Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Breast Cancer:
Specific Situations

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Breast Cancer:
Specific Situations

- **Versions 2005–2023:**
  Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Gluz / Göhring / Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass / Mundhenke / Müller / Oberhoff / Rody / Scharl / Schmidt / Schneeweiss / Schütz / Sinn / Solomayer / Stickeler / Thomssen

- **Version 2024**
  Harbeck / Sinn / Thomssen

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Content – Specific Situations

- Young patients ≤ 40 years
- Pregnancy and breast feeding-associated BC
- Elderly patients
  - Geriatric assessment
- Male patients
- Inflammatory breast cancer (IBC, cT4d)
- Occult breast cancer - axillary CUP („Cancer of Unknown Primary“)
- Paget‘s disease
- Malignant and Boderline Phylloides-Tumor
- Sarcoma, Angiosarcoma
- Metaplastisc breast cancer

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Breast Cancer in Young Women ≤ 40 Years

	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	++
▪ ET interruption (max. 2 years after at least 18 months of previous therapy) in case of desire to have children without short-term survival disadvantage	2b	B	+
▪ 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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	Oxford		
	LoE	GR	AGO
▪ Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)	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)	2a	B	+
▪ 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 (not tested in pregnant animals or humans)	4	C	--

* Participation in register study recommended

Breast Cancer During Pregnancy or Breast Feeding - (Neo-)adjuvant Therapy

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	Oxford		
	LoE	GR	AGO
▪ Radiation therapy during pregnancy	4	C	-
▪ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
▪ Anthracyclines: AC	2b	B	++
▪ Dose-dense regimens with short-acting G-CSF	4	C	+/-
▪ Taxanes	2a	B	++
▪ Platinum salts (carboplatin, cisplatinum)	4	C	+/-
▪ MTX (e.g. CMF)	4	D	--
▪ Endocrine treatment	4	D	--
▪ HER2-targeted treatment	3a	C	--
▪ Checkpoint inhibitors	4	D	--
▪ Bisphosphonates, denosumab	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* or Breast Feeding – 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	++

* Participation in register study recommended

Breast Cancer and Pregnancy* or Breast Feeding – Family Planning

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	Oxford		
	LoE	GR	AGO
▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
▪ Assisted reproductive treatment after breast cancer	4	D	+/-
▪ Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients	3b	D	
▪ Breast cancer patients should not be advised against getting pregnant independent of their tumor‘s hormone receptor status and g*BRCA* status	2a	B	

* Participation in register study recommended

Breast Cancer During Pregnancy* and Breast Feeding - Outcome -

	Oxford LoE
▪ **BC during pregnancy**	
▪ **Prognosis is not worse if adequately treated**	3a
▪ **BC during lactation and within the first year after pregnancy**	
▪ **Prognosis worse than in BCP and if unrelated to pregnancy**	3a
▪ **Pregnancy / lactation after BC**	
▪ **Outcome not compromised**	3a

* **Participation in register study recommended**

Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

	Oxford		
	LoE	GR	AGO
▪ **Clinical geriatric assessment**	2b	B	++
▪ **Treatment according to guidelines**	2a	C	++
▪ Surgery similar to „younger“ age	2b	B	++
▪ Endocrine treatment (HR+)	1a	A	++
▪ Chemotherapy (standard regimens)			
▪ ≤ 70 years	1a	A	+
▪ > 70 years (especially N+, ER / PR-)	2a	C	+*
▪ Radiotherapy	1a	A	+
▪ Omit radiotherapy after BCS if low-risk, and if endocrine treatment is administered	1b	B	+
▪ Anti-HER2-therapy	2b	C	+

* Study participation recommended

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Treatment for Frail Patients

(Life Expectancy < 5 yrs., Substantial Comorbidities)

	Oxford		
	LoE	GR	AGO
▪ **Reduced standard treatment**	2b	C	++
▪ **Options extrapolated from trials in elderly:**			
▪ No breast surgery (consider endocrine therapy)	2b	C	+
▪ No axillary clearing (≥ 60 y, cN0, HR-pos)	2b	B	+
▪ No radiotherapy (Tumor size < 3 cm, pN0, HR-pos)	1b	B	++
▪ Hypofractionated radiotherapy	2b	B	+
▪ No chemotherapy if > 70 yrs. and negative risk-benefit analysis	2b	C	+

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Geriatric Assessment

- **Ability to tolerate treatment varies greatly („functional reserve“)**
- **Comprehensive geriatric assessment describes a multidisciplinary evaluation of independent predictors of morbidity & mortality for older individuals (CGA)**
  - **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**
- **General assessment tools:**
  - **Charlson Comorbidity Index (CCI, 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 (Age plus Malnutrition Assessment, MNA)**
    - **Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (food intake in the last 3 months, >3 prescribed drugs, moblity and autonomy)**
    - **Timed-up-and-go-test**
    - **Frailty Index (FI), Carolina Frailty Index (CFI)**

Links to current frailty scales:

CCI

IADL

G8

GPI

Timed up&go

FI

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

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Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Diagnostic work-up as in women	4	C	+
▪ Ultrasound	2b	B	++
▪ Mammography	3b	C	+
▪ Standard-surgery: Mastectomy	4	C	++**
▪ BCT is an option (tumor / breast relation)	4	C	+**
▪ Sentinel-node excision (SLNE)	2b	B	+
▪ In occult breast cancer	2b	B	+
▪ Radiotherapy as in women (consider tumor / breast relation!)	4	C	+
▪ Genetic counseling (see genetics chapter)	2b	B	++
▪ Screening for 2nd malignancies according to guidelines	GCP		++

* Treatment in certified breast cancer centers recommended; ** Participation in register study recommended

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Male Breast Cancer: Prognostic Factors

	Oxford		
	LoE	GR	AGO
▪ Nodal status	2b	A	++
▪ Age	2b	B	+
▪ Tumor size	2b	A	++
▪ ER / PR Expression	2b	A	++
▪ Ki-67 Expression	2b	C	+/-
▪ Grade	2b	C	+/-
▪ Genomic signatures	2b	B	+

Male Breast Cancer: Systemic Therapy

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	Oxford		
	LoE	GR	AGO
▪ (Neo-)adjuvant chemotherapy as in women	2a	B	++
▪ HER2-targeted therapy (if HER2-positive)	5	D	++
▪ Endocrine therapy	4	D	++
▪ Tamoxifen	2b	B	++
▪ GnRHa and AI	4	C	+
▪ Aromatase inhibitors without GnRHa	2b	B	-
▪ Fulvestrant (metastatic BC)	4	C	+/-
▪ CDK4/6i (in combination)	2b	B	+
▪ Palliative chemotherapy as in women	4	C	++

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Inflammatory Breast Cancer (IBC, cT4d)

	Oxford		
	LoE	GR	AGO
▪ Invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d			++
▪ Staging (including adequate breast imaging)	2c	B	++
▪ Skin punch biopsy (at least 2; detection rate < 75%)	2c	B	+
▪ Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)	2c	B	++
▪ Mastectomy after chemotherapy	2c	B	+
▪ Breast conserving therapy in case of pCR (individual)	2b	C	+/-
▪ Delayed breast reconstruction	3b	C	+
▪ Sentinel excision only	3b	C	-
▪ Radiotherapy of the chest wall including regional lymph nodes independent of therapy response	2c	B	++

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

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	Oxford		
	LoE	GR	AGO
▪ **Breast imaging incl. Breast-MRI**	3	B	++
▪ **Exclude contralateral cancer**	3	B	++
▪ **Staging** (CT thorax / abdomen, pelvis, bone scan)	3	B	++
If histological diagnosis is not certain			
▪ **Exclude non-breast malignancy, especially in case of TNBC** (e.g. NEC, female genital tract, lung, thyroid gland, stomach, skin, ENT)	5	D	++
▪ **PET / PET-CT**	3b	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 compared to breast cancer with similar tumor biology and tumor stage**

Axillary Metastasis in Occult Breast Cancer (ex. CUP)

Pathology, Molecular Pathology

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	Oxford		
	LoE	GR	AGO
▪ Immunohistochemistry (ER, PR, HER2, Ki-67, GATA)	5	D	++
▪ Immunohistochemistry (e.g. Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, Synaptophysin etc.) to exclude other primary malignancies in case of TNBC phenotype or unusual histology, e.g. NEC, female genital tract, lung, ENT tumors, thyroid, stomach, skin	5	D	++
▪ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)	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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Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Axillary dissection	3a	C	++
▪ Targeted axillary dissection after NACT (in case of clinical complete remission	3b	C	+/-
▪ Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)	3b	B	+
▪ Breast irradiation if breast MRI is negative (acc. BCT)	2c	B	+
▪ Mastectomy if breast MRI is negative	3a	C	--
▪ (Neo-)adjuvant systemic therapy according to breast cancer guidelines (AGO)	5	D	++

„BCT“ in patients with axillary met‘s and occult primary (AxCUP, OBC)

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Kim H, Park W, Kim SS et al. Prognosis of patients with axillary lymph node metastases from occult breast cancer analysis of multicenter data. Radiat Oncol J. 2021 Jun;39(2):107-112.
Retrospective analysis, n = 53 with AxCUP and OBC (adenocarcinoma); exclusion of a primary by extensive imaging. Eleven pts received blind upper quadrantectomy, 42 no breast surgery; 46 pts received whole breast irradiation (WBI), 7 did not; median F/U 85 months .
Result: 2 in-breast recurrences, 1 RLN rec., 1 combined in-breast and RLN, no distant metastases.
5 year DFS with WBI: 97.8% without WBI 83,3% (p = 0.01 univariate; in multivariate analysis nor biology nor extent of the disease nor therapy had a significant impact).
Discussion: ..in patients confirmed to have no lesion in the breast by contemporary imaging studies, it is necessary to include the ipsilateral breast in the radiation field in females with OBC presenting as AxCUP.

Tsai C, Zhao B, Chan T, Blair SL. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am J Surg. 2020 Jul;220(1):153-160.
Given the equipoise in overall survival among the treatment options, we conclude that after axillary clearance, **breast preservation and radiation therapy alone may be sufficient** in the treatment of patients with occult breast cancer.

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Paget‘s Disease of the Breast Diagnosis

„Mammary Paget Disease is a Sentinel Sign“

	Oxford		
	LoE	GR	AGO
▪ Histological verification by skin biopsy*			++
▪ Mammography, sonography	4	D	++
▪ MRI of the breast if other imaging negative	4	C	+
▪ Immunohistochemistry (ER, PR, HER2, CK7) to detect benign and HER2-negative cases	5	D	++

* including all skin strata (e.g. by punch biospy or wedge excision)

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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 Therapy

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	Oxford		
	LoE	GR	AGO
Paget‘s disease with underlying disease (invasive breast cancer, DCIS)			
▪ Therapy according to standard of 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 (SLNE)	2b	B	--

Borderline and Malignant Phyllodes Tumor Diagnosis

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	Oxford		
	LoE	GR	AGO
▪ Mammography, sonography	3	C	++
▪ Diagnosis on core biopsy, grade determination on resection specimen	3	C	++
▪ Breast MRI	3	C	+/-
▪ Staging only malignant PT (CT thorax / abdomen, bone scan)	5	D	++

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Borderline and Malignant Phyllodes Tumor

- 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

- **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%

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

Borderline and Malignant Phyllodes Tumor Surgery

	Oxford		
	LoE	GR	AGO
▪ Fibroepithelial lesions with rapid growth or size > 3 cm should be excised (independently from the any CNB result)	5	D	++
▪ If the result of the CNB is unclear or suspicious for PT, excision with clear margins should be performed	5	D	++
▪ SLNE / Axillary dissection (if clinically unsuspicious)	4	C	--
▪ Treatment of local recurrence			
▪ R0 resection or simple mastectomy	4	C	++

Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology

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Canadian Phyllodes Tumor Consensus Panel (23 panelists): Example of one out of 109 state-ments on diagnosis and therapy of phyllodes tumors that were discussed (73 with consensus).

The following statements are referring to MALIGNANT phyllodes (diagnosed on biopsy)

If the diagnosis of malignant PT is known preoperatively, malignant PT should under-go wide excision (clinical 1 cm), with the goal of negative microscopic margins 87%

- In patients with negative margins who undergo wide excision (clinical 1cm) – if the
- microscopic margin is:
  - < 2 mm: reexcision of margin can be offered 82%
  - 2–10 mm: no re-excision should be offered 65%
  - > 10 mm: no reexcision should be offered 100%
- Patients with tumor on ink after breast conservation, should be offered reexcision (this includes "shelled out" and positive margins) 96%

Bogach J et al. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.

Borderline and Malignant Phyllodes Tumor
- Margins -

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	Oxford		
	LoE	GR	AGO
■ **Intended lesion-free surgical margins are*** **- in borderline PT: ≥ 2 mm** **- in malignant PT: ≥ 10 mm**	2b	B	++
■ **Intended pathologically lesion-free margins are*** **- in borderline PT: negative („no ink on the tumor“)** **- in malignant PT: ≥ 2 mm**	2b	B	++
■ **Re-resection recommended** **- in borderline PT: if margin* positive („tumor on ink“)** **- in malignant PT: if margin < 2 mm**	2b	B	++

* Margins related to breast tissue only (but not to skin or to the thoracic wall)

Borderline and Malignant Phyllodes Tumor
- Adjuvant Radiotherapy -

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Adjuvant radiotherapy of the breast and the thoracic wall is aimed at local control.

	Oxford		
	LoE	GR	AGO
■ **BCS, R0-resection** - Borderline PT: no - Malignant PT: yes (independently from the size of the lesion)	2b	B	+
■ **Mastectomy, R0-resection** - Borderline PT: no - Malignant PT: < 5 cm: no - Malignant PT: ≥ 5 cm: with aggressive pathology or growth	2b	B	+
■ **Mastectomy, R1-resection** - Borderline PT: no - Maligner PT: ja (independently from the size of the lesion)	2b	B	+

Borderline and Malignant Phyllodes Tumor
Systemic Adjuvant Therapy

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	Oxford		
	LoE	GR	AGO
Systemic adjuvant therapy (chemo, endocrine)			
Adjuvant endocrine therapy (irrespect. of ER/PR)	5	D	-
Adjuvant chemotherapy	4	C	-
Primary systemic therapy, if complete resection (R0) presumably cannot be achieved (Adriamycin/Ifosfamid)	4	C	+
Adjuvant Treatment of local recurrence			
Radiotherapy, chemotherapy after R1 resection	4	C	+/-
Distant metastasis (very rare)			
Multidisciplinary case discussion („Sarcoma board“)	5	D	++
Treatment like soft tissue sarcomas	4	C	++
Surgical resection of metastatic lesions	4	C	+

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Primary Angiosarcoma of the Breast*
Diagnosis

	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	++

* Therapy in specialized centers recommended

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Sarcomas of the Breast

- **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**

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Primary Angiosarcoma of the Breast

- 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
- Metastasize early, often to the lung and liver

Primary Angiosarcoma of the Breast* Therapy

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	Oxford		
	LoE	GR	AGO
▪ Surgery with wide clear margins, mostly as mastectomy	2b	C	++
▪ Breast-conserving therapy	3a	C	-
▪ SLNE or axillary dissection if cN0	3a	C	--
▪ Adjuvant chemotherapy (anthracycline / taxane-based)	4	C	+/-
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	4	C	+/-

* Therapy in specialized centres recommended

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Secondary Angiosarcoma of the Breast Therapy

	Oxford		
	LoE	GR	AGO
▪ Tumor resection (BCT / mastectomy)	3a	C	+
Radical surgery ist not associated with better outcome			
▪ (Neo-)adjuvant chemotherapy	3a	C	+/-
▪ Consider „trimodality treatment“ in case of locally advanced angiosarcoma (neoadjuvant taxanes => neoadjuvant radiochemotherapy => surgical resektion)	3a	C	+
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	2b	B	+/-
▪ Regional hyperthermia (to improve local control) plus chemotherapy and / or radiotherapy	2b	B	+/-

Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast (RAASB)

38 patients (median age 69 years) with RAASB; median F/U 5,6 y

- **Trimodality therapy** consisted of

(i) taxane induction therapy, followed by
(ii) concurrent taxane and irradiation therapy, followed by
(iii) surgical resection with wide margins.

Results:

- n = 16 trimodal therapy: pCR 12/16.
  Loc.rec.: 0/16; dist.met.: 1/16; death 1/16
  Wound break / sec. wound-healing: 100%
- n = 22 monotherapy/dual therapy:
  Loc.rec.: 10/22; dist.met.: 8/22; death 7/22
  Wound break / sec. wound-healing: 48% ($p < 0.001$)
- **RFS; 93.8% vs. 42.9%; P = 0.004; HR, 7.6 (95% CI: 1.3-44.2)**

Degnim AC, Siontis BL, Ahmed SK et al. Clin Cancer Res. 2023 Aug 1;29(15):2885-2893.

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%**

Angiosarcoma of the Breast
Treatment of Local Recurrence and Metastases

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	Oxford		
	LoE	GR	AGO
Treatment of Local Recurrence:			
▪ R0 resection	4	C	++
▪ Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)	4	C	+/-
Distant Metastases / Unresectable Tumors:			
▪ Treatment like as for soft tissue sarcomas (according to S3 guideline)	4	C	++
▪ Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)	2b	B	+
▪ Antiangiogenic treatment (e.g. in angiosarcoma)	4	C	+/-
If clinically resistant to therapy			
▪ Molecular diagnostics (Multidisciplinary molecular board)	5	D	+

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Metaplastic Breast Carcinoma
- High-Grade -

Consider reference pathology and subtyping.

	Oxford LoE	Oxford GR	AGO
▪ Surgical therapy and axillary staging as in case of NST	4	C	++
▪ Neoadjuvant chemotherapy (frequently chemoresistant)*			
▪ ER pos.	4	C	--
▪ ICPi (Pembrolizumab)-basierte PST (TNBC)	4	C	+/-
▪ HER2 pos. (inkl. Anti-HER2-Therapie)	4	C	+
▪ Adjuvant chemotherapy (frequently chemoresistant)	4	C	-
▪ Consider platin/taxane combination in case of mesenchymal differentiation (e.g. spindle cell)	4	C	+
▪ Adjuvant endocrine therapy if HR-positive	4	C	+
▪ Adjuvant radiotherapy according therapy of NST	4	C	+ +

* Note: control of local response in short intervals

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Metaplastic Breast Carcinoma – Low Grade With Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)*

	Oxford		
	LoE	GR	AGO
▪ Surgical therapy and axillary staging as in case of NST	4	C	++
▪ Adjuvant chemotherapy (frequently chemoresistant)	4	C	-
▪ Neoadjuvant chemotherapy (frequently chemoresistant)	4	C	- -
▪ Adjuvant endocrine therapy (not applicable, since triple-negative tumors)	4	C	-
▪ Adjuvant radiotherapy according therapy of NST	4	C	+

* Reference pathology recommended

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Metaplastic Breast Cancer

Definition: Metaplastic transformation of epithelial tumor cells

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

Clinical and pathological characteristics:

- < 1 % of malignant breast neoplasms
- Similar age group as NST breast cancer
- Localized, mostly palpable
- Rapidly growing, poor response to chemotherapy
- > 90 % triple-negative

Subtypes:

- Highly aggressive with squamous cell or high-grade spindle-cell differentiation
- Less aggressive (low-grade) with mesenchymal, low grade adenosquamous or fibromatosis-like differentiation

Frequent mutations:

- *TP53, EGFR, PIK3CA, PTEN*
- Possible association to *gBRCA1*-mutation/HRD-positivity