Anaplastic Lymphoma (BI-ALCL)
- **Rare: intramammary sarcoma metastases**
- **Staging: TNM (UICC) or AJCC scheme of the soft tissue sarcoma analogous to sarcoma of the breast**
- **Grading: Analogous to the FNCLCC system for sarcoma or according to Rosen (1988) for angiosarcomas**

# Primary Angiosarcoma of the Breast

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- **Most common primary sarcoma of the breast**
- **Young age (median: 24–46 years)**
- **Indistinct tumor borders**
- **Large tumor (median: 5–7 cm)**
- **Uncharacteristic findings on mammography and sonography**
- **High local recurrence risk, even after mastectomy**
- **More unfavorable prognosis than other primary sarcoma of the breast**

# Primary Angiosarcoma of the Breast\*

## Diagnosis

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	Oxford		
	LoE	GR	AGO
■ Mammography, sonography to determine extent of disease	3a	C	--
■ Preoperative MRI to determine the extent of disease	3a	C	++
■ Diagnosis by core biopsy	3a	C	++
■ Diagnosis by FNB	3a	C	--
■ Staging (CT thorax & abd.; angiosarcoma: MRI brain)	4	D	++
■ Prognostic factors: size, grade, margins	3a	C	++

# Primary Angiosarcoma of the Breast\*

## Therapy

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- **Surgery with wide clear margins, mostly as mastectomy**
  - Breast-conserving therapy
- **SLNE or axillary dissection if cN0**
- **Adjuvant chemotherapy (anthracycline/taxane-based)**
- **Adjuvant radiotherapy if high risk (size > 5 cm, R1)**

Oxford		
LoE	GR	AGO
<b>2b</b>	<b>C</b>	<b>++</b>
<b>3a</b>	<b>C</b>	<b>-</b>
<b>3a</b>	<b>C</b>	<b>--</b>
<b>4</b>	<b>C</b>	<b>+/-</b>
<b>4</b>	<b>C</b>	<b>+/-</b>

# Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

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- **Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years**
- **Clinical presentation**
  - > 5 years after BCT or mastectomy with irradiation
  - usually intracutaneously or subcutaneously in the irradiation area with livid discoloration
  - multiple foci
  - most often in advanced stages (II–III)
  - metastasis mostly pulmonary
  - lymph node metastasis possible
- **Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma**
- **Survival: after 5 yrs up to 50.5%, after 10 yrs up to 25.2%**

# Secondary Angiosarcoma of the Breast Therapy

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- **Secondary mastectomy**
- **Adjuvant chemotherapy  
(anthracycline/taxane-based)**
- **Adjuvant radiotherapy if high-risk  
(size > 5 cm, R1)**
- **Regional hyperthermia (to improve local control)  
plus chemotherapy and/or radiotherapy**

Oxford		
LoE	GR	AGO
3a	C	++
2b	B	+/-
2b	B	+/-
2b	B	+/-

# Angiosarcoma of the Breast

## Treatment of Local Recurrence and Metastases

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### Treatment of Local Recurrence:

- R0 resection
- Adjuvant radiotherapy for high-risk patients  
(tumor size > 5 cm, R1)

### Distant Metastases / Unresectable Tumors:

- Treatment like soft tissue sarcomas
- Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)

Oxford		
LoE	GR	AGO
4	C	++
4	C	+/-
4	C	++
2b	B	+
4	C	+/-

# Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)



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- **Aproximately 10.000.000 implant carriers**
- **Rare disease, 3 % of Non-Hodgkin Lymphomas, 0.04-0.5 % of all malignant breast diseases**
- **1:3.000 – 30.000 in women with textured implants (caveat: underreporting!)**
- **Estimated incidence 0.6-1.2 / 100.000 women with implants (median age: 54 y)**
- **Mainly associated with textured implants**
- **Interval to diagnosis: 8 years (median)**
- **Clinical symptoms**
  - **Swelling and seroma. (60 %)**
  - **Solid tumor (17 %)**
  - **Seroma and solid tumor (20 %)**
  - **Axillary lymphadenopathia (20%)**
- **Histology: CD30+ / ALK-T-Cell Lymphoma**
- **Mandatory registration as SAE (§3 MPSV to BfArM)**

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# BIA-ALCL - Surfaces of Breast Implants

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- The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface. **The risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces.**

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/ Nano
Surface Area	high	intermediate	intermediate	low	low	minimal
Roughness	high	intermediate	low	low	low	minimal
<b>SURFACE TYPE</b>	4	3	3	2	2	1

# BIA-ALCL– Diagnosis

## Oxford

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

- |   |    |   |    |
|---|----|---|----|
| <ul style="list-style-type: none"> <li>▪ <b>Breast US (assessment of new seromas &gt; 1 year after implant insert, solid lesion (sensitivity: 84%, specificity: 75%))</b></li> </ul>  | 3a | D | ++ |
| <ul style="list-style-type: none"> <li>▪ <b>Breast-MRI in confirmed cases</b></li> </ul>  | 3a | D | ++ |
| <ul style="list-style-type: none"> <li>▪ <b>Staging (Imaging, e.g. CT, PET-CT)</b></li> </ul>   | 3a | D | ++ |
| <ul style="list-style-type: none"> <li>▪ <b>Cytology of late seromas</b> <ul style="list-style-type: none"> <li>▪ - &gt; 50 ml</li> <li>▪ - Complete assessment</li> <li>▪ - flow-cytology (T-cell clone)</li> <li>▪ - BIA-ALCL specific cytologic diagnostic (CD 30+)</li> </ul> </li> </ul> | 3a | D | ++ |
| <ul style="list-style-type: none"> <li>▪ <b>Core needle biopsy in solid lesions</b></li> </ul>  | 3a | D | ++ |
| <ul style="list-style-type: none"> <li>▪ <b>Lymphoma assessment of resected tissue and histologic staging</b></li> </ul>  |    |   |    |
| <ul style="list-style-type: none"> <li>▪ <b>Documentation of the implant (manufacturer, size, volume, surface, Batch-number) and entry in registry</b></li> </ul>   | 5  | D | ++ |

# BIA-ALCL – Therapy

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- **Implant resection and complete capsulectomy including tumorectomy**
- **Resection of suspicious lymph nodes, no routine use of Sentinel-Node-Biopsy, no axillarx dissection**
- **Polychemotherapy (e.g. CHOP) in cases of extra capsular extension**
- **Radiotherapy in unresectable tumors**
- **Case discussion in an interdisciplinary tumor board in the presence of a lymphoma specialist**

Oxford		
LoE	GR	AGO
3a	C	++
4	D	++
4	D	+
5	D	+/-
5	D	++

# TNM Staging of BIA-ALCL (proposed)

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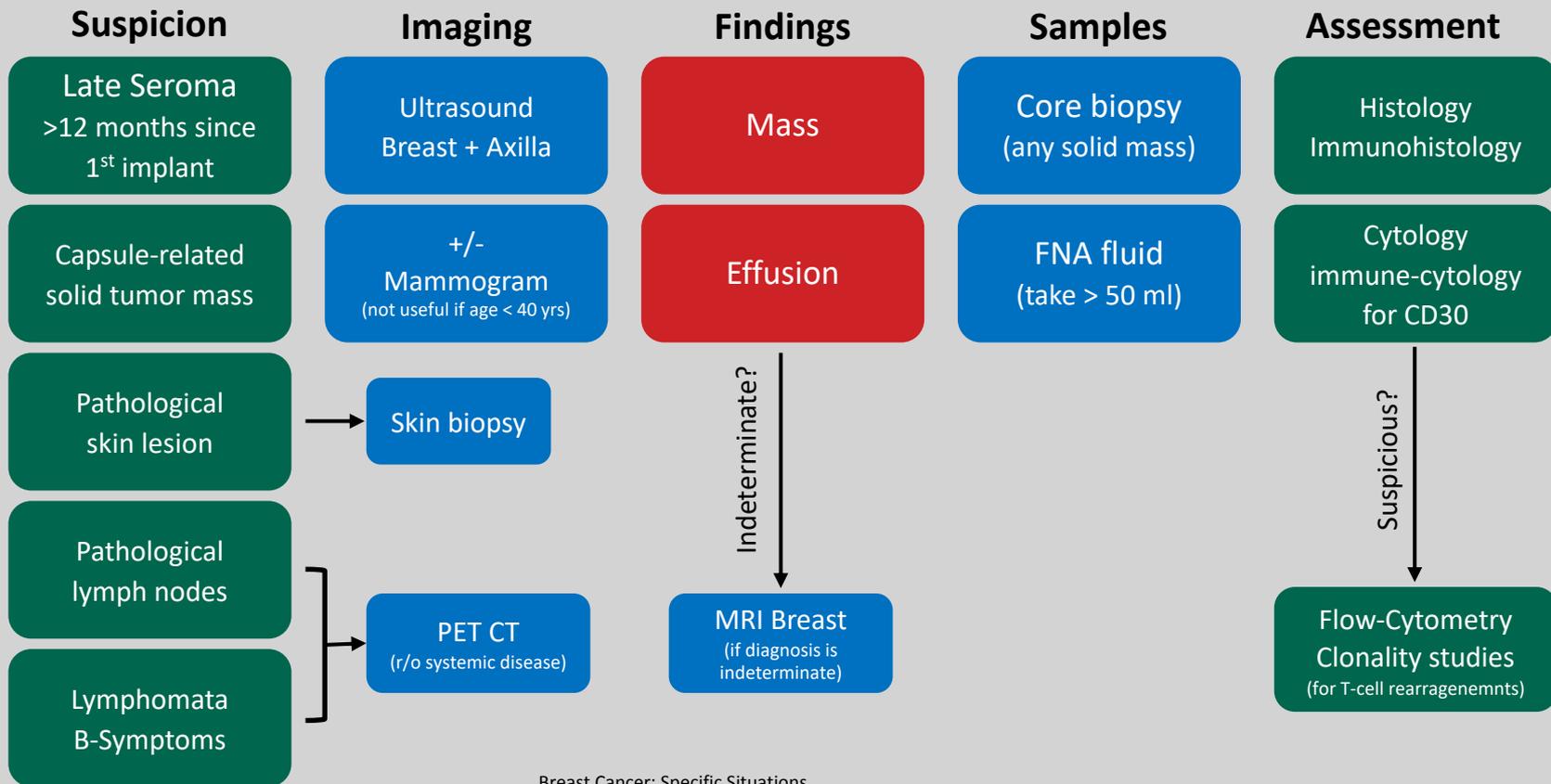
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TNM - Category		Definition
Tumor extent (cT/pT)	T1	Confined to seroma or a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
Regional lymph nodes (cN/pN)	N0	No lymph node involvement
	N1	One regional lymph node positive
	N2	Multiple regional lymph nodes positive
Metastasis (cM/pM)	M0	No distant spread
	M1	Spread to other organs or distant sites

Stage	Definition
IA	T1 N0 M0
IB	T2 N0 M0
IC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	T any N any M1

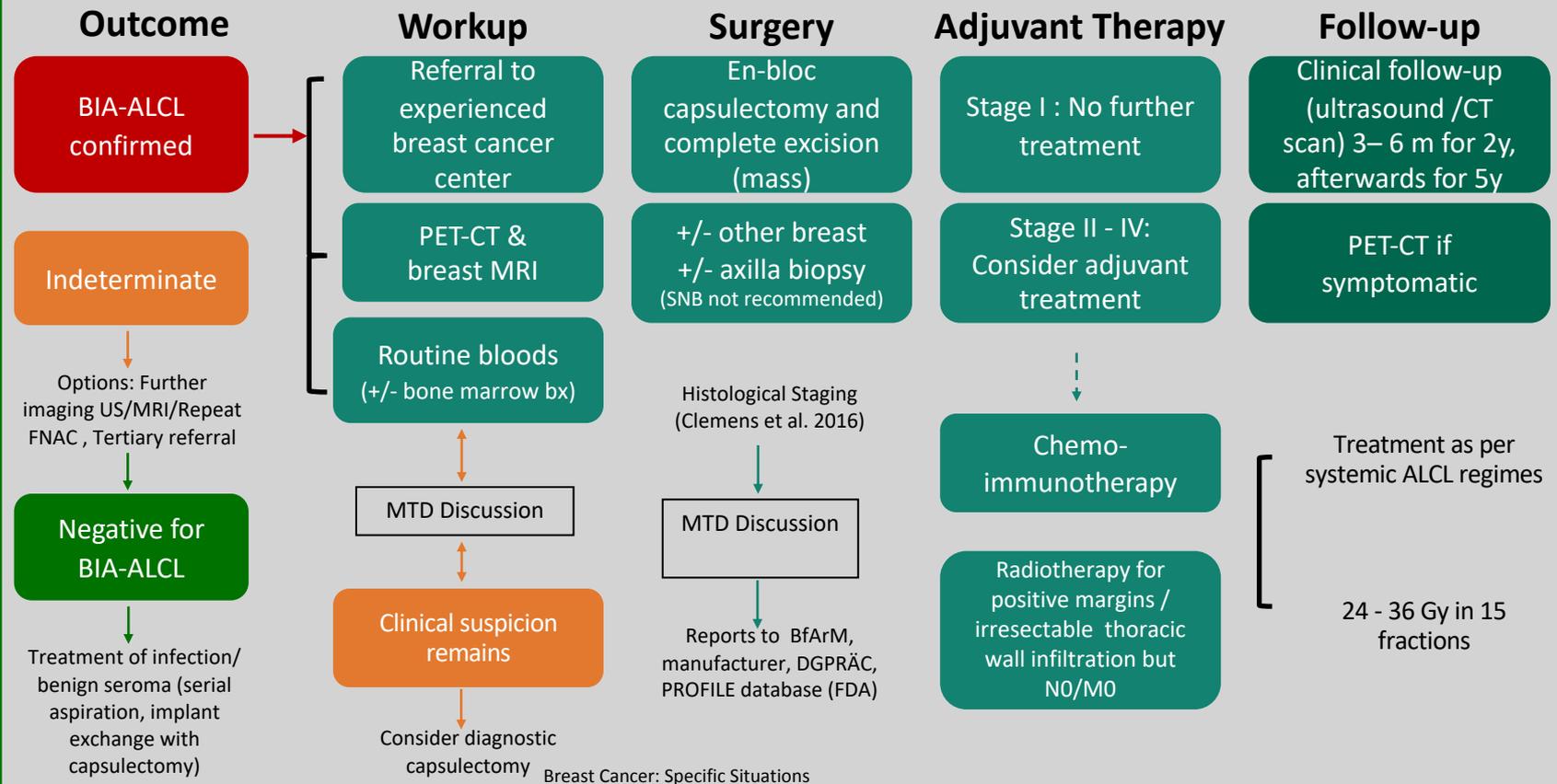
# BIA-ALCL: Diagnostic Pathways and Assessment

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# BIA-ALCL Treatment Pathways

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# BIA-ALCL – EUSOMA-Recommendation

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- **Despite an increase of BIA-ALCL in association with texture implants the use of textured implants is still permitted!**

**„For the moment, textured implants can safely continue to be used with patient's fully informed consent, and that women that have these type of implants already in place don't need to remove or substitute them, which would undoubtedly cause harm to many tens of thousands of women, to prevent an exceptionally rare, largely curable and currently poorly understood disease.“**

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# Metaplastic breast carcinoma

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## **Definition: Metaplastic transformation of glandular tumor cells.**

- Epithelial differentiation: squamous cell carcinoma, spindle cell carcinoma
- Heterologous (mesenchymal) differentiation: chondroid, osseous, or rhabdoid metaplastic breast carcinoma

## **Clinicopathologic characteristics:**

- < 1% of malignancies of the breast
- Same age group as NST carcinomas
- Circumscribed, palpable
- Rapidly growing, poor response to chemotherapy
- > 90% triple-negative

## **Aggressive:**

- Highly malignant with heterologous (mesenchymal), squamous or high-grade spindle cell differentiation
- Uncertain malignant potential (low-grade) in adenosquamous or fibromatosis-like differentiation

# Metaplastic breast carcinoma - high-grade -

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	Oxford		
	LoE	GR	AGO
▪ <b>Surgical therapy and axillary staging according to standard</b>	4	C	++
▪ <b>Adjuvant chemotherapy (rather chemoresistant)</b>	4	C	++
▪ <b>Neoadjuvant chemotherapy (rather chemoresistant)</b>	4	C	+/-
▪ <b>Adjuvant endocrine therapy if receptor-positive</b>	4	C	+
▪ <b>Adjuvant radiotherapy according to standard</b>	4	C	++

# Metaplastic breast carcinoma with uncertain malignant potential (fibromatous and adenosquamous Ca.)\*

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- **Surgical therapy and axillary staging according to standard**
- **Adjuvant chemotherapy**
- **Neoadjuvant chemotherapy**
- **Adjuvant endocrine therapy (not applicable, since triple-negative tumors)**
- **Adjuvant radiotherapy according to standard**

	Oxford		
	LoE	GR	AGO
Surgical therapy and axillary staging according to standard	4	C	++
Adjuvant chemotherapy	4	C	-
Neoadjuvant chemotherapy	4	C	--
Adjuvant endocrine therapy (not applicable, since triple-negative tumors)	4	C	-
Adjuvant radiotherapy according to standard	4	C	+