

# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Brustkrebs: Spezielle Situationen

### Screened data bases:

Pubmed 2007 - 2024, ASCO 2010 – 2024, SABCS 2010 – 2024, Cochrane Data Base (2024)

### Screened Guidelines:

1. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol 2022;33:1097–1118.
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
3. <https://www.esmo.org/guidelines/breast-cancer>
4. ASCO (American Association of Clinical Oncology, Practice Guidelines) <http://www.asco.org>
5. CMA (Canadian Medical Association): <http://www.cmaj.ca>
6. NCCN (National Comprehensive Cancer Network) vs. 6/2024: <http://www.nccn.org>
7. [https://www.awmf.org/uploads/tx\\_szleitlinien/032-045Olk\\_S3\\_Mammakarzinom\\_2021-07\\_1.pdf](https://www.awmf.org/uploads/tx_szleitlinien/032-045Olk_S3_Mammakarzinom_2021-07_1.pdf)

# Brustkrebs: Spezielle Situationen

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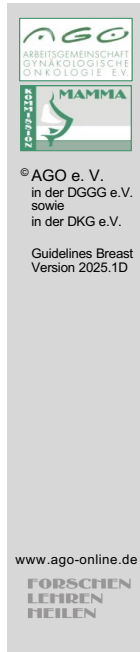
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- **Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP)**
- **Morbus Paget**
- **Maligner und Borderline Phylloides-Tumor**
- **Sarkome, Angiosarkome**
- **Metaplastisches Karzinom**



## Behandlung der älteren Patientin

### AGO ++

- Prinzipiell gilt die Therapieempfehlung wie bei der „jüngeren Patientin“ unter Berücksichtigung unterschiedlicher biologischer, körperlicher, psychologischer wie behandlungsbedingter Faktoren und des geriatrischen Assessment (GA).
- Behandlungsoptionen und -empfehlungen basieren auf Grundlage der Bewertung des körperlichen Zustands, der Anfälligkeit, der Gebrechlichkeit, der Lebenserwartung und der individuellen Ziele der Patientin und nicht nur anhand des Alters.
- Es erfolgt die Integration in einen kooperativen Entscheidungsprozess unter Berücksichtigung der Werte und Ziele der individuellen Patientin.

1. Biganzoli L, et al: Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) .Review Lancet Oncol. 2021 Jul;22(7):e327-e340. doi: 10.1016/S1470-2045(20)30741-5. Epub 2021 May 14.
2. Carmona-Gonzalez Ca, et al: Current approaches to the pharmacological management of metastatic breast cancer in older women. Review. Pages 1785-1794 | Received 22 Apr 2024, Accepted 04 Sep 2024, Published online: 16 Sep 2024
3. Shi J, et al.: Frailty status among the elderly of different genders and the death risk. A follow-up study. Front. Med., 13 August 2021. Sec. Geriatric Medicine Volume 8 - 2021 | <https://doi.org/10.3389/fmed.2021.715659>
4. Lorentsen MK, Vohra S, Muss HB, et al.: Age and competing concerns in treatment selection for women with non-metastatic HR+ and HER2- breast cancer: Current clinical practice. J Geriatr Oncol 2022;13:839–843.
5. Dietz JR, Partridge AH, Gemignani ML, et al. Breast Cancer Management Updates: Young and Older, Pregnant, or Male. Ann Surg Oncol. 2015 Oct;22(10):3219-24.
6. Minami CA, et al: Trends in Locoregional Therapy in Older Women with Early-Stage Hormone Receptor-Positive Breast Cancer by Frailty and Life Expectancy. Ann Surg Oncol 2024 Feb;31(2):920-930. doi: 10.1245/s10434-023-14446-8. Epub 2023 Oct 18.
7. Wyld L, et al: Improving outcomes for women aged 70 years or above with early breast cancer: research programme including a cluster RCT.Programme Grants for Applied Research, No. 10.6. National Institute for Health and Care Research; 2022 Jun.
8. Eochagain CM: Reporting of older subgroups in registration breast cancer trials 2012-2021. Breast Cancer Res Treat. 2023

Dec;202(3):411-421.doi: 10.1007/s10549-023-07081-0. Epub 2023 Sep 4.

Statement: Treatment according to standard

1. Shachar SS, Jolly TA, Jones E et al. Management of Triple-Negative Breast Cancer in Older Patients: How Is It Different? Oncology (Williston Park) 2018;32(2):58-63.
2. Bouchardy C et al., Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol. 2003;21(19):3580-71.
3. Quinten C, Kenis C, Hamaker M et al. The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged  $\geq 70$  with early stage invasive breast cancer. Journal of geriatric oncology 2018;9(2):152-62.
4. Schuil H, Derks M, Liefers GJ et al. Treatment strategies and survival outcomes in older women with breast cancer: A comparative study between the FOCUS cohort and Nottingham cohort. Journal of geriatric oncology 2018;9(6):635-41.
5. Ward SE, Richards PD, Morgan JL, Holmes GR, Broggio JW, Collins K, et al. Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival. Br J Surg 2018;105(11):1454-63.
6. Enger SM: Breast cancer treatment of older women in integrated health care settings. J Clin Oncol. 2006 Sep 20;24(27):4377-83
7. Mustacchi G, Breast cancer in elderly women: a different reality? Results from the NORA study. Ann Oncol. 2007 Jun;18(6):991-6.
8. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg. 2008 Jan;206(1):66-75
9. Luque M et al. Breast cancer management in the elderly. Clin Transl Oncol. 2013 epub

Statement: Surgery similar to „younger“ age

1. Swaminathan V. et al. Choices in Surgery for older women with breast cancer Breast Care 2012;7:445-451
2. Hind D: Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. Br J Cancer 2007 Apr 10;96(7):1025-9.
3. Rudenstam CM Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol. 2006 Jan 20;24(3):337-44.
4. Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol. 2011;18(1):125-33
5. Johnston SJ et al. A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with

invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up. *Ann Oncol* 2012;9:2296-300.

6. Chakrabarti J et al. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up. *Crit Rev Oncol Hematol*. 2011;78(3):260-4.
7. Hills RK, et al (EBCTCG).: Immediate breast surgery versus deferral of any surgery in women aged 70+ years with operable breast cancer: patient-level meta-analysis of the three randomised trials among 1,082 patients. SABCS, 2024
8. Daly GR, et al: Impact of Sentinel Lymph Node Biopsy on Management of Older Women With Clinically Node-Negative, Early-Stage, ER+/HER2-, Invasive Breast Cancer: A Systematic Review and Meta-Analysis. *Clin Breast Cancer* 2024 Dec;24(8):e681-e688.e1. doi: 10.1016/j.clbc.2024.07.012. Epub 2024 Aug 8.
9. Reimer T., et al: Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial. DOI: 10.1056/NEJMoa2412063

#### Statement: Endocrine treatment (endocrine resp.)

1. Rugo HS, Turner NC, Finn RS et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. *Eur J Cancer* 2018;101:123-33.
2. Muss H et al. Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. *J Clin Oncol*. 2008 Apr 20;26(12):1956-64
3. Silliman RA: Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer. *J Clin Oncol*. 2002 Jun 1;20(11):2680-8
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-717

#### Statement: Chemotherapy in pts. < 70 years

1. Loibl S, von Minckwitz G, Harbeck N, et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. *Breast Cancer Res*. 2008 Sep16;10(5):R77
2. Fisher B: Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials. *J Natl Cancer Inst*. 2004 Dec 15;96(24):1823-31.
3. Du XL: Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. *J Gerontol A Biol Sci Med Sci*. 2005 Sep;60(9):1137-44
4. Muss HB et al., Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 2005,

293:1073-81.

5. Hurria A et al., Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat.* 2005 92:151-6.
6. Brunello A et al., Adjuvant chemotherapy for elderly patients (> or =70 years) with early high-risk breast cancer: a retrospective analysis of 260 patients. *Ann Oncol.* 2005 16:1276-82.

#### Statement: Chemotherapy in pts. > 70 years

1. Battisti NML, Glas N de, Soto-Perez-de-Celis E, et al.: Chemotherapy and gene expression profiling in older early luminal breast cancer patients: An International Society of Geriatric Oncology systematic review. *Eur J Cancer* 2022;172:158–170
2. Brain E, Viansone AA, Bourbouloux E, et al. Final results from a phase III randomized clinical trial of adjuvant endocrine therapy ± chemotherapy in women ≥ 70 years old with ER+ HER2- breast cancer and a high genomic grade index: The Unicancer ASTER 70s trial. *JCO.* 2022;40(16\_suppl):500. doi:10.1200/JCO.2022.40.16\_suppl.500.
3. Qin A, Thompson CL, Silverman P. Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. *J Cancer Surviv.* 2015 Jun;9(2):252-9.
4. von Minckwitz G, Reimer T, Potenberg J, et al. The phase III ICE study: Adjuvant Ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. *SABCS 2014 (S3-04).*
5. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients *Breast Care* 2012;7:439-444
6. Muss HB, Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med.* 2009 May 14;360(20):2055-65.
7. Muss HB: CLGB: Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol.* 2007 Aug 20;25(24):3699-704
8. Muss HB: Adjuvant treatment of elderly breast cancer patients. *Breast.* 2007 Nov;16 Suppl 2:159-65
9. Crivellari D et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a "standard chemotherapy regimen": the CASA randomized trial. *Breast.* 2013;22(2):130-7.
10. Tamirisa N, Lin H, Shen Y, et al. Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor-Positive, Node-Positive Breast Cancer. *JAMA Oncol* 2020;6:1548-54.
11. Pu S, et al: Evaluation of outcome of chemotherapy for breast cancer patients older than 70 years: A SEER-based study. 2023 Mar 28:13:992573. doi: 10.3389/fonc.2023.992573. eCollection 2023.

#### Statement: Radiotherapy

1. Kunkler I Radiotherapy issues in elderly breast cancer patients Breast Cancer Patients Breast Care 2012;7:453-459
2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control Strahlenther Onkol 2012 :1-5
3. Giordano SH Radiotherapy in older women with low-risk breast cancer: why did practice not change? 2012 J Clin Oncol 30 (14): 1577-1578
4. Prescott RJ: A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technol Assess. 2007 Aug;11(31):1-149, iii-iv
5. Hughes KS et al: Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382-7
6. Kunkler IH, Williams LJ, Jack WJ, et al: On behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.

Statement: Trastuzumab

1. Freedman RA, Vaz-Luis I, Barry WT, et al. Patterns of chemotherapy, toxicity, and short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. Breast Cancer Res Treat. 2014 Jun;145(2):491-501.
2. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol. 2013 Nov 20;31(33):4222-8
3. Tan-Chiu E: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.J Clin Oncol. 2005 Nov 1;23(31):7811-9
4. Smith I, HERA study team: 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007 Jan 6;369(9555):29-36
5. Adamo V et al. The Risk of Toxicities from Trastuzumab, Alone or in Combination, in an Elderly Breast Cancer Population. Oncology 2013;86(1):16-21.
6. Albanell J et al. Trastuzumab in small tumours and in elderly women. Cancer Treat Rev. 2014;40(1):41-7.
7. Brollo J et al. Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. Cancer Treat Rev. 2013;39(1):44-50
8. Wilbers A, et al: Systemic Therapy in Elderly Patients With Her2/Neu-Positive Breast Cancer: A SEER Database Study.Am Surg. 2023 Dec;89(12):5690-5696. doi: 10.1177/00031348231173993. Epub 2023 May 3.

## Therapie der „gebrechlichen älteren“ Patientin (Lebenserwartung < 5 Jahre, erhebliche Komorbiditäten) frühes Mammakarzinom

Oxford

	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Reduzierte Standardtherapie</b></li> </ul>	<b>2b</b>	<b>C</b>	<b>++</b>
<ul style="list-style-type: none"> <li>▪ <b>Therapieoptionen abgeleitet aus Studien mit älteren Patientinnen:</b> <ul style="list-style-type: none"> <li>▪ Keine Brustoperation hinsichtlich Lebensverlängerung (endokrine Therapie erwägen)</li> <li>▪ Brustoperation zur lokalen Kontrolle</li> <li>▪ Keine Axilla-Op bei cN0</li> <li>▪ Endokrine Therapie (bei HR+)</li> <li>▪ alleinige endokrine Therapie (ohne OP /Radiatio bei ED)</li> <li>▪ Verzicht auf endokrine adj. Therapie bei BEO und Radiotherapie</li> <li>▪ Verzicht Radiotherapie bei pT1, pN0, R0, ER / PR positiv, HER2-negativ, endokrine adj. Therapie</li> <li>▪ Verzicht Radiotherapie bei pT2-3, ER /PR positiv, HER2- negativ, endokrine adj. Therapie</li> </ul> </li> </ul>	2b	C	+
	1a <sup>a</sup>	A	+
	2b	B	+
	1a	A	+
	2b	B	+
	1b	B	+
	1a	B	+
	2b	B	+/-

1. Walzer DE Measuring the value of radiotherapy in older women with breast cancer J Clin Oncol 2012 30 (23) 2809-2811
2. Audisio RA et al When reporting on older patients with cancer , frailty information is needed Ann Surg Oncol 2011; 18: 4-5
3. Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
4. Hughes KS et al Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer 2010 J Clin Oncol 28:69s (suppl 15, abstr 507).

Statement: Reduced standard treatment

Statement: No breast surgery (consider endocrine options)

1. Hind D: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004272.
2. Fentiman IS, et al. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. Eur J Cancer (2003) 39(3):309-16
3. Fentiman IS, et al: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen. Eur J Cancer. 2003 Feb;39(3):300-8-
4. Balakrishnan A et al. Early operable breast cancer in elderly women treated with an aromatase inhibitor letrozole as sole therapy. Br J

Cancer. 2011;105(12):1825-9.

5. Hamaker ME et al. Omission of surgery in elderly patients with early stage breast cancer. Eur J Cancer 2013;49(3):545-52.
6. Wink CJ et al. Hormone treatment without surgery for patients aged 75 years or older with operable breast cancer. Ann Surg Oncol. 2012;19(4):1185-91.

Statement: No axillary clearing ( $\geq 60$  y, cN0, ER+)

1. Rudenstam CM, Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol. 2006 Jan 20;24(3):337-44.
2. Martelli G: A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. Ann Surg. 2005 Jul;242(1):1-6
3. Reimer T., et al: Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial. DOI: 10.1056/NEJMoa2412063
4. Castelo M, et al: The Association Between Surgical Axillary Staging, Adjuvant Treatment Use and Survival in Older Women with Early Stage Breast Cancer: A Population-Based Study. Ann Surg Oncol 2023 Jul;30(7):3901-3912. doi: 10.1245/s10434-023-13274-0. Epub 2023 Mar 14.

Statement: No radiotherapy ( $\geq 70$  y, pT1, pN0, ER+)

1. Kim YJ, Shin KH, Kim K. Omitting Adjuvant Radiotherapy for Hormone ReceptorPositive Early-Stage Breast Cancer in Old Age: A Propensity Score Matched SEER Analysis. Cancer research and treatment : official journal of Korean Cancer Association 2018.
2. Hannoun-Levi JM, et al. Breast cancer in elderly women: is partial breast irradiation a good alternative? Breast Cancer Res Treat. 2003 Oct;81(3):243-51
3. Hughes KS, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):971-
4. Fyles AW: Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70
5. Kunkler IH, Williams LJ, Jack WJ, et al: on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.
6. Stueber TN, Diessner J, Bartmann C, et al. Effect of adjuvant radiotherapy in elderly patients with breast cancer. PLOS ONE 2020;15:e0229518.

Statement: Hypofractionated radiotherapy

1. Vaidya JS, Wenz F, Bulsara M, et al: TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
2. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77.
3. Ortholan C, et al. Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. *Int J Radiat Oncol Biol Phys*. 2005 Jan 1;61(1):154-62.
4. Kirova YM, Campana F, Savignoni A, et al: for the Institut Curie Breast Cancer Study Group Breast-Conserving Treatment in the Elderly: Long-Term Results of Adjuvant Hypofractionated and Normofractionated Radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009 Jan 2
5. Hausmann J, Budach W, et al: Whole Breast Irradiation in Comparison to Endocrine Therapy in Early Stage Breast Cancer—A Direct and Network Meta-Analysis of Published Randomized Trials. *Cancers* 2023, 15, 4343. [https:// doi.org/10.3390/cancers15174343](https://doi.org/10.3390/cancers15174343)

Statement: No chemotherapy > 70 years and negative risk benefit analysis

1. Du XL, Jones DV, Zhang D. Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. *J Gerontol A Biol Sci Med Sci*. 2005 Sep;60(9):1137-44.
2. Kehl KL, Niu J, Chavez-MacGregor M et al. Hospitalization by cytotoxic chemotherapy regimen among older women with stage IV breast cancer. *Cancer* 2018;124(24):4685-91.



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## Geriatric Assessment

Links to current frailty indices:

- **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, mobility and autonomy)
    - Timed-up-and-go-test
    - Frailty Index (FI), Carolina Frailty Index (CFI)



1. Jung C, Bruno RR, Wernly B et al. Frailty as a Prognostic Indicator in Intensive Care. Dtsch Arztebl Int. 2020 Oct 2;117(40):668-673.
2. van Walree IC, Scheepers E, van Huis-Tanja L et al. A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. J Geriatr Oncol. 2019 Nov;10(6):847-858.
3. Williams GR, Deal AM, Sanoff HK et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer. 2019 Jul;27(7):2693-2698.
4. Overcash J. Comprehensive Geriatric Assessment: Interprofessional Team Recommendations for Older Adult Women With Breast Cancer. Clinical journal of oncology nursing 2018;22(3):304-15.
5. van Abbema D, van Vuuren A, van den Berkmoortel F et al. Functional status decline in older patients with breast and colorectal cancer after cancer treatment: A prospective cohort study. J Geriatr Oncol. 2017 May;8(3):176-184.
6. Martinez-Tapia C, Canoui-Poitrine F, Bastuji-Garin S et al. Optimizing the G8 Screening Tool for Older Patients With Cancer: Diagnostic Performance and Validation of a Six-Item Version. Oncologist. 2016 Feb;21(2):188-95.
7. Aaldriks AA, Maartense E, Nortier HJ, et al. Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. Acta Oncol. 2016 Jan;55(1):15-23.
8. Wildes TM et al. Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer. J Geriatr Oncol. 2013;4(3):227-34.
9. Aaldriks AA. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy et al.

Breast 2013;22(5):753-60.

10. Bellera CA et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol.* 2012;23(8):2166-72
11. Hamaker ME, Jonker JM, de Rooij SE et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol.* 2012 Oct;13(10):e437-44.
12. Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13(4):e148-60.
13. Farhat JS, Velanovich V, Falvo AJ et al. Are the frail destined to fail? Frailty index as predictor of surgical morbidity and mortality in the elderly. *J Trauma Acute Care Surg.* 2012 Jun;72(6):1526-30; discussion 1530-1.
14. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006 295:801-08.
15. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev.* 1996 Jan;54(1 Pt 2):S59-65.
16. Charlson et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987 40:373-383.
17. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969 Autumn;9(3):179-86.

## Mammakarzinom des Mannes\*: Diagnostik und lokale Therapie

	Oxford		
	LoE	GR	AGO
▪ <b>Diagnostische Aufarbeitung wie bei Frauen</b>	<b>4</b>	<b>C</b>	<b>+</b>
▪ Ultraschall	2b	B	++
▪ Mammographie	3b	C	+
▪ <b>Standard-Op: Mastektomie</b>	<b>4</b>	<b>C</b>	<b>++**</b>
▪ BEO (Tumor-Brust-Relation!)	4	C	++
▪ Sentinel-Node Biopsie (SLNE)	2a	B	+
▪ Bei Mammakarzinom mit okkultem Primärtumor	2b	B	+
▪ <b>Radiotherapie wie bei Frauen (beachte Tumor-Brust-Relation!)</b>	<b>2a</b>	<b>C</b>	<b>+</b>
▪ <b>Genetische Beratung (siehe Kapitel Genetik)</b>	<b>2b</b>	<b>B</b>	<b>++</b>
▪ <b>Krebsfrüherkennungsuntersuchungen gemäß Empfehlungen der DKG e.V.</b>	<b>GCP</b>		<b>++</b>

\* Behandlung in zertifizierten Brustzentren empfohlen; \*\*Teilnahme an Registerstudie empfohlen

### International registry

1. Cardoso F, Bartlett JMS, Slaets L et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018;29(2):405-17.
2. Doebar SC, Slaets L, Cardoso F et al. Male breast cancer precursor lesions: analysis of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Mod Pathol 2017;30(4):509-18.
3. Vermeulen MA, Slaets L, Cardoso F et al. Pathological characterisation of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Eur J Cancer 2017;82:219-27.

### General

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2. Fentiman IS. Unmet needs of men with breast cancer. Eur J Surg Oncol 2018;44(8):1123-26.
3. Vetto J et al. Accurate and cost-effective evaluation of breast masses in males. Am J Surg 1998 175: 3831.
4. Giordano SH. Breast Cancer in Men. N Engl J Med 2018;378(24):2311-20.
5. Kanakis GA, Jorgensen N, Goulis DG. Breast Cancer in Men. N Engl J Med 2018;379(14):1385.
6. Liu N, Johnson KJ, Ma CX. Male Breast Cancer: An Updated Surveillance, Epidemiology, and End Results Data Analysis. Clin Breast Cancer 2018;18(5):e997-e1002

7. Wang J, Sun Y, Qu J, et al. Survival analysis for male ductal and lobular breast cancer patients with different stages. *Future Oncol* 2018.
8. Gucalp A, Traina TA, Eisner JR, et al. Male breast cancer: a disease distinct from female breast cancer. *Breast Cancer Res Treat* 2018.
9. Wang K, Wang QJ, Xiong YF, et al. Survival Comparisons Between Early Male and Female Breast Cancer Patients. *Scientific reports* 2018;8(1):8900.
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11. Thalib L ,Hall P. Survival of male breast cancer patients: Population-based cohort study. *Cancer Sci.* 2008
12. Dietz JR, Partridge AH, Gemignani ML, et al. Breast Cancer Management Updates: Young and Older, Pregnant, or Male. *Ann Surg Oncol.* 2015 Oct;22(10):3219-24.
13. Deb S, Lakhani SR, Ottini L, et al. The cancer genetics and pathology of male breast cancer. *Histopathology.* 2016 Jan;68(1):110-8.

Statement: Diagnostic work up as in women

Statement: Mammography

1. Chesebro AL, Rives AF, Shaffer K. Male Breast Disease: What the Radiologist Needs to Know. *Current problems in diagnostic radiology* 2018.
2. Dershaw DD. et al. Mammographic findings in men with breast cancer. *Am J Roentgenol* 1993 160: 267
3. Hines SL: The role of mammography in male patients with breast symptoms. *Mayo Clin Proc.* 2007 Mar;82(3):297-300

Statement: Ultrasound

1. Caruso G: High-frequency ultrasound in the study of male breast palpable masses. *Radiol Med (Torino).* 2004 Sep;108(3):185-93

Statement: Standard-surgery: Mastectomy – men

1. Shen. I et al Skin-sparing mastectomy: a survey based approach to defining standard of care. *Am Surg.* 2008 Oct;74(10):902-51.
2. Fentiman IS. Surgical options for male breast cancer. *Breast Cancer Res Treat* 2018;172(3):539-44.
3. Kuo SH et al. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence, *Int J Radiat Oncol Biol Phys.* 2008 Dec 1;72(5):1456-64. Epub 2008 Aug 7

4. Fogh S et al. Therapy for Male Breast Cancer: Functional Advantages With Comparable Outcomes Using Breast Conservation. Clin Breast Cancer. 2013;13(5):344-9.
5. Fields EC et al. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. J Radiat Oncol Biol Phys 2013;87(4):747-52
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8. Wong WG, Perez Holguin RA, Kanwar R, et al. Management of Male Patients With Occult Breast Cancer: Analysis of the National Cancer Database. J Surg Res 2024; 293: 685-692

Statement: Surgery: BEO – men

1. Cloyd JM, Hernandez-Boussard T, Wapnir IL. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983–2009. Ann Surg Oncol. 2013;20(5):1545–50.
2. Bratman SV, Kapp DS, Horst KC. Evolving trends in the initial locoregional management of male breast cancer. Breast. 2012;21(3):296–302. <https://doi.org/10.1016/j.breast.2012.01.008>.
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Statement: Sentinel-node excision (SNE)

1. Flynn LW et al. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg. 2008 Apr;206(4):616-21
2. Boughey JC: Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. J Am Coll Surg. 2006 Oct;203(4):475-80. Epub 2006 Aug 23
3. Parpex G, et al: Accuracy of sentinel lymph node biopsy in male breast cancer: Systematic review and meta-analysis.,Breast. 2024 Mar 5;75:103703. doi: 10.1016/j.breast.2024.103703

Statement: Radiotherapy as in women (consider tumor breast relation!)

1. Eggemann H et al. Male breast cancer: 20-year survival data for post-mastectomy radiotherapy. *Breast Care (Basel)*. 2013;8(4):270-5.
2. Colciago RR, et al: The role of radiation therapy in the multidisciplinary management of male breast cancer: A systematic review and meta-analysis on behalf of the Clinical Oncology Breast Cancer Group (COBCG). *Crit Rev Oncol Hematol*. 2024 Dec;204:104537. doi: 10.1016/j.critrevonc.2024.104537. Epub 2024 Oct 23.

Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer)

1. Pellini F, Granuzzo E, Urbani S et al. Male Breast Cancer: Surgical and Genetic Features and a Multidisciplinary Management Strategy. *Breast Care (Basel)*. 2020 Feb;15(1):14-20.

Statement: Screening for 2nd malignancies according guidelines

1. Wernberg JA. Multiple primary tumors in men with breast cancer diagnoses: a SEER database review. *J Surg Oncol*. 2009 Jan 1;99(1):16-9

Statement: Systemic therapy

1. Doyen J et al., *Ann Oncol*. 2009 Oct 27. Aromatase inhibition in male breast cancer patients: biological and clinical implications.
2. Eggemann H et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat*. 2013;137(2):465-70.
3. Patten DK et al. New Approaches in the Management of Male Breast. *Cancer Clinical Breast Cancer* 2013;13(5) 309–314
4. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. *Br J Cancer*. 2013;108(11):2259-63

Review articles

1. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. *Lancet*. 2006 Feb 18;367(9510):595-604. Review. Erratum in: *Lancet*. 2006 Jun 3;367(9525):1818
2. Agrawal A, Ayantunde AA, Rampaul R et al. Male breast cancer: a review of clinical management. *Breast Cancer Res Treat*. 2006 Oct 11;
3. Korde LA et al: Multidisciplinary meeting on male breast cancer; summary and research recommendations *J Clin Oncol* 28: 2114-2122, 2010

4. Patten DK et al. New Approaches in the Management of Male Breast. *Cancer Clinical Breast Cancer* 2013;13(5) 309–314
5. Sousa B et al. An update on male breast cancer and future directions for research and treatment. *Eur J Pharmacol* 2013;717(1-3)
6. Ruddy KJ et al. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann Oncol* 2013; 24(6):1434-43.

## Mammakarzinom des Mannes: Prognosefaktoren

- Nodalstatus
- Alter
- TumorgroÙe
- ER / PR Expression
- Ki-67 Expression
- Grading
- Genomische Signaturen

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

### Registries

1. Cardoso F, Bartlett JMS, Slaets L et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Ann Oncol* 2018;29(2):405-17.
2. Doebar SC, Slaets L, Cardoso F et al. Male breast cancer precursor lesions: analysis of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Mod Pathol* 2017;30(4):509-18.
3. Vermeulen MA, Slaets L, Cardoso F et al. Pathological characterisation of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Eur J Cancer* 2017;82:219-27.
4. Wang F, Reid S, Zheng W, et al. Sex Disparity Observed for Oncotype DX Breast Recurrence Score in Predicting Mortality Among Patients with Early Stage ER-Positive Breast Cancer. *Clinical Cancer Research* 2020;26:101-9.
5. Massarweh SA, Sledge GW, Miller DP, McCullough D, Petkov VI, Shak S. Molecular Characterization and Mortality From Breast Cancer in Men. *Journal of Clinical Oncology* 2018;36:1396-404.

## Mammakarzinom des Mannes: Systemtherapie

	Oxford		
	LoE	GR	AGO
▪ <b>(Neo-)adjuvante Chemotherapie wie bei Frauen</b>	<b>2a</b>	<b>B</b>	<b>++</b>
▪ <b>HER2 zielgerichtete Therapie (falls HER2 pos.)</b>	<b>5</b>	<b>D</b>	<b>++</b>
▪ <b>Endokrine Therapie bei HR pos.</b>	<b>4</b>	<b>D</b>	<b>++</b>
▪ Tamoxifen	<b>2b</b>	<b>B</b>	<b>++</b>
▪ GnRHa + AI	<b>4</b>	<b>C</b>	<b>+</b>
▪ Aromataseinhibitoren ohne GnRHa	<b>2b</b>	<b>B</b>	<b>-</b>
▪ Fulvestrant (metastasiert)	<b>4</b>	<b>C</b>	<b>+/-</b>
▪ CDK4/6i (in Kombinationstherapie)	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Palliative Chemotherapie wie bei Frauen</b>	<b>4</b>	<b>C</b>	<b>++</b>

### Statement: Adjuvant Chemotherapy

1. Giordano SH, Perkins GH, Broglio K, et al. Adjuvant systemic therapy for male breast cancer. Cancer 2005; 104: 235-264
2. Walshe JM: A prospective study of adjuvant CMF in males with node positive breast cancer: 20-year follow-up. Breast Cancer Res Treat. 2007 Jun;103(2):177-83

### Statement Trastuzumab

1. Carmona-Bayonas A. Potential benefit of maintenance trastuzumab and anastrozole therapy in male advanced breast cancer. Breast. 2007 Jun;16(3):323-5

### Statement CDK4/6i

1. Wedam S, Fashoyin-Aje L, Bloomquist E, et al.:FDA Approval Summary: Palbociclib for Male Patients with Metastatic Breast Cancer. Clin Cancer Res. 2019 Oct 24. doi: 10.1158/1078-0432.CCR-19-2580.

### Statement endocrine therapy

1. Ribeiro G et al. Adjuvant tamoxifen for male breast cancer (MBC). Br J Cancer 1992 65: 252
2. Agrawal: Fulvestrant in advanced male breast cancer. Breast Cancer Res Treat. 2007 Jan;101(1):123. Epub 2006 Jun 29.

3. Zabolotny BP: Successful use of letrozole in male breast cancer: a case report and review of hormonal therapy for male breast cancer. *J Surg Oncol*. 2005 Apr 1; 90(1):26-30
4. Goss PE: Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955–1996. *Cancer* 1999; 85: 629-639
5. Giordano SH: Efficacy of anastrozole in male breast cancer. *Am J Clin Oncol* 2002 25: 235-237
6. Giordano SH: Leuprolide acetate plus aromatase inhibition for male breast cancer. *J Clin Oncol*. 2006 Jul 20;24(21):e42-3. No abstract available.
7. Arriola E: Aromatase inhibitors and male breast cancer. *Clin Transl Oncol*. 2007 Mar;9(3):192-4
8. Eggemann H, Ignatov A, Smith BJ, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat*. 2013 Jan;137(2):465-70.
9. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer *Breast Cancer Res Treat*. 2013;141(1):119-23
10. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. *Br J Cancer*. 2013;108(11):2259-63
11. Eggemann H, Brucker C, Schrauder M, et al. Survival benefit of tamoxifen in male breast cancer: prospective cohort analysis. *British journal of cancer* 2020;123:33-7.
12. Reinisch M, et al. Efficacy of Endocrine Therapy for the Treatment of Breast Cancer in Men: Results from the MALE Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2021 Apr 1;7(4):565-572.

#### Statement palliative chemotherapy

1. Chitapanarux I: Gemcitabine plus cisplatin (GC): a salvage regimen for advanced breast cancer patients who have failed anthracycline and/or taxane therapy. *Gan To Kagaku Ryoho*. 2006 Jun;33(6):761-6

## Inflammatorisches Mammakarzinom (IBC, cT4d)

	Oxford		
	LoE	GR	AGO
▪ Stadium cT4d definiert durch invasive Komponente in der Mamma und klinische Zeichen einer Inflammation (z. B. $\geq 1/3$ der betroffenen Brust)			++
▪ Staging (inkl. adäquate Mamma-Bildgebung)	2c	B	++
▪ Hautbiopsie (mind. 2; Detektionsrate jedoch < 75 %)	2c	B	+
▪ Leitliniengerechte Systemtherapie (neoadjuvant bzw. adjuvant - wie bei non-IBC)	2b	B	++
▪ Neoadjuvante Chemotherapie	2b	B	++
▪ Mastektomie nach Chemotherapie	2c	B	+
▪ Brusterhaltende Therapie im Fall von pCR (Individualfall)	2b	C	+/-
▪ Spätrekonstruktion (zweizeitig)	3b	C	+
▪ Sentinel-Node-Biopsie	3b	C	-
▪ Postoperative Radiotherapie der Brustwand inklusive Lymphabflußwege unabhängig vom Therapieansprechen	2c	B	++

### Guidelines:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 6.2024 NCCN.org (Inflammatory Breast Cancer. IBC-1)

### General

1. Ueno NT, Espinosa Fernandez JR, Cristofanilli M et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. Journal of Cancer 2018;9(8):1437-47.1
2. Audisio RA. Inflammatory Breast Cancer: Updates on diagnosis and treatment options. Eur J Surg Oncol 2018;44(8):1127.
3. Copson E, Shaaban AM, Maishman T et al. The presentation, management and outcome of inflammatory breast cancer cases in the UK: Data from a multi-centre retrospective review. Breast 2018;42:133-41.
4. Romanoff A, Zabor EC, Petruolo O et al. Does nonmetastatic inflammatory breast cancer have a worse prognosis than other nonmetastatic T4 cancers? Cancer 2018;124(22):4314-21.
5. Wu SG, Zhang WW, Wang J et al. Inflammatory breast cancer outcomes by breast cancer subtype: a population-based study. Future Oncol 2018.
6. Boudin L, Goncalves A, Sfumato P et al. Prognostic impact of hormone receptor- and HER2-defined subtypes in inflammatory breast

- cancer treated with high-dose chemotherapy: a retrospective study. *Journal of Cancer* 2016;7(14):2077-84.
- Costa R, Santa-Maria CA, Rossi G et al. Developmental therapeutics for inflammatory breast cancer: Biology and translational directions. *Oncotarget* 2017;8(7):12417-32.
  - van Uden DJ, Bretveld R, Siesling S et al. Inflammatory breast cancer in the Netherlands; improved survival over the last decades. *Breast Cancer Res Treat* 2017;162(2):365-74.

In case of invasive BC and clinical signs of inflammation (e.g.  $\geq 1/3$  of the breast affected) determine stage cT4d

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 6.2024 NCCN.org (Inflammatory Breast Cancer. IBC-1)

Survival benefit by trimodal treatment (NACT, MRM, RT)

- Rueth NM, Lin HY, Bedrosian I, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J Clin Oncol* 2014; 32: 2018–24.

Statement: Staging

- Ueno NT, Espinosa Fernandez JR, Cristofanilli M et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. *Journal of Cancer* 2018;9(8):1437-47.

Statement: Regimens as in non-inflammatory BC

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 6.2024 NCCN.org (Inflammatory Breast Cancer. IBC-1)

Statement: Neoadjuvant chemotherapy

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 6.2024 NCCN.org (Inflammatory Breast Cancer. IBC-1)
- Ueno NT, Espinosa Fernandez JR, Cristofanilli M et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. *Journal of Cancer* 2018;9(8):1437-47.

3. Rueth NM, Lin HY, Bedrosian I, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J Clin Oncol* 2014; 32: 2018–24.

Statement: Mastectomy after chemotherapy

1. Chen H, Wu K, Wang M, et al: A standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: A large population-based study in the Surveillance, Epidemiology, and End results database 18. *Breast*. 2017 Oct;35:48-54.
2. Tsai CJ et al. Outcomes after multidisciplinary treatment of inflammatory breast cancer in the era of neoadjuvant HER2-directed therapy. *Am J Clin Oncol* 2013 [Epub ahead of print].
3. Adesoye T, Lucci A. Current Surgical Management of Inflammatory Breast Cancer. *Ann Surg Oncol*. 2021 Oct;28(10):5461-5467. doi: 10.1245/s10434-021-10522-z. Epub 2021 Aug 3. PMID: 34346020.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 6.2024 NCCN.org (Inflammatory Breast Cancer. IBC-1)

Statement: Immediate breast reconstruction:

1. Nakhlis F, Regan MM, Chun YS, et al. Patterns of breast reconstruction in patients diagnosed with inflammatory breast cancer: The Dana-Farber Cancer Institute’s Inflammatory Breast Cancer Program experience. *Breast J* 2020;26(3):384–90.
2. Adesoye T, Lucci A. Current Surgical Management of Inflammatory Breast Cancer. *Ann Surg Oncol*. 2021 Oct;28(10):5461-5467.

Statement: Sentinel lymph node

1. Adesoye T, Lucci A. Current Surgical Management of Inflammatory Breast Cancer. *Ann Surg Oncol*. 2021 Oct;28(10):5461-5467. doi: 10.1245/s10434-021-10522-z..

Statement: Radiotherapy

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 6.2024 NCCN.org (Inflammatory Breast Cancer. IBC-1)

## Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP) Bildgebende Diagnostik

	Oxford		
	LoE	GR	AGO
▪ <b>Mammadiagnostik inkl. Mamma-MRT</b>	<b>3</b>	<b>B</b>	<b>++</b>
▪ <b>Ausschluss eines kontralateralen Tumors</b>	<b>3</b>	<b>B</b>	<b>++</b>
▪ <b>Staging</b> (CT-Thorax, CT-Abdomen/Becken, Skelettszintigramm)	<b>3</b>	<b>B</b>	<b>++</b>
<b>Falls Histologie nicht eindeutig:</b>			
▪ <b>Ausschluss eines anderen Primarius</b> (v. a. NEC, weibl. Genitaltrakt, Lunge, Schilddrüse, Magen, Haut, HNO)	<b>5</b>	<b>D</b>	<b>++</b>
▪ <b>PET / PET-CT</b>	<b>3b</b>	<b>B</b>	<b>+</b>

### Statement: Mammography / Breast ultrasound/ Breast MRI

1. Schneeweiss, A. & Buschhorn, L. „Breast-like cancer of unknown primary“. Implikationen für die radiologische Diagnostik. Die Radiol. 63, 366–370 (2023)
2. Fehm, T., & Souchon, R. (2013). Axillary lymph node metastasis in CUP. Der Onkologe, 19(1), 40–43. <http://doi.org/10.1007/s00761-012-2314-y>
3. Foroudi, F., & Tiver, K. W. (2000). Occult breast carcinoma presenting as axillary metastases. International Journal of Radiation Oncology, Biology, Physics, 47(1), 143–147. <http://doi.org/10.1007/s10147-005-0485-x>
4. Ofri A, Moore K. Occult breast cancer: Where are we at? Breast. 2020 Dec;54:211-215. doi: 10.1016/j.breast.2020.10.012. Epub 2020 Oct 27.
5. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (Version3.2024).

### Statement: Staging


1. Steunebrink: Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. Breast. 2005 Apr;14(2):165-8
2. Jerusalem, G., Rorive, A., Ancion, G. et al. (2006). Diagnostic and therapeutic management of carcinoma of unknown primary:

radio-imaging investigations. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 17 Suppl 10(suppl\_10), x168–76. <http://doi.org/10.1093/annonc/mdl255>

3. Hemminki, K., Bevier, M., Sundquist, J., et al. (2013). Site-specific cancer deaths in cancer of unknown primary diagnosed with lymph node metastasis may reveal hidden primaries. *International Journal of Cancer Journal International Du Cancer*, 132(4), 944–950. <http://doi.org/10.1002/ijc.27678>

#### Statement: PET

1. Jerusalem, G., Rorive, A., Ancion, G., et al. (2006). Diagnostic and therapeutic management of carcinoma of unknown primary: radio-imaging investigations. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 17 Suppl 10(suppl\_10), x168–76. <http://doi.org/10.1093/annonc/mdl255>
2. Kwee, T. C., & Kwee, R. M. (2009). Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. *European Radiology*, 19(3), 731–744. <http://doi.org/10.1007/s00330-008-1194-4>
3. Varadhachary, G. R., Abbruzzese, J. L., & Lenzi, R. (2004). Diagnostic strategies for unknown primary cancer. *Cancer*, 100(9), 1776–1785. <http://doi.org/10.1002/cncr.20202>
4. Pelosi, E., Pennone, M., Deandreis, D., et al. (2006). Role of whole body positron emission tomography/computed tomography scan with 18F-fluorodeoxyglucose in patients with biopsy proven tumor metastases from unknown primary site. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*: 50(1), 15–22.



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

- **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 or better compared to breast cancer with similar tumor biology and tumor stage**

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### Guidelines

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (3.2024). Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) .
2. Krämer A. et al. Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆. Ann Oncol 34, 228–246 (2023).
3. NICE (2010). Metastatic malignant disease of unknown primary origin in adults: diagnosis and management. Retrieved January Dec 26th, 2018, <https://www.nice.org.uk/guidance/cg104/resources/metastatic-malignant-disease-of-unknown-primary-origin-diagnosis-and-management-of-metastatic-malignant-disease-of-unknown-primary-origin-35109328970437>

### Reviews

1. Khoury, T., Mendez, A. L. R., Peng, X., Yan, L. & Racila, E. Clinicopathologic characteristics of malignant non-hematopoietic tumors first presented as an axillary mass with emphasis on occult breast carcinoma. International Journal of Clinical Oncology 25, 292–300 (2020).
2. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast Cancer Research and Treatment, 119(1), 1–11.
3. Lanitis, S., Behranwala, K. A., Al-Mufti, R., et al.(2009). Axillary metastatic disease as presentation of occult or contralateral breast

- cancer. *Breast (Edinburgh, Scotland)*, 18(4), 225–227. <http://doi.org/10.1016/j.breast.2009.07.002>
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## Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP) Pathologie, Molekularpathologie

	Oxford		
	LoE	GR	AGO
▪ Immunhistologie: ER, PR, HER2, Ki-67, GATA3	5	D	++
▪ Immunhistochemie (z. B. Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, Synaptophysin u.a.) zum Ausschluss anderer Primärtumoren bei TNBC oder ungewöhnlicher Histologie, z.B. neuroendokrine Ca, weibl. Genitaltrakt, Lunge, Kopf-Hals-Tumoren, Schilddrüse, Magen, Haut	5	D	++
▪ Genexpressionsprofile zur Bestimmung des Primarius (z. B. CUPprint, Pathwork, TOT, CancerTYPE)	2c	B	+/-
▪ NGS, Epigenetik zur Bestimmung des Primarius (Panel-Sequenzierung, z. B. EPICup)	2c	B	+/-
▪ Prognostische Genexpressionstests	5	D	--

### Immunohistochemistry

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primary: clinical presentation, immunohistochemistry, and molecular analysis. *Case Reports in Oncology*, 5(1), 9–16.  
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9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Occult Primary (Cancer of Unknown Primary [CUP]), Version 2.2025 — September 11, 2024, NCCN.org

#### Gene expression profiling and other molecular approaches in CUP disease

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3. Horlings, H. M., van Laar, R. K., Kerst, J.-M., et al. (2008). Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 26(27), 4435–4441. <http://doi.org/10.1200/JCO.2007.14.6969>
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## Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP) Therapie

	Oxford		
	LoE	GR	AGO
▪ Axilladissektion	3a	C	++
▪ Targeted axillary dissection nach NACT (bei klinischer Komplettremission)	3b	C	+/-
▪ Bestrahlung der regionären LK	3b	B	+
▪ Brust-Bestrahlung bei negativem Mamma-MRT (wie BET)	2c	B	+
▪ Mastektomie bei unauffälligem MRT	3a	C	--
▪ Leitliniengerechte (neo-)adjuvante Systemtherapie	5	D	++

### Guidelines

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (Version3.2024).
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### Reviews

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2. Ofri A, Moore K. Occult breast cancer: Where are we at? Breast. 2020 Dec;54:211-215. doi: 10.1016/j.breast.2020.10.012. Epub 2020 Oct 27.

### Statement: Axillary dissection

1. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast Cancer Research and Treatment, 119(1), 1–11. <http://doi.org/10.1007/s10549-009-0554-3>

2. Schmidt, T., & Ulrich, A. (2014). [Surgical options in cancer of unknown primary (CUP)]. *Der Radiologe*, 54(2), 140–144. <http://doi.org/10.1007/s00117-013-2549-7>
3. Botty Van den Bruele A, Lavery J, Plitas G, Pilewskie ML. Axillary Downstaging in Occult Primary Breast Cancer After Neoadjuvant Chemotherapy. *Ann Surg Oncol*. 2021 Feb;28(2):968-974. doi: 10.1245/s10434-020-08863-2. Epub 2020 Aug 19.

#### Statement TALD + RT nach NACT

1. Cohen BL, Collier AL, Kelly KN et al. Surgical Management of the Axilla in Patients with Occult Breast Cancer (cT0 N+) After Neoadjuvant Chemotherapy. *Ann Surg Oncol*. 2020 Jun;27(6):1830-1841.

#### Statement: Mastectomy without (in-)breast tumor

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2. Ofri A, Moore K. Occult breast cancer: Where are we at? *Breast*. 2020 Dec;54:211-215. doi: 10.1016/j.breast.2020.10.012. Epub 2020 Oct 27. PMID: 33130487; PMCID: PMC7599122.
3. 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.
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7. Pavlidis, N., Briasoulis, E., Hainsworth et al. (2003). Diagnostic and therapeutic management of cancer of an unknown primary. *European Journal of Cancer (Oxford, England : 1990)*, 39(14), 1990–2005.



#### Statement: Breast irradiation if breast MRI is negative

1. 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.

2. 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.
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Statement: Systemic treatment according N+ tumor


1. Pavlidis, N., Briasoulis, E., Hainsworth J. et al. (2003). Diagnostic and therapeutic management of cancer of an unknown primary. *European Journal of Cancer (Oxford, England : 1990)*, 39(14), 1990–2005. [http://doi.org/10.1016/S0959-8049\(03\)00547-1](http://doi.org/10.1016/S0959-8049(03)00547-1)
2. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. *Breast Cancer Research and Treatment*, 119(1), 1–11. <http://doi.org/10.1007/s10549-009-0554-3>
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## „BCT“ in Patients with Axillary Met’s and Occult Primary (AxCUP, OBC)

**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.

1. 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.
2. Tsai, C., Zhao, B., Chan, T. & Blair, S. L. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am. J. Surg. 220, 153–160 (2020).

# Morbus Paget der Mamille (MPD) Diagnostik

## „Mammary Paget Disease is a Sentinel Sign“

	Oxford		
	LoE	GR	AGO
▪ <b>Bioptische histologische Sicherung*</b>			++
▪ <b>Mammographie, Mammasonographie</b>	4	D	++
▪ <b>Mamma-MR (falls andere Bildgebung nicht aussagekräftig)</b>	4	C	+
▪ <b>Immunhistologie (ER, PR, HER2, CK7) zur Abgrenzung benignen und HER2-negativer Befunde</b>	5	D	++

\* unter Mitnahme aller Hautschichten (z. B. Punchbiopsie oder Keilexzision)

### General recommendations / Guidelines:


1. Mariano L, Nicosia L, Pupo D et al. A Pictorial Exploration of Mammary Paget Disease: Insights and Perspectives. Cancers (Basel). 2023 Nov 3;15(21):5276.
2. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Paget Disease (PAGET-1)

### Imaging

1. Mariano L, Nicosia L, Pupo D et al. A Pictorial Exploration of Mammary Paget Disease: Insights and Perspectives. Cancers (Basel). 2023 Nov 3;15(21):5276.
2. Morrogh, M., Morris, E. A., Liberman, L. et al. (2008). MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. Journal of the American College of Surgeons, 206(2), 316–321. <http://doi.org/10.1016/j.jamcollsurg.2007.07.046>
3. Capobianco, G., Spaliviero, B., Dessole, S., et al. (2006). Paget's disease of the nipple diagnosed by MRI. Archives of Gynecology and Obstetrics, 274(5), 316–318. <http://doi.org/10.1007/s00404-006-0160-0>
4. Moon, J. Y., Chang, Y.-W., Lee, E. H., et al. (2013). Malignant invasion of the nipple-areolar complex of the breast: usefulness of breast MRI. American Journal of Roentgenology, 201(2), 448–455. <http://doi.org/10.2214/AJR.12.9186>
5. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Paget Disease (PAGET-1)

## Pathology

1. Sandoval-Leon, A. C., Drews-Elger, K., Gomez-Fernandez, C. R., et al. (2013). Paget's disease of the nipple. *Breast Cancer Research and Treatment*, 141(1), 1–12. <http://doi.org/10.1007/s10549-013-2661-4>
2. Saeed, D., & Shousha, S. (2014). Toker cells of the nipple are commonly associated with underlying sebaceous glands but not with lactiferous ducts. *Journal of Clinical Pathology*, 67(11), 1010–1012. <http://doi.org/10.1136/jclinpath-2014-202280>
3. Sek, P., Zawrocki, A., Biernat, W., et al(2010). HER2 molecular subtype is a dominant subtype of mammary Paget's cells. An immunohistochemical study. *Histopathology*, 57(4), 564–571. <http://doi.org/10.1111/j.1365-2559.2010.03665.x>



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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

### Review

1. Streng A, Gutjahr E, Aulmann S, et al. Pathologie der Mamillenregion : I. Morbus Paget der Mamille, Varianten und Differenzialdiagnosen. *Der Pathologe*. 2020;29(4):14-399. doi:10.1007/s00292-020-00772-

### Clinical Presentation

1. Dalberg, K., Hellborg, H., & Wärnberg, F. (2008). Paget's disease of the nipple in a population based cohort. *Breast Cancer Research and Treatment*, 111(2), 313–319. <http://doi.org/10.1007/s10549-007-9783-5>
2. Onoe, S., Kinoshita, T., Tamura, N. et al. (2011). Feasibility of breast conserving surgery for Paget's disease. *Breast (Edinburgh, Scotland)*, 20(6), 515–518. <http://doi.org/10.1016/j.breast.2011.05.010>
3. Siponen, E., Hukkinen, K., Heikkilä, P., et al. (2010). Surgical treatment in Paget's disease of the breast. *American Journal of Surgery*, 200(2), 241–246. <http://doi.org/10.1016/j.amjsurg.2009.07.044>

### Pathology and Immunohistochemistry

1. Lester, T., Wang, J., Bourne, P., et al. (2009). Different panels of markers should be used to predict mammary Paget's disease associated with in situ or invasive ductal carcinoma of the breast. *Annals of Clinical and Laboratory Science*, 39(1), 17–24.
2. Liegl, B., Horn, L.-C., & Moinfar, F. (2005). Androgen receptors are frequently expressed in mammary and extramammary Paget's

disease. *Modern Pathology*, 18(10), 1283–1288. <http://doi.org/10.1038/modpathol.3800437>

3. Sanders, M. A., Dominici, L., Denison, C., et al. (2013). Paget disease of the breast with invasion from nipple skin into the dermis: an unusual type of skin invasion not associated with an adverse outcome. *Archives of Pathology & Laboratory Medicine*, 137(1), 72–76. <http://doi.org/10.5858/arpa.2011-0611-OA>

## Morbus Paget der Mamille Therapie

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Morbus Paget mit Mamma-Tumor (invasives MaCa, DCIS)</b> <ul style="list-style-type: none"> <li>▪ Therapie entsprechend Standards der Grunderkrankung</li> <li>▪ Operation mit R0 Resektion</li> </ul> </li> <li>▪ <b>Isolierter Morbus Paget des NAC:</b> <ul style="list-style-type: none"> <li>▪ R0-Resektion inkl. NAC</li> <li>▪ keine adjuvante Bestrahlung bei R0</li> <li>▪ Sentinel-Lymphknoten-Exzision (SLNE) bei BEO</li> <li>▪ Sentinel-Lymphknoten-Exzision (SLNE) bei Mastektomie</li> </ul> </li> </ul>			
	5	D	++
	1c	B	++
	1c	B	++
	4	D	++
	2b	B	--
	2b	B	+

### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Paget Disease (PAGET-1)

### Surgical Treatment of Paget's disease associated with breast tumor (invasive carcinoma or DCIS)

1. Lin C-W, Chiang M-H, Tam K-W: Treatment of Mammary Paget Disease: A systematic review and meta-analysis of real-world data. Int J Surg 2022;107:106964.
2. Markarian S, Holmes DR: Mammary Paget's Disease: An Update. Cancers (Basel) 2022;14
3. Bijker, N., Rutgers, E. J., Duchateau, L., EORTC Breast Cancer Cooperative Group et al. (2001). Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer, 91(3), 472–477.
4. Dominici, L. S., Lester, S. C., Liao, G.-S., et al. (2012). Current surgical approach to Paget's disease. American Journal of Surgery, 204(1), 18–22. <http://doi.org/10.1016/j.amjsurg.2011.07.01>

### Treatment of isolated Paget's disease

1. Durkan, B., Bresee, C., Bose, S. et al. (2013). Paget's disease of the nipple with parenchymal ductal carcinoma in situ is associated

with worse prognosis than Paget's disease alone. *The American Surgeon*, 79(10), 1009–1012.

2. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Paget Disease (PAGET-1)

Statement: Sentinel-node excision (SNE)

1. Bijker, N., Rutgers, E. J., Duchateau, L EORTC Breast Cancer Cooperative Group et al. (2001). Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer*, 91(3), 472–477.
2. Laronga, C., Hasson, D., Hoover, S., et al. (2006). Paget's disease in the era of sentinel lymph node biopsy. *American Journal of Surgery*, 192(4), 481–483. <http://doi.org/10.1016/j.amjsurg.2006.06.023>
3. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Paget Disease (PAGET-1)

## Borderline und maligner Phylloides tumor - Diagnostik -

	Oxford		
	LoE	GR	AGO
▪ Mammographie / Mamma-Ultraschall (MG / MS)	3	C	++
▪ Stanzbiopsische Diagnostik, Dignitätsbeurteilung am Resektat	3	C	++
▪ Mamma-MRT	3	C	+/-
▪ Staging nur beim malignen PT (CT-Thorax / Abdomen, Skelettszintigramm)	5	D	++

### Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Phyllodes tumor (PHYLL-1)

### Review

1. Ofri, A. et al. Diagnosis and management of phyllodes tumours for the surgeon: An algorithm. *Surg. 20*, e355–e365 (2022).

### Imaging

1. Plaza, M. J., Swintelski, C., Yaziji, H., et al. (2015). Phyllodes tumor: review of key imaging characteristics. *Breast Disease*, 35(2), 79–86. <http://doi.org/10.3233/BD-150399>
2. Kamitani, T., Matsuo, Y., Yabuuchi, H., et al. (2014). Differentiation between benign phyllodes tumors and fibroadenomas of the breast on MR imaging. *European Journal of Radiology*, 83(8), 1344–1349. <http://doi.org/10.1016/j.ejrad.2014.04.031>

### Core biopsy

1. Abdulcadir, D., Nori, J., Meattini, I., et al. (2014). Phyllodes tumours of the breast diagnosed as B3 category on image-guided 14-gauge core biopsy: analysis of 51 cases from a single institution and review of the literature. *European Journal of Surgical Oncology* 40(7),

859–864. <http://doi.org/10.1016/j.ejso.2014.02.222>

2. Jung, H. K., Moon, H. J., Kim, M. J., et al. (2014). Benign core biopsy of probably benign breast lesions 2 cm or larger: correlation with excisional biopsy and long-term follow-up. *Ultrasonography (Seoul, Korea)*, 33(3), 200–205. <http://doi.org/10.14366/usg.14011>



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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**


### Review

1. Tan, B. Y., Acs, G., Apple, S. K et al. (2016). Phyllodes tumours of the breast: a consensus review. *Histopathology*, 68(1), 5–21. <http://doi.org/10.1111/his.12876>

### Pathology and Outcome

1. Tan, P. H., Thike, A. A., Tan, W. J., et al. (2012). Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *Journal of Clinical Pathology*, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>
2. Chao X, Chen K, Zeng J, et al.: Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer*. 2019 Apr 23;19(1):372. doi: 10.1186/s12885-019-5585-5
3. Choi N, Kim K, Shin KH, et al.: The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and Borderline Phyllodes Tumors of the Breast (KROG 16-08). *Clin Breast Cancer*. 2019 Oct;19(5):345-353.e2. doi: 10.1016/j.clbc.2019.04.003.
4. Lu Y, Chen Y, Zhu L, et al.: Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019 May;26(5):1263-1275. doi: 10.1245/s10434-018-07134-5
5. Spanheimer PM, Murray MP, Zabor EC, et al.: Long-Term Outcomes After Surgical Treatment of Malignant/ Borderline Phyllodes

Tumors of the Breast. *Ann Surg Oncol* (2019) 26:2136–2143 <https://doi.org/10.1245/s10434-019-07210-4>



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## Phyllodes Tumor

■ **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>

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

### Review

1. Tan, B. Y., Acs, G., Apple, S. K et al. (2016). Phyllodes tumours of the breast: a consensus review. *Histopathology*, 68(1), 5–21. <http://doi.org/10.1111/his.12876>

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- Spanheimer PM, Murray MP, Zabor EC, et al.: Long-Term Outcomes After Surgical Treatment of Malignant/ Borderline Phyllodes Tumors of the Breast. *Ann Surg Oncol* (2019) 26:2136–2143 <https://doi.org/10.1245/s10434-019-07210-4>

## Borderline und maligner Phylloides tumor - Operative Therapie -

	Oxford		
	LoE	GR	AGO
▪ <b>Fibroepitheliale Läsionen, mit einer Größe von &gt; 3 cm oder schnellem Wachstum sollen (unabhängig vom Befund der Stanzbiopsie) exzidiert werden</b>	5	D	++
▪ <b>Bei unklarem oder auf PT verdächtigem Befund der Stanzbiopsie, soll eine Exzision mit läsionsfreien Rändern durchgeführt werden</b>	5	D	++
▪ <b>SLNE / Axilladissektion (wenn klinisch unauffällig)</b>	4	C	--
▪ <b>Therapie des Lokalrezidivs</b>			
▪ <b>R0-Resektion oder einfache Mastektomie</b>	4	C	++

### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Phyllodes Tumor (Phyll-1)
2. Bogach J, Sriskandarajah A, Wright FC, et al.; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
3. Louie AD, Rosenberger LH. Phyllodes Tumors of the Breast: Addressing the Gaps in Consensus Recommendations for Clinical Management. Ann Surg Oncol. 2023 Oct;30(11):6296-6298.
4. Goodwin B, Oyinlola AF, Palhang M et al.. Metastatic and Malignant Phyllodes Tumors of the Breast: An Update for Current Management. Am Surg. 2023 Aug 23:31348231198114.
5. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. Cancers (Basel). 2023 Aug 2;15(15):3933.
6. Sars C, Sackey H, Frisell J et al. Current clinical practice in the management of phyllodes tumors of the breast: an international cross-sectional study among surgeons and oncologists. Breast Cancer Res Treat. 2023 Jun;199(2):293-304.
7. Papas Y, Asmar AE, Ghandour F, Hajj I. Malignant phyllodes tumors of the breast: A comprehensive literature review. Breast J. 2020 Feb;26(2):240-244.
8. Lerwill, M. F., Lee, A. H. S. & Tan, P. H. Fibroepithelial tumours of the breast—a review. Virchows Arch. 480, 45–63 (2022).

#### Surgical margins: Observational study:

1. Ranjbar A, Zangouri V, Shokripour M. Margin status impact on recurrence of phyllodes tumors in high-risk groups: a retrospective observational study. *BMC Cancer*. 2024 Jan 9;24(1):48.

#### Surgical margins: Systematic review

1. Bogach J, Sriskandarajah A, Wright FC, et al. ; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. *Ann Surg Oncol*. 2023 Oct;30(11):6386-6397.
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#### Operative management and prognosis of Phyllodes Tumors



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2. Macdonald, O. K., Lee, C. M., Tward, J. D., et al. (2006). Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. *Cancer*, 107(9), 2127–2133. <http://doi.org/10.1002/cncr.22228>
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5. Spanheimer PM, Murray MP, Zabor EC, et al.: Long-Term Outcomes After Surgical Treatment of Malignant/ Borderline Phyllodes Tumors of the Breast. *Ann Surg Oncol* (2019) 26:2136–2143 <https://doi.org/10.1245/s10434-019-07210-4>

Statement: SNE / Axillary dissection in cN0

1. Mishra, S. P., Tiwary, S. K., Mishra, M., et al. (2013). Phyllodes tumor of breast: a review article. *ISRN Surgery*, 2013(3), 361469–10. <http://doi.org/10.1155/2013/361469>
2. Kim, Y.-J., & Kim, K. (2017). Radiation therapy for malignant phyllodes tumor of the breast: An analysis of SEER data. *Breast (Edinburgh, Scotland)*, 32, 26–32. <http://doi.org/10.1016/j.breast.2016.12.006>

Statement: Staging

1. Tan, B. Y., Acs, G., Apple, S. K., et al. (2016). Phyllodes tumours of the breast: a consensus review. *Histopathology*, 68(1), 5–21. <http://doi.org/10.1111/his.12876>
2. Belkacémi, Y., Bousquet, G., Marsiglia, H., et al. (2008). Phyllodes tumor of the breast. *International Journal of Radiation Oncology, Biology, Physics*, 70(2), 492–500. <http://doi.org/10.1016/j.ijrobp.2007.06.059>

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## 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 statements 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.*

1. Bogach J, Sriskandarajah A, Wright FC, et al.; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.

## Borderline und maligner Phylloides tumor - Sicherheitsabstand -

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Anzustrebender operativer Randsaum*</b> <ul style="list-style-type: none"> <li>- Borderline PT: <math>\geq 2</math> mm</li> <li>- Maligner PT: <math>\geq 10</math> mm</li> </ul> </li> </ul>	<b>2b</b>	<b>B</b>	<b>++</b>
<ul style="list-style-type: none"> <li>■ <b>Minimaler pathologischer Randsaum*</b> <ul style="list-style-type: none"> <li>- Borderline PT: negativ (no ink on tumor)</li> <li>- Maligner PT: <math>\geq 2</math> mm</li> </ul> </li> </ul>	<b>2b</b>	<b>B</b>	<b>++</b>
<ul style="list-style-type: none"> <li>■ <b>Nachresektion empfohlen</b> <ul style="list-style-type: none"> <li>- Borderline PT: Rand* positiv (ink on tumor)</li> <li>- Maligner PT: <math>&lt; 2</math> mm</li> </ul> </li> </ul>	<b>2b</b>	<b>B</b>	<b>++</b>

\* Randsaum nur bezogen auf Brustgewebe (nicht auf Haut bzw. Brustwand)

### General recommendations / Guidelines:

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2. Bogach J, Sriskandarajah A, Wright FC, et al. Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
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3. Mishra, S. P., Tiwary, S. K., Mishra, M., et al. (2013). Phyllodes tumor of breast: a review article. *ISRN Surgery*, 2013(3), 361469–10. <http://doi.org/10.1155/2013/361469>
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#### Statement: SNE / Axillary dissection in cN0

1. Mishra, S. P., Tiwary, S. K., Mishra, M., et al. (2013). Phyllodes tumor of breast: a review article. *ISRN Surgery*, 2013(3), 361469–10. <http://doi.org/10.1155/2013/361469>

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Statement: Staging

1. Tan, B. Y., Acs, G., Apple, S. K., et al. (2016). Phyllodes tumours of the breast: a consensus review. *Histopathology*, 68(1), 5–21. <http://doi.org/10.1111/his.12876>
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## Borderline und maligner Phylloides tumor - Adjuvante Radiotherapie -

### Adjuvante Radiotherapie der Brust / Brustwand mit dem Therapieziel der lokalen Kontrolle

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>BEO, R0-Resektion</b></li> <li>- Borderline PT: nein</li> <li>- Maligner PT: ja (unabhängig von der Größe der Läsion)</li> </ul>	<b>2b</b>	<b>B</b>	<b>+</b>
<ul style="list-style-type: none"> <li>▪ <b>Mastektomie, R0-Resektion</b></li> <li>- Borderline PT: nein</li> <li>- Maligner PT: &lt; 5 cm: nein</li> <li>- Maligner PT: ≥ 5 cm: wenn besonders aggressiver Tu</li> </ul>	<b>2b</b>	<b>B</b>	<b>+</b>
<ul style="list-style-type: none"> <li>▪ <b>Mastektomie, R1-Resektion</b></li> <li>- Borderline PT: nein</li> <li>- Maligner PT: ja (unabhängig von der Größe der Läsion)</li> </ul>	<b>2b</b>	<b>B</b>	<b>+</b>

### General recommendations / Guidelines:

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### Surgical margins: Systematic review

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2. Thind A, Patel B, Thind K, et al. Surgical margins for borderline and malignant phyllodes tumours. *Ann R Coll Surg Engl*. 2020;102(3):165-173. doi:10.1308/rcsann.2019.0140.
3. Lu Y, Chen Y, Zhu L, et al. Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019;90:342–13. doi:10.1245/s10434-018-07134-5.
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## Borderline und maligner Phylloides tumor - Systemische adjuvante Therapie -

	Oxford		
	LoE	GR	AGO
• <b>Systemische Therapie (Chemotherapie, endokrine Th.)</b>			
▪ Adjuvante endokrine Therapie (unabh. vom ER/PR-Status)	4	C	-
▪ Adjuvante Chemotherapie	4	C	-
▪ Primär syst. Th., wenn nicht in-sano operabel (Adriamycin/Ifosfamid)	4	C	+
▪ <b>Adjuvante Therapie des Lokalrezidivs</b>			
▪ Radiotherapie, Chemotherapie nach R1-Resektion	4	C	+/-
▪ <b>Fernmetastasen (sehr selten)</b>			
▪ Vorstellung im Sarkomboard	5	D	++
▪ Therapie wie bei Weichteilsarkomen	4	C	++
▪ Chirurgische Metastasenresektion	4	C	+

### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (6.2024). Phyllodes Tumor (Phyll-1)
2. Bogach J, Sriskandarajah A, Wright Fcet al.; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
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Statement: Treatment of local recurrence => R0 Resection: References (retrospective analysis , case reports)

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Statement: Distant metastases (very rare) => Treatment like soft tissue sarcomas

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## Primäres Angiosarkom der Brust\* - Diagnostik -

	Oxford		
	LoE	GR	AGO
▪ <b>MG / MS zur Bestimmung der Tumorausdehnung</b>	<b>3a</b>	<b>C</b>	<b>-</b>
▪ <b>Präop. MRT zur Bestimmung der Tumorausdehnung</b>	<b>3a</b>	<b>C</b>	<b>++</b>
▪ <b>Diagnose durch Stanzbiopsie</b>	<b>3a</b>	<b>C</b>	<b>++</b>
▪ <b>Diagnose durch Feinnadelbiopsie</b>	<b>3a</b>	<b>C</b>	<b>--</b>
▪ <b>Staging (CT Thorax, Abd.; bei Angiosarkom MRI Kopf)</b>	<b>4</b>	<b>D</b>	<b>++</b>
▪ <b>Prognostische Faktoren:</b>			
<b>Größe, Grading, Tumorränder</b>	<b>3a</b>	<b>C</b>	<b>++</b>

\* Behandlung in spezialisierten Zentren empfohlen

### Review

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

### Imaging

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### Pathology

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### Prognostic Factors

1. Wang, L., Lao, I. W., Yu, L., et al. (2016). Primary Breast Angiosarcoma: A Retrospective Study of 36 Cases from a Single Chinese Medical Institute with Clinicopathologic and Radiologic Correlations. *Breast Journal*. <http://doi.org/10.1111/tbj.12731>
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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**

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.
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## 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**
- **Metastasize early, often to the lung and liver**

### Reviews

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.
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## Primäres Angiosarkom der Brust - Therapie -

	Oxford		
	LoE	GR	AGO
▪ <b>Operation mit weiten freien Tumorrändern, i.d.R. Mastektomie</b>	<b>2b</b>	<b>C</b>	<b>++</b>
▪ Brusterhaltende Operation (wide excision)	3a	C	+/-
▪ <b>SLNE oder axilläre Dissektion im Falle cN0</b>	<b>3a</b>	<b>C</b>	<b>--</b>
▪ <b>Adjuvante Chemotherapie (Anthrazyklin / Taxan-basiert)</b>	<b>4</b>	<b>C</b>	<b>+/-</b>
▪ <b>Adjuvante Radiotherapie, wenn high risk (Größe &gt; 5 cm, R1)</b>	<b>4</b>	<b>C</b>	<b>+/-</b>
▪ <b>Vorstellung in einem Sarkomboard</b>	<b>5</b>	<b>D</b>	<b>++</b>

\* Behandlung in spezialisierten Zentren empfohlen

### Reviews / Guidelines

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers* (Basel). 2023 Aug 2;15(15):3933.
2. Zhu Y, Nakamoto S, Tsukioki T, et al. Primary angiosarcoma of the breast: a literature review. *Chin Clin Oncol*. 2024 Oct;13(5):68. doi: 10.21037/cco-24-16. Epub 2024 Sep 5. PMID: 39260429.
3. Palassini E, Baldi GG, Sulfaro S, et al. Clinical recommendations for treatment of localized angiosarcoma: A consensus paper by the Italian Sarcoma Group. *Cancer Treat Rev*. 2024 May;126:102722. doi: 10.1016/j.ctrv.2024.102722. Epub 2024 Mar 30. PMID: 38604052.

### Surgery

1. Sato F, Yamamoto T: Breast angiosarcoma after primary breast cancer surgery: A systematic review. *J Plast Reconstr Aesthet Surg* 2022;75:2882–2889.
2. Hui, A., Henderson, M., Speakman, D., et al. (2012). Angiosarcoma of the breast: a difficult surgical challenge. *Breast* (Edinburgh, Scotland), 21(4), 584–589. <http://doi.org/10.1016/j.breast.2012.01.001>
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#### Adjuvant Treatment (Chemotherapy, Radiotherapy)

1. Ghareeb, E. R., Bhargava, R., Vargo, J. A., et al. (2016). Primary and Radiation-induced Breast Angiosarcoma: Clinicopathologic Predictors of Outcomes and the Impact of Adjuvant Radiation Therapy. *American Journal of Clinical Oncology*, 39(5), 463–467. <http://doi.org/10.1097/COC.0000000000000077>
2. Sher, T., Hennessy, B. T., Valero, V., et al. (2007). Primary angiosarcomas of the breast. *Cancer*, 110(1), 173–178. <http://doi.org/10.1002/cncr.22784>
3. Schlemmer, M., Reichardt, P., Verweij, J., et al. (2008). Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. *European Journal of Cancer (Oxford, England : 1990)*, 44(16), 2433–2436. <http://doi.org/10.1016/j.ejca.2008.07.037>
4. Teng L, Yan S, Du J, et al.. Clinicopathological analysis and prognostic treatment study of angiosarcoma of the breast: a SEER population-based analysis. *World J Surg Oncol*. 2023 May 9;21(1):144. doi: 10.1186/s12957-023-03030-9. PMID: 37158932; PMCID: PMC10169469.

## Sekundäres Angiosarkom der Brust - Therapie -

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Resektion (BEO / Mastektomie)</b></li> </ul> <p style="margin-left: 20px;">Die Radikalität der Operation führt nicht zu einer Prognoseverbesserung</p>	<b>3a</b>	<b>C</b>	<b>+</b>
<ul style="list-style-type: none"> <li>▪ <b>(Neo-)adjuvante Chemotherapie</b></li> </ul>	<b>3a</b>	<b>C</b>	<b>+/-</b>
<ul style="list-style-type: none"> <li>▪ Trimodale Therapie bei lokal fortgeschrittenem Angiosarkom erwägen (neoadjuvant Taxane =&gt; neo-adjuvante Radiochemotherapie =&gt; chirurgische Resektion)</li> </ul>	<b>3a</b>	<b>C</b>	<b>+</b>
<ul style="list-style-type: none"> <li>▪ <b>Adjuvante Radiotherapie bei Hochrisiko (Größe &gt; 5 cm, R1)</b></li> </ul>	<b>2b</b>	<b>B</b>	<b>+/-</b>
<ul style="list-style-type: none"> <li>▪ <b>Regionale Hyperthermie (Verbesserung lokale Kontrolle) plus Chemotherapie und / oder Radiotherapie</b></li> </ul>	<b>2b</b>	<b>B</b>	<b>+/-</b>

### Review / Guidelines

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.
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### Surgery (BEO/mastectomy)

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4. Cohen-Hallaleh RB, Smith HG, Smith RC, et al. Radiation induced angiosarcoma of the breast: outcomes from a retrospective case

series. Clin Sarcoma Res. 2017 Aug 7;7:15. doi: 10.1186/s13569-017-0081-7.

#### (Neo-)Adjuvant Chemotherapy

1. Jallali, N., James, S., Searle, A., et al. (2012). Surgical management of radiation-induced angiosarcoma after breast conservation therapy. *American Journal of Surgery*, 203(2), 156–161. <http://doi.org/10.1016/j.amjsurg.2010.12.011>
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4. Perez-Ruiz, E., Ribelles, N., Sanchez-Muñoz, A., et al. (2009). Response to paclitaxel in a radiotherapy-induced breast angiosarcoma. *Acta Oncologica*, 48(7), 1078–1079. <http://doi.org/10.1080/02841860902777115>
5. Penel, N., Bui, B. N., Bay, J.-O., et al. (2008). Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 26(32), 5269–5274. <http://doi.org/10.1200/JCO.2008.17.3146>
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#### Trimodale Therapie (Mayo)

1. Degnim AC, Siontis BL, Ahmed SK et al.. Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast. Clin Cancer Res. 2023 Aug 1;29(15):2885-2893.

#### Adjuvant Radiotherapy


1. Ghareeb, E. R., Bhargava, R., Vargo, J. A. et al.(2016). Primary and Radiation-induced Breast Angiosarcoma: Clinicopathologic Predictors of Outcomes and the Impact of Adjuvant Radiation Therapy. *American Journal of Clinical Oncology*, 39(5), 463–467. <http://doi.org/10.1097/COC.0000000000000077>
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## 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%**

### Review / Guidelines


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## 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.

### Trimodality Therapy (Mayo)

1. Degnim AC, Siontis BL, Ahmed SK et al.. Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast. Clin Cancer Res. 2023 Aug 1;29(15):2885-2893.

# Angiosarkome der Brust

## Therapie von Lokalrezidiven und Metastasen

	Oxford		
	LoE	GR	AGO
<b><u>Therapie des Lokalrezidivs:</u></b>			
▪ R0-Resektion	4	C	++
▪ Adjuvante Radiotherapie bei Hochrisiko (Größe > 5 cm, R1)	4	C	+/-
<b><u>Fernmetastasierung / nicht resektable Tumoren:</u></b>			
▪ Therapie wie bei Weichteilsarkomen (gemäß S3-Leitlinie)	4	C	++
▪ Paclitaxel weekly / liposomales Doxorubicin (bei Angiosarkomen)	2b	B	+
▪ Antiangiogene Therapie (z. B. bei Angiosarkom)	4	C	+/-
<b><u>Bei klinischer Therapieresistenz</u></b>			
▪ Molekulare Diagnostik (molekulares Tumorboard)	5	D	+

### Review

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### Molecular Diagnostics if clinically resistant to therapy

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

## Metaplastisches Mammakarzinom\* - high-grade -

### Referenzpathologie und Subtypisierung empfohlen.

	Oxford		
	LoE	GR	AGO
▪ Operative Therapie und axilläres Staging wie bei NST	4	C	++
▪ Neoadjuvante Chemotherapie (eher chemoresistent)*			
▪ Falls primär inoperabel	5	D	+
▪ ER pos.	4	C	--
▪ TNBC, falls ICPI (Pembrolizumab) indiziert	4	C	+
▪ HER2 pos. (inkl. Anti-HER2-Therapie)	4	C	+
▪ Adjuvante Chemotherapie (eher chemoresistent)	4	C	+/-
▪ Mesenchymale Differenzierung (v.a. spindelzellig): mit Platin / Taxan	4	C	+
▪ Adjuvante endokrine Therapie (HR+)	4	C	+
▪ Adjuvante Radiotherapie (wie bei NST)	4	C	++

\* Cave: engmaschige lokale Kontrolle zur Kontrolle des Ansprechens

### Therapy review:

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Metaplastic Breast Cancer Treatment and Outcomes in 2500 Patients: A Retrospective Analysis of a National Oncology Database. *Ann Surg Oncol*. 2018 Aug;25(8):2249–2260. PMID: PMC6039971

### Surgery

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### Axilla

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2. Drekolias D, Mamounas EP. Metaplastic breast carcinoma: Current therapeutic approaches and novel targeted therapies. *Breast Journal*. 2019 Nov;25(6):1192–1197. PMID: 31250492
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#### Adjuvant endocrine therapy

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#### Adjuvant radiotherapy

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3. Haque W, Verma V, Naik N, et al. Metaplastic Breast Cancer: Practice Patterns, Outcomes, and the Role of Radiotherapy. *Ann Surg*

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## Metaplastisches Mammakarzinom – low grade mit unsicherem malignem Potential (fibromatoseartiges und adenosquamöses Ca.)\*

	Oxford		
	LoE	GR	AGO
▪ Operative Therapie und axilläres Staging (wie bei NST)	4	C	++
▪ Adjuvante Chemotherapie (eher chemoresistent)	4	C	-
▪ Neoadjuvante Chemotherapie (eher chemoresistent)	4	C	--
▪ Adjuvante endokrine Therapie (entfällt, da low-grade immer triple-negativ)	4	C	-
▪ Adjuvante Radiotherapie (wie bei NST)	4	C	+

\* Referenzpathologie empfohlen

### Review

1. Corso G, Criscitiello C, Nicosia L et al. Metaplastic breast cancer: an all-round multidisciplinary consensus. Eur J Cancer Prev. 2023 Jul 1;32(4):348-363.
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### Fibromatose-ähnliches Mammakarzinom (low-grade)


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5. Cserni G, Quinn CM, Foschini MP, et al, European Working Group For Breast Screening Pathology. Triple-Negative Breast Cancer Histological Subtypes with a Favourable Prognosis. *Cancers (Basel)*. 2021 Nov 14;13(22):5694. doi: 10.3390/cancers13225694.



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# Metaplastic Breast Cancer

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**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

## Background

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## Outcome

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