

Diagnosis And Treatment Of Patients With Primary And Metastatic Breast Cancer



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Guidelines Breast
Version 2018.1

Breast Cancer: Specific Situations

Brustkrebs: Spezielle Situationen

- **Versions 2005-2017:**

**Dall / Fehm / Fersis / Friedrich / Gerber / Göhring /
Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass /
Mundhenke / Oberhoff / Rody / Scharl / Schütz / Schneeweiss / Sinn /
Solomayer / Thomssen**

- **Versions 2018:**

Harbeck / Rody

Breast Cancer: Specific Situations

- **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 ≤ 35 Years

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	Oxford		
	LoE	GR	AGO
■ Aggressive biological behavior with worse prognosis	2a	B	
■ Surgery like patients ≥ 35 y	2b	B	+
■ Guidelines adapted (neo-)adjuvant systemic treatment (see chapters there)	1b	A	++
■ GnRHa as ovarian protection (see chapter gyn. 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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	Oxford		
	LoE	GR	AGO
▪ Breast imaging & biopsy like in non-pregnant	4	C	++
▪ Staging if indicated (Bone scan after delivery)	5	D	+
▪ Full body MRI (without contrast agent)	4	C	+/-
▪ Surgery like in non-pregnant patients	4	C	++
▪ Sentinel node excision (technetium only)	4	C	+
▪ SLNE during 1st trimester	5	D	+/-
▪ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
▪ Blue dye (has not been tested in pregnant animals or humans)	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
 - Platin salts (carboplatin, cisplatin)
 - MTX (e.g. CMF)
- Endocrine treatment
- HER2-neu targeted treatment
- Bisphosphonates, denosumab

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

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 ≤3 weeks from last cycle of chemotherapy**
- **If further systemic therapy is needed after delivery, breast feeding may be contraindicated 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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	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 deliver a child are lower in breast cancer patients in comparison to non-cancer patients	5	D	++
■ Breast cancer patients of reproductive age should be offered a fertility counseling before starting any kind of treatment	5	D	++
■ Breast cancer patients should not be advised against getting pregnant regardless of tumor's hormone receptor status	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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	Oxford		
	LoE	GR	AGO
■ Clinical geriatric assessment	2b	B	++
■ Treatment according to guidelines	2a	C	++
■ Surgery similar to „younger“ age	2b	B	++
■ Endocrine treatment (endocrine resp.)	1a	A	++
■ Chemotherapy (standard regimens)			
■ < 70 years	1a	A	+
■ > 70 years (especially N+, ER/PgR-)	2a	C	+*
■ Radiotherapy	1a	A	+
■ Omit radiotherapy after BCT in low risk with endocrine treatment	1b	B	+
■ Trastuzumab	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, rec.-pos)**
 - **No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)**
 - **Hypofractionated radiotherapy**
 - **No chemotherapy if >70 years 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 (SNE)
- **Radiotherapy as in women
(consider tumor breast relation!)**
- **Genetic counselling 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		++

* Participation in register study recommended

Male Breast Cancer: Systemic Therapy

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- **Adjuvant chemotherapy as in women**
- **HER2-targeted therapy**
- **Endocrine therapy**
 - Tamoxifen
 - Aromatase inhibitors (adjuvant)
 - Aromatase inhibitors (metastatic BC)
 - GnRHa and AI (metastatic BC)
 - Fulvestrant (metastatic BC)
- **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	+/-
4	C	++

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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

Inflammatory Breast Cancer (IBC, cT4d)

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d 			++
<ul style="list-style-type: none"> Staging 	2c	B	++
<ul style="list-style-type: none"> Skin punch biopsy (at least 2; detection rate < 75%) 	2c	B	+
<ul style="list-style-type: none"> Neoadjuvant chemotherapy (regimens as in noninflammatory BC) 	2c	B	++
<ul style="list-style-type: none"> Adjuvant systemic treatment according to guidelines 	2c	B	++
<ul style="list-style-type: none"> Mastectomy after chemotherapy <ul style="list-style-type: none"> Breast conserving therapy in case of pCR (individual) Sentinel excision only 	2c	B	+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Breast conserving therapy in case of pCR (individual) 	2b	C	+/-
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Sentinel excision only 	3b	C	-
<ul style="list-style-type: none"> Radiotherapy (PMRT) 	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 or better than in breast cancer with similar tumor biology and tumor stage**

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

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- **Mammography, Breast-ultrasound, 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, thyroid scintigraphy, 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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- ER, PgR, HER2, GATA3
- Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.
- Gene expression profiling for determination or primary site (CUPprint, Pathwork, TOT, Theros CTID)
- NGS, epigenetics for determination of primary site (Panel-Sequencing, EPICup)
- Prognostic gene expression tests

Oxford		
LoE	GR	AGO
5	D	++
5	D	++
2c	B	+/-
2c	B	+/-
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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- **Paget's disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer. Isolated Paget's disease of the nipple is more rarely seen, and less aggressive.**

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%)

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**
- **Immunhistology (ER, PgR, 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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	Oxford		
	LoE	GR	AGO
■ Paget's disease with underlying disease (invasive breast cancer, DCIS)			
■ Therapy according to standard of the underlying disease	5	D	++
■ Surgery must achieve R0	1c	B	++
■ Isolated Paget's disease of the NAC:			
■ Surgery must achieve R0	1c	B	++
■ Surgical resection only, no adjuvant radiotherapy	4	D	++
■ Sentinel-node excision (SNE)	2b	B	--

Borderline and Malignant Phyllodes Tumor

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- **Differential diagnosis may be problematic on core biopsy**
- **In-Breast recurrence relatively frequently seen (10 - 30%)**
- **Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.**

Feature	Frequency
Grading	Benign PT (75%) Borderline PT (16%) Malignant PT (9%)
Median age on diagnosis	Benign PT: 39 J. Borderline PT: 45 J. Malignant PT: 47 J.
Local recurrence	Benign PT: 10 - 17% Borderline PT: 14 - 25% Malignant PT: 23 - 30%

Borderline and Malignant Phyllodes Tumor Diagnosis

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- Mammography, sonography
- Diagnosis on core biopsy, grading
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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- **R0-Excision**
- **SNE / Axillary dissection when cN0**
- **Treatment of local recurrence**
 - **R0 resection or simple mastectomy**

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

Borderline and Malignant Phyllodes Tumor

Adjuvant Therapy

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	Oxford		
	LoE	GR	AGO
■ Adjuvant radiotherapy	4	C	--
■ If T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy)	2b	C	+/-
■ Systemic adjuvant therapy (chemo, endocrine)	4	C	--
■ Treatment of local recurrence			
■ R0 resection or simple mastectomy	4	C	+
■ 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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- Mammography, sonography to determine extent of disease
- Preoperative MRI to determine the extent of disease
- Diagnosis by core biopsy
- Diagnosis by FNB
- Staging (CT thorax & abd.; angiosarcoma: MRI brain)
- Prognostic factors: size, grade, margins

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

Primary Angiosarcoma of the Breast*

Therapy

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

Oxford		
LoE	GR	AGO
3a	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 years: 15%**

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 (in
angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)

	Oxford		
	LoE	GR	AGO
R0 resection	4	C	++
Adjuvant radiotherapy for high risk patients (tumor size > 5 cm, R1)	4	C	+/-
Treatment like soft tissue sarcomas	4	C	++
Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)	2b	B	+
Antiangiogenic treatment (e.g. in angiosarcoma)	4	C	+/-

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

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- **Rare, estimated annual incidence <1 per 100,000 women with implants (median age 54 years)**
- **Occurrence predominantly of textured implants**
- **5-year OAS 89%**
- **Interval for lymphoma diagnosis: 8 years (median)**
- **Clinical presentation**
 - Effusion only (60%)
 - Mass only (17%)
 - Effusion and mass (20%)
- **Histological: CD30 + / ALK-T cell lymphoma**
- **Reporting obligation as SAE according to § 3 MPSV to the BfArM**

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

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	Oxford		
	LoE	GR	AGO
▪ Sonography (for newly occurring seromas 1 year after implant placement, tumor mass)	5	D	++
▪ Breast MRI on confirmation of the diagnosis	5	D	++
▪ Nodal status, PET-CT, bone marrow biopsy	5	D	++
▪ Cytology of effusion (for newly occurring seromas 1 year after implant placement) with requisition "r/o BIA-ALCL"	5	D	++
▪ Lymphoma diagnosis on resection specimen and histological staging (acc. to Clemens 2016)	5	D	++
▪ Documentation of the implant (manufacturer, size, filling, surface, batch number)	5	D	++

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

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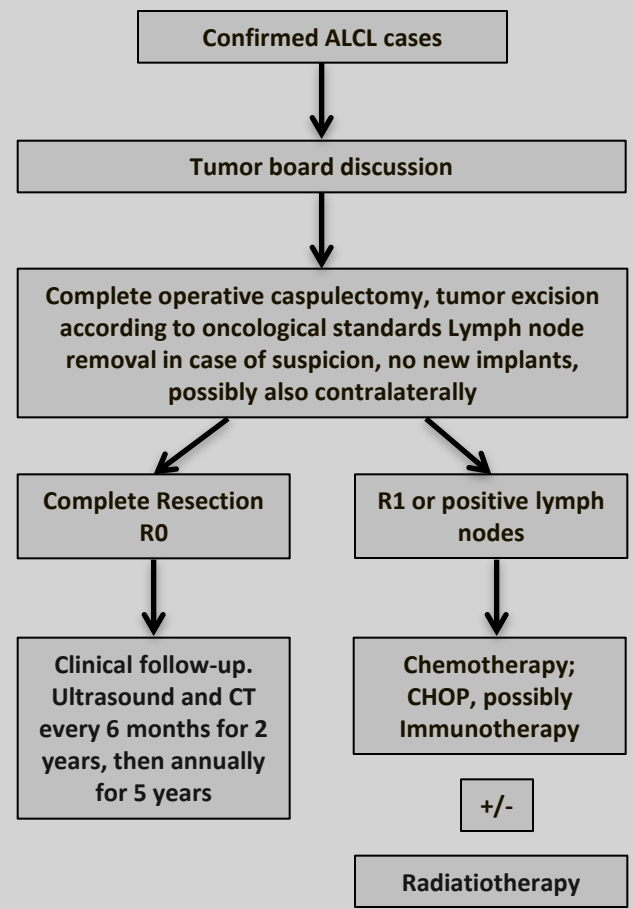
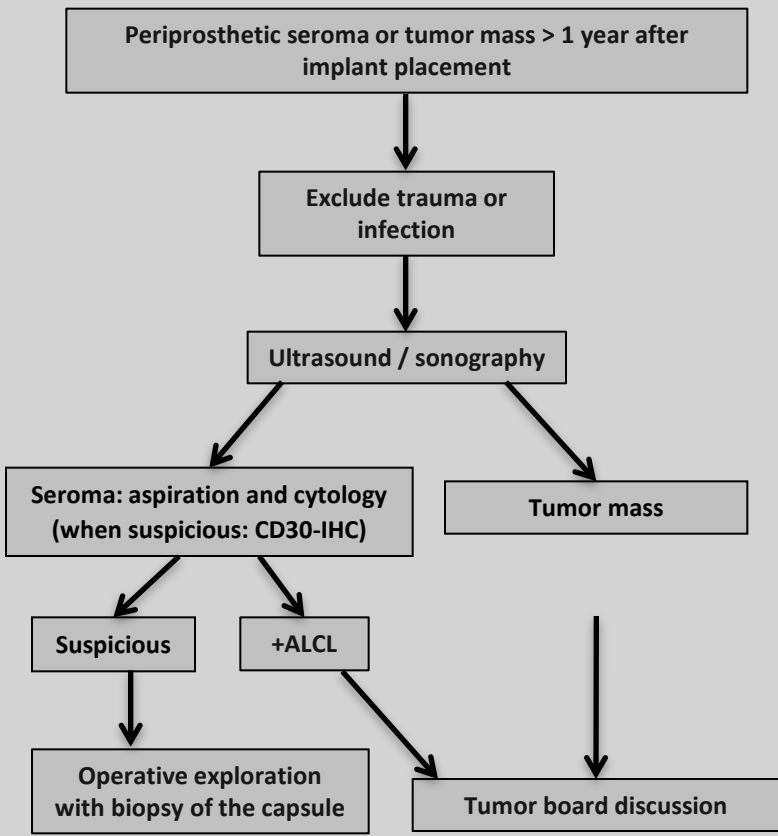
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	Oxford		
	LoE	GR	AGO
■ Implant removal and complete capsulectomy including tumor removal	3a	C	++
■ Removal of suspicious lymph nodes, no routine sentinel-node biopsy, no axillary dissection	4	D	++
■ Polychemotherapy (e.g., CHOP) when extracapsular tumor infiltration	4	D	+
■ Radiation for unresectable tumors or R1	5	D	+/-
■ Reconstruction after 1 year disease-free interval	5	D	+

Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Summary of the Management (acc. to Noah 2017) -

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Metaplastic Breast Cancer

Oxford

	LoE	GR	AGO
■ Imaging and histology for diagnosis according to standard	5	D	++
■ Staging including chest and abdominal CT (hematogenous metastasis)	4	C	++
■ Surgical treatment according to standard (more often MRM necessary due to advanced tumor stage, RR > 3 cm)	4	C	++
■ SNB	4	C	+
■ Adjuvant chemotherapy (tumors more chemoresistant)	4	C	+
■ Adjuvant endocrine standard therapy	4	C	+/-
■ Adjuvant standard radiotherapy	4	C	+

Metaplastic Breast Cancer

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Incidence:: 0,2-5 % of all breast cancers (1)

Histology: epithelial and mesenchymal components with two to three different components within a tumor;
high proliferation rate

subtypes: according to WHO (4)

Metaplastic carcinoma of no special type

Low-grade adenosquamous carcinoma

Fibromatosis-like carcinoma

Squamous cell carcinoma

Spindle cell carcinoma

Metaplastic carcinoma with mesenchymal differentiation

Chondroid differentiation

Osseous differentiation

Other types of mesenchymal differentiation

Mixed metaplastic carcinoma

Myoepithelial carcinoma

Molecular biology: > 90 % ER-, PR-, HER2-

~. 70 % overexpression of HER1, CK 5/6-expression (stem-cell-like and BRCA-like)(2)

molecular profile mostly basal-like (3)

frequent mutations in PIK3CA and PTEN (mTOR-overactivity)

Clinical features:

- Large tumors at diagnosis (> 5 cm)
- Frequent hematogenous metastases; nodal involvement in ~ 20 % (no nodal involvement in spindle cell carcinoma carcinosarcoma)
- Poor clinical course compared to TNBC
- Impaired prognosis in asian women (MRM more frequently, poor grading, more often squamous cell carcinoma, spindle cell carcinoma less frequent)