

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Breast Cancer: Specific Situations

Breast Cancer: Specific Situations

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- **Versions 2005–2020:**

Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Göhring /
Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass /
Mundhenke / Müller / Oberhoff / Rody / Scharl / Schneeweiss / Schütz /
Sinn / Solomayer / Stickeler / Thomssen

- **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**

Breast Cancer in Young Women ≤ 40 Years

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

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* Participation in register study recommended

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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| | Oxford | | |
|---|--------|----|-----|
| | LoE | GR | AGO |
| ■ Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity) | 2b | C | ++ |
| ■ Termination of pregnancy does not improve maternal outcome | 3b | C | |
| ■ Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir | 4 | C | ++ |
| ■ If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities | 5 | D | ++ |

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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 |
| 5 | D | ++ |
| 5 | D | ++ |
| 5 | D | ++ |
| 5 | D | ++ |

Pregnancy Associated Breast Cancer*: Outcome

**Oxford
LoE**

- **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 |
| 2b | B | ++ |
| 2a | C | ++ |
| 2b | B | ++ |
| 1a | A | ++ |
| 1a | A | + |
| 2a | C | +* |
| 1a | A | + |
| 1b | B | + |
| 2b | C | + |

* 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

| Oxford | | |
|--------|----|-----|
| LoE | GR | AGO |
| 2b | C | ++ |
| 2b | C | + |
| 2b | B | + |
| 1b | B | ++ |
| 2b | B | + |
| 2b | C | + |

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

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- **Diagnostic work-up as in women**
 - Mammography
 - Ultrasound
- **Standard-surgery: Mastectomy**
 - BCT is an option (tumor/breast relation)
 - Sentinel-node excision (SLNE)
- **Radiotherapy as in women
(consider tumor/breast relation!)**
- **Genetic counseling if one additional relative affected
(breast/ovarian cancer)**
- **Screening for 2nd malignancies according to guidelines**

| Oxford | | |
|--------|----|-----|
| LoE | GR | AGO |
| 4 | C | + |
| 3b | C | +/- |
| 2b | B | ++ |
| 4 | C | ++* |
| 4 | C | ++* |
| 2b | B | + |
| 4 | C | + |
| 2b | B | ++ |
| GCP | | ++ |

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Breast Cancer: Specific Situations

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)**

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

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| Median survival probability | | |
|-----------------------------|-----------|--------|
| Trimodal therapy | 72 months | p<0.05 |
| Surgery alone | 26 months | |

| Overall survival-probability (OS) | 10 years-OS | 5 years-OS |
|-----------------------------------|-------------|------------|
| Trimodal therapy | 55.4% | 37.3% |
| Surgery & chemotherapy | 42.9% | 28.5% |
| Surgery & radiotherapy | 40.7% | 23.5% |
| Surgery alone | | 16.5% |

| Multivariate analysis of OS | Hazard Ratio | 95% CI |
|--|--------------|--------------|
| 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 | |
|--|---------|----------|
| pCR | 77% | p<0.0001 |
| Non-pCR | 54% | |
| TN-IBC | 37% | p<0.0001 |
| other biologic subtypes (HR+/HER2-, HR+/HER2+, HR-/HER2+) | 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**
- **Immunhistology**
 - 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 |
| ■ ER, PR, HER2, GATA3 (in some cases Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, and others) | 5 | D | ++ |
| ■ Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca. | 5 | D | ++ |
| ■ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, Theros CTID) | 2c | B | +/- |
| ■ NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup) | 2c | B | +/- |
| ■ Prognostic gene expression tests | 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

- **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

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

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

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

Borderline and Malignant Phyllodes Tumor Diagnosis

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- **Mammography, sonography**
- **Diagnosis on core biopsy, grade determination on resection specimen**
- **Breast MRI**
- **Staging only malignant PT (CT thorax, skeletal system)**

| Oxford | | |
|--------|----|-----|
| LoE | GR | AGO |
| 3 | C | ++ |
| 3 | C | ++ |
| 3 | C | +/- |
| 5 | D | ++ |

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)

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

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Borderline and Malignant Phyllodes Tumor

Adjuvant Therapy

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| | Oxford | | |
|--|--------|----|-----|
| | LoE | GR | AGO |
| ■ Adjuvant radiotherapy (younger age, increased tumor volume > 5 cm, close resection margin) | | | |
| ■ Local control | 2b | B | + |
| ■ Effect on disease-free survival | 2b | B | - |
| ■ Systemic adjuvant therapy (chemo, endocrine) | 4 | C | -- |
| ■ Adjuvant Treatment of local recurrence | | | |
| ■ Radiotherapy, chemotherapy after R1 resection | 4 | C | +/- |
| ■ Distant metastasis (very rare) | | | |
| ■ Treatment like soft tissue sarcomas | 4 | C | ++ |

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 | ++ |

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* Therapy in specialized centers recommended

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 |
| 2b | C | ++ |
| 3a | C | - |
| 3a | C | -- |
| 4 | C | +/- |
| 4 | C | +/- |

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)

- Approximately 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 |
| SURFACE TYPE | 4 | 3 | 3 | 2 | 2 | 1 |

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BIA-ALCL– Diagnosis

Oxford

LoE GR AGO

- | | LoE | GR | AGO |
|--|-----|----|-----|
| ▪ Breast US (assessment of new seromas > 1 year after implant insert, solid lesion (sensitivity: 84%, specificity: 75%)) | 3a | D | ++ |
| ▪ Breast-MRI in confirmed cases | 3a | D | ++ |
| ▪ Staging (Imaging, e.g. CT, PET-CT) | 3a | D | ++ |
| ▪ Cytology of late seromas | 3a | D | ++ |
| ▪ - > 50 ml | | | |
| ▪ - Complete assessment | | | |
| ▪ - flow-cytology (T-cell clone) | | | |
| ▪ - BIA-ALCL specific cytologic diagnostic (CD 30+) | | | |
| ▪ Core needle biopsy in solid lesions | 3a | D | ++ |
| ▪ Lymphoma assessment of resected tissue and histologic staging | | | |
| ▪ Documentation of the implant (manufacturer, size, volume, surface, Batch-number) and entry in registry | 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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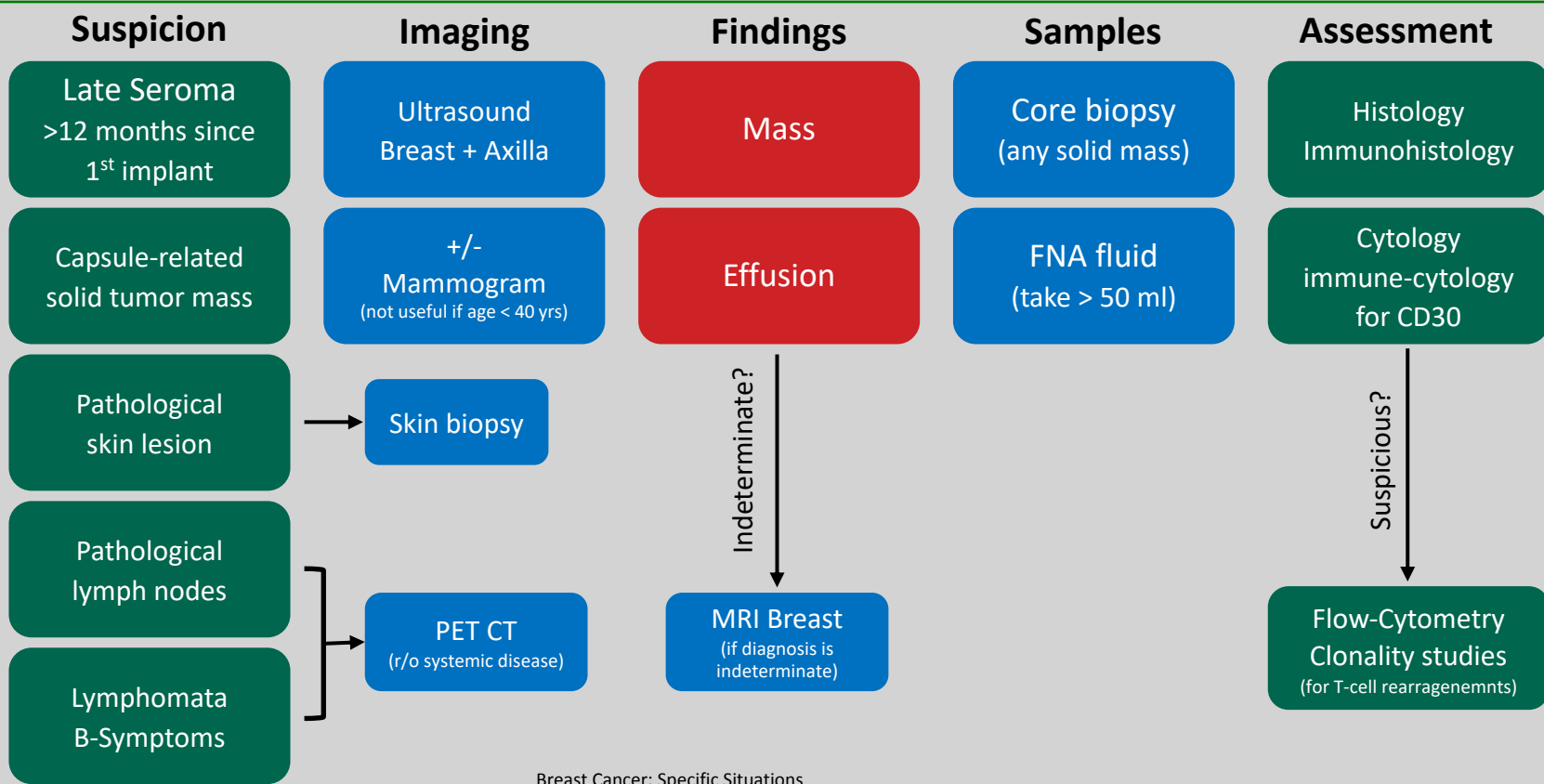
| TNM - Category | | Definition |
|---------------------------------|----|--|
| Tumor extent (cT/pT) | T1 | Confined to seroma or a layer on luminal side of capsule |
| | T2 | Early capsule infiltration |
| | T3 | Cell aggregates or sheets infiltrating the capsule |
| | T4 | Lymphoma infiltrates beyond 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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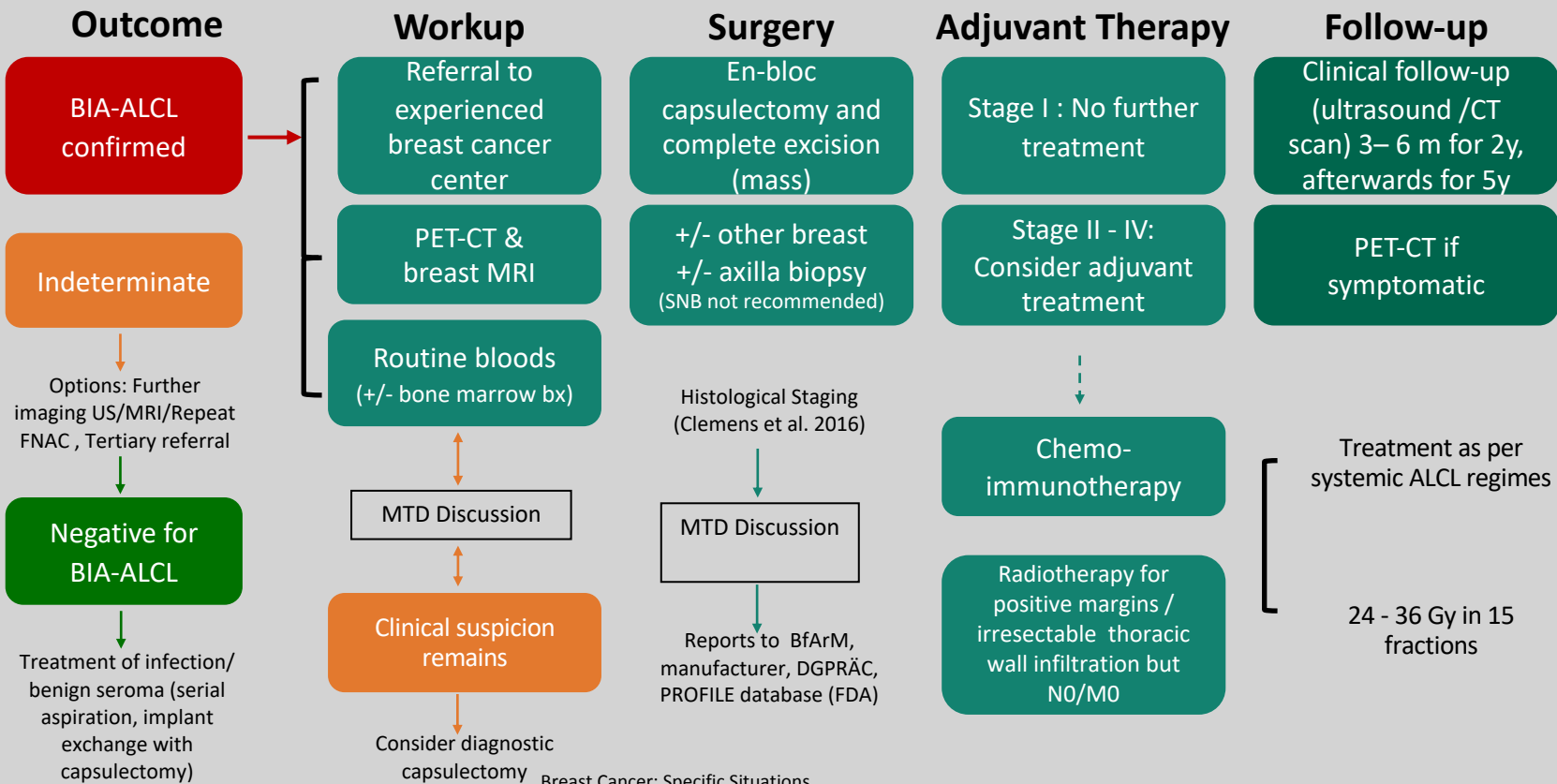
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BIA-ALCL Treatment Pathways

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BIA-ALCL – EUSOMA-Recommendation

- **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.“

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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- **Surgical therapy and axillary staging according to standard**
- **Adjuvant chemotherapy (rather chemoresistant)**
- **Neoadjuvant chemotherapy (rather chemoresistant)**
- **Adjuvant endocrine therapy if receptor-positive**
- **Adjuvant radiotherapy according to standard**

| Oxford | | |
|--------|----|-----|
| LoE | GR | AGO |
| 4 | C | ++ |
| 4 | C | ++ |
| 4 | C | +/- |
| 4 | C | + |
| 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 |
| 4 | C | ++ |
| 4 | C | - |
| 4 | C | -- |
| 4 | C | - |
| 4 | C | + |

* Reference pathology recommended

Breast Cancer: Specific Situations