

#### Screened data bases:

Pubmed 2007 - 2021, ASCO 2010 – 2021, SABCS 2010 – 2021, Cochrane Data Base (2021)

#### Screened Guidelines:

1. 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
2. <https://www.esmo.org/guidelines/breast-cancer>
3. ASCO (American Association of Clinical Oncology, Practice Guidelines) <http://www.asco.org>
4. CMA (Canadian Medical Association): <http://www.cmaj.ca>
5. NCCN (National Comprehensive Cancer Network): <http://www.nccn.org>
6. [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)



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Guidelines Breast  
Version 2022.1E

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## Breast Cancer: Specific Situations

- **Versions 2005–2021:**  
 Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Gluz / Göhring /  
 Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass /  
 Mundhenke / Müller / Oberhoff / Rody / Scharl / Schneeweiss / Schütz /  
 Sinn / Solomayer / Stickeler / Thomssen
  
- **Version 2022:**  
 Fehm / Loibl

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### Screened Guidelines:

1. 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
2. <https://www.esmo.org/guidelines/breast-cancer>
3. ASCO (American Association of Clinical Oncology, Practice Guidelines) <http://www.asco.org>
4. CMA (Canadian Medical Association): <http://www.cmaj.ca>
5. NCCN (National Comprehensive Cancer Network): <http://www.nccn.org>
6. [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)



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## Breast Cancer: Specific Situations

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

| Breast Cancer in<br>Young Women ≤ 40 Years                                       |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ▪ Aggressive biological behavior with worse prognosis                            | 2a     | B  |     |
| ▪ Local therapy independent of young age   | 2b     | B  | +   |
| ▪ Guidelines adapted (neo-)adjuvant systemic treatment (see respective chapters) | 1b     | A  | ++  |
| ▪ GnRHa as ovarian protection (see chapter gynecological problems)               | 1a     | B  | +   |
| ▪ Genetic and fertility counseling   | 2b     | B  | ++  |
| ▪ Contraception counseling   | 2b     | B  | ++  |

1. Ribnikar D, Ribeiro JM, Pinto D et al.: Breast cancer under age 40: a different approach. Curr Treat Options Oncol. 2015 Apr;16(4):16.
2. Pursche T, Hedderich M, Heinrichs A et al. Guideline conformity treatment in young women with early-onset breast cancer in Germany. Breast Care (Basel). 2014 Oct;9(5):349-54
3. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4). Annals of Oncology 2020;31:674-96.

#### Prognosis in young women

1. Shoemaker ML, White MC, Wu M et al. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013. Breast Cancer Res Treat 2018;169(3):595-606.
2. Ann H. Partridge et al. Model Program to Improve Care for a Unique Cancer Population: Young Women With Breast Cancer J Oncol Pract. 2012; 8(5): e105–e110.

3. Hironaka-Mitsubishi A, Tsuda H, Yoshida M et al. Invasive breast cancers in adolescent and young adult women show more aggressive immunohistochemical and clinical features than those in women aged 40-44 years. Breast Cancer 2018.
4. Johansson ALV, Trewin CB, Hjerkind KV et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. Int J Cancer 2018.
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6. Kroman N. et al, Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ. 2000 Feb 19;320(7233):474-8.
7. Gonzalez-Angulo AM et al., Women age < or = 35 years with primary breast carcinoma: Disease features at presentation. Cancer 2005;103: 2466-2472
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11. Freedman RA et al. Management of breast cancer in very young women. Breast. 2013;22 Suppl 2:S176-9. J Natl Compr Canc Netw. 2013;11(9):1060-9.
12. Tichy JR et al. Breast cancer in adolescents and young adults: a review with a focus on biology. J Natl Compr Canc Netw. 2013;11(9):1060-9.

### Chemotherapy in young women

1. Passildas J, Collard O, Savoye AM et al. Impact of Chemotherapy-induced Menopause in Women of Childbearing Age With Non-

metastatic Breast Cancer - Preliminary Results From the MENOCOR Study. Clin Breast Cancer 2018.

2. Oktay K, Harvey BE, Partridge AH et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36(19):1994-2001.
3. Aebi S. Special issues related to the adjuvant therapy in very young women. Breast 2005, 14: 594-599 (Review)
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: 1687–1717
5. M. De Laurentiis et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol 2008;26 (1),44–53.
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#### Endocrine therapy in young women

1. Cuzick J, Ambroisine L, Davidson N, et al. LHRH-agonists in Early Breast Cancer Overview group Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet. 2007;369(9574):1711-23.
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#### Benefit from trastuzumab

1. 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;369(9555):29-36
2. A.H. Partridge et al. The effect of age on breast cancer outcomes in women with her-2 positive breast cancer: results from the HERA trial J Clin Oncol 2013;44,2692–2698

#### Benefit from temporary amenorrhoea after adjuvant chemotherapy (chemotherapy induced or GnRHa-related)

1. M. Gnant et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360 (7) 679–691
2. Gerber B et al. Effect of Luteinizing Hormone-Releasing Hormone Agonist on ovarian function after adjuvant breast cancer chemotherapy: by the GBG 37 ZORO study. J. Clin Oncol 2011;29 (17) 2334-2341
3. Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial J Natl Cancer Inst 2007 ;99:516–525
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5. Del Mastro L et al. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: Systematic review and meta-analysis of randomized trials. Cancer Treat Rev 2013 in press
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premenopausal women with breast cancer: a meta-analysis of randomized controlled trials Breast 2013;22(2):150-7.

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#### Surgery in young women (Surgery like $\geq 35y$ - in particular BCT)

1. de Bock GH et al., Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy; Long-term results of European Organisation for Research and Treatment of Cancer Studies. Eur J Cancer 2005, 25.
2. Garg AK et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys. 2007 Dec 1;69(5):1478-83. – Radiation boost therapy can reduce in-breast recurrence [Bartelink H, Horiot JC, Poortmans PM, Struikmans H, et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10 year results of the EORTC trial 22881-10882. Br Cancer Res Treat 2006;100:S8-10].
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4. Cao JQ et al. Comparison of recurrence and survival rates after breast-conserving therapy and mastectomy in young women with breast cancer. Curr Oncol. 2013;20(6):e593-e601. Review.



5. Recio-Saucedo A, Gerty S, Foster C, et al. Information requirements of young women with breast cancer treated with mastectomy or breast conserving surgery: A systematic review. *Breast*. 2016 Feb;25:1-13.
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7. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young ( $\leq 40$  years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *Breast*. 2015 Jun;24(3):175-81.

#### Genetic and fertility counselling

1. Copson ER, Maishman TC, Tapper WJ et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol* 2018;19(2):169-80.
2. Engel C, Rhiem K, Hahnen E et al. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. *BMC Cancer* 2018;18(1):265.
3. Yang B et al: Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: A meta-analysis of randomized controlled trials. *Breast* 2013 Jan 5. pii: S0960-9776(12)00252-4.
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5. Del Mastro L et al: Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer *JAMA* 306 (3); 269-276 2011
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7. Lee MC et al.: Fertility and reproductive considerations in premenopausal patients with breast cancer. *Cancer Control*. 2010

Jul;17(3):162-72.

8. Partridge AH EP, Gelber S, Peppercorn J et al. Fertility and menopausal outcomes in young breast cancer survivors. Clin Breast Cancer 2008; (:65-69
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| Breast Cancer During Pregnancy*<br>or Breast Feeding – Diagnostics and Surgery                                |        |    |     |
|---|--------|----|-----|
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| ▪ Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)                  | 4      | C  | ++  |
| ▪ Staging if indicated (bone scan after delivery)   | 5      | D  | +   |
| ▪ Full body MRI (without contrast agent)  | 4      | C  | +/- |
| ▪ Surgery like in non-pregnant patients   | 4      | C  | ++  |
| ▪ Sentinel node excision (technetium only)  | 2b     | B  | +   |
| ▪ SLNE during 1 <sup>st</sup> trimester   | 5      | D  | +/- |
| ▪ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs | 4      | C  | ++  |
| ▪ Blue dye (not tested in pregnant animals or humans)   | 4      | C  | --  |

\* Participation in register study recommended

Study link: <http://germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft.html>

1. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70
2. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

#### Outcome information (e.g. GBG registry)

1. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013 Jul 10;31(20):2532-9.
2. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012 Sep;13(9):887-96.
3. Raphael J, Trudeau ME, Chan K. Outcome of patients with pregnancy during or after breast cancer: a review of the recent literature. Curr Oncol. 2015 Mar;22(Suppl 1):S8-S18

#### Statement: Breast imaging & biopsy like in non-pregnant

1. diFlorio-Alexander RM, Slanetz PJ, Moy L et al. ACR Appropriateness Criteria((R)) Breast Imaging of Pregnant and Lactating Women.

Journal of the American College of Radiology : JACR 2018;15(11s):S263-s75.

2. Bock K. et al., Rationale for a diagnostic chain in gestational breast tumor diagnosis. Arch Gynecol Obstet 2005
3. Ahn BY et al., Pregnancy and lactation-associated breast cancer: mammographic and sonographic findings. J Ultrasound Med 2003, 491-497
4. Nicklas AH et al., Imaging strategies in the pregnant cancer patient. Semin Oncol 2000, 27: 623-632
5. Hogge JP et al., Imaging and management of breast masses during pregnancy and lactation. Breast J 1999, 5: 272-283.
6. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70

Statement: Staging: ultrasound, chest X-ray if indicated

1. Wang PI, et al. Imaging of pregnant and lactating patients: part 2, evidence-based review and recommendations. AJR Am J Roentgenol 2012;198:785-792.

Statement: Whole Body MRI

1. Han SN, Amant F, Michielsen K, et al. Feasibility of whole-body diffusion-weighted MRI for detection of primary tumor, nodal and distant metastases in women with cancer during pregnancy: a pilot study. Eur Radiol. 2017 Dec 7.
2. Peccatori FA, Codacci-Pisanelli G, Del Grande M, et al. Whole body MRI for systemic staging of breast cancer in pregnant women. Breast. 2017 Oct;35:177-181.

Statement: Surgery like in non-pregnant patients

1. Annane K et al. Infiltrative breast cancer during pregnancy and conservative surgery. Fetal Diagn Ther 2005, 20: 442-444
2. Kuerer H et al., Conservative surgery and chemotherapy for breast carcinoma during pregnancy. Surgery 2002, 131: 108-110
3. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861
4. Genin AS, De Rycke Y, Stevens D, et al. Association with pregnancy increases the risk of local recurrence but does not impact overall survival in breast cancer: A case-control study of 87 cases. Breast. 2015 Oct 8. pii: S0960-9776(15)00207-6.

Statement: „Sentinel node biopsy“ during pregnancy

1. Han SN, Amant F, Cardonick EH, et al. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. Breast Cancer Res Treat 2018;168(2):551-57.

2. Gropper AB, Calvillo KZ, Dominici L, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. *Ann Surg Oncol*. 2014 Aug;21(8):2506-11.
3. Khera SY, Kiluk JV, Hasson DM et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J*. 2008 May-Jun;14(3):250-4

### Reviews

1. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. *Cancer*. 2006 Jan 15;106(2):237-46.
2. Shachar SS, Gallagher K, McGuire K, et al. Multidisciplinary Management of Breast Cancer During Pregnancy. *Oncologist* 2017;22(3):324-34.
3. Lee GE, Mayer EL, Partridge A. Prognosis of pregnancy-associated breast cancer. *Breast Cancer Res Treat* 2017;163(3):417-21.
4. Ruiz R, Herrero C, Strasser-Weippl K, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review. *Breast* 2017;35:136-41.
5. Talele AC, Slanetz PJ, Edmister WB, et al. The lactating breast: MRI findings and literature review. *Breast J* 2003, 9: 237-240
6. hachar SS, Gallagher K, McGuire K et al. Multidisciplinary Management of Breast Cancer During Pregnancy. *Oncologist* 2017;22(3):324-34.
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9. Gadducci A, Cosio S, Fanuchi A, et al; Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and a review of the literature. *Anticancer Res* 2003; 23: 5225-5229
10. Ben Brahim E, Mrad K, Driss M, et al. Placental metastasis of breast cancer. *Gynecol Obstet Fertil* 2001, 29: 545-548
11. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5
12. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi160-70

| Breast Cancer During Pregnancy<br>- (Neo-)adjuvant Therapy -                             |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ■ Radiation therapy during pregnancy   | 4      | C  | -   |
| ■ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant) |        |    | ++  |
| ■ Anthracyclines: AC, EC   | 2b     | B  | ++  |
| ■ Taxanes  | 2b     | B  | +   |
| ■ Platinum salts (carboplatin, cisplatin)  | 4      | C  | +/- |
| ■ MTX (e.g. CMF)   | 4      | D  | --  |
| ■ Endocrine treatment  | 4      | D  | --  |
| ■ HER2-targeted treatment  | 3a     | C  | --  |
| ■ Checkpoint inhibitors  | 4      | D  | --  |
| ■ Bisphosphonates, denosumab   | 4      | D  | -   |

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

### General principles

1. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70
2. Loibl S, Schmidt A, Gentilini O et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

### Statement: Radiotherapy during pregnancy

1. Kal HB et al., Radiotherapy during pregnancy: fact and fiction. Lancet Oncol 2005, 6: 328-333 (Review)

### Statement: (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)

1. Loibl S, Han S, Mayer K, et al. Neoadjuvant chemotherapy for patients with breast cancer during pregnancy (BCP). J Clin Oncol 32:5s, 2014 (suppl; abstr 1071)
2. Ring et al, Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. J Clin Oncol 2005, 23: 4192-4197
3. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2008 Apr;19(4):607-13.
4. Del Gobbo A, et al. Chemotherapy for breast cancer during pregnancy induces vascular alterations and impaired development of

- placental villi: A preliminary histopathological study. Eur J Obstet Gynecol Reprod Biol. 2020;250:155–161 (11).
5. Vandenbroucke T, et al. Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. International Network on Cancer, Infertility and Pregnancy (INCIP). Eur J Cancer 2020;138:57–67

Statement: Anthracyclines: AC, EC

1. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. Cancer. 2006 Jan 15;106(2):237-46.
2. Peccatori F et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast Cancer Res Treat 2008; Aug 20 [epub ahead of print]
3. Loibl S, Han SN, Amant F. Being Pregnant and Diagnosed with Breast Cancer. Breast Care (Basel). 2012 Jun;7(3):204-209. Epub 2012 Jun 27.
4. Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. Obstet Gynecol. 2012 Dec;120(6):1267-72.
5. Loibl S et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012 13(9):887-96.
6. Amant F et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol 2012;13:256-264.

Omission of 5FU based on the same evidence as in non-pregnant patients (GIM2 study) - see also chapter on adjuvant chemotherapy

1. Del Mastro L, De Placido S, Bruzzi P et al. Gruppo Italiano Mammella (GIM) investigators. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early stage breast cancer: an open-label, 2x2 factorial, randomised phase 3 trial. Lancet. 2015 May 9;385(9980):1863-72.

Statement: Taxanes

1. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2008 Apr;19(4):607-13.
2. Gadducci A, Cosio S, Fanuchi A, et al; Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and a review of the literature. Anticancer Res 2003; 23: 5225-5
3. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.
4. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. Clin Breast Cancer 2013;13:16-23.

5. Cardonick E et al. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012;23:3016-3023.

#### Statement: Platinum salts

1. Köhler C, Oppelt P, Favero G, et al. How much platinum passes through the placental barriers? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. *Am J Obstet Gynecol*. 2015 Aug;213(2):206.
2. Zheng X, Zhu Y, Zhao Y, et al. Taxanes in combination with platinum derivatives for the treatment of ovarian cancer during pregnancy: A literature review. *International journal of clinical pharmacology and therapeutics* 2017;55(9):753-60.
3. Calsteren KV, Verbesselt R, Devlieger R, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. *Int J Gynecol Cancer* 2010 Dec;20(9):1456-64.
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#### Statement: MTX (e.g. CMF)

1. Ring et al., Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. *J Clin Oncol* 2005, 23: 4192-4197

#### Statement: Endocrine treatment

1. Cunha GR, Taguchi O, Namikawa R, et al. Teratogenic effects of clomiphene, tamoxifen, and diethylstilbestrol on the developing human female genital tract *Hum Pathol*. 1987;18:1132–1143.
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3. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381,805–816.

#### Statement Trastuzumab during pregnancy

1. Lambertini M, Martel S, Campbell C et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. *Cancer* 2018.



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4. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. *Obstetrics and Gynecology* 2005, 105: 642-643 (Case Report)
5. Loibl S. New Therapeutic Options for Breast Cancer during Pregnancy. *Breast Care* 2008; 3:171-176. (table overview of trastuzumab cases)
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10. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* 2013; 5(7):733-41.
11. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Lambertini M, et al. *Cancer.* 2019

#### Statement Immunotherapy during pregnancy

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2. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. *Lancet.* 2012 Feb 11;379(9815):570-9. Review.

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

\* Participation in register study recommended



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### General principles

1. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9.
2. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:87-896.
3. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4). Annals of Oncology 2020;31:674-96.
4. Loibl S, Schmidt A, Gentilini O et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

### Statements: Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome

1. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.

### Statements: Delivery mode like in non-pregnant; Avoid delivery in leucocyte nadir

1. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861

Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities

1. Williams Obstetrics lecture book
2. Pistilli B et al. Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: how should we counsel cancer patients about breastfeeding? Cancer Treat Rev. 2013;39(3):207-11.
3. Hays KE, Ryu RJ, Swisher EM et al. Duration of cisplatin excretion in breast milk. Journal of human lactation : official journal of International Lactation Consultant Association 2013;29(4):469-72.

| Breast Cancer and Pregnancy<br>– Family Planning –  |        |    |     |
|---|--------|----|-----|
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| ▪ After breast cancer diagnosis, reproductive techniques can be used to induce pregnancy  | 3b     | D  |     |
| ▪ Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients               | 3b     | D  |     |
| ▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment                     | 5      | D  | ++  |
| ▪ Breast cancer patients should not be advised against getting pregnant independent of their tumor's hormone receptor status and gBRCA status | 3a     | D  |     |

1. Rosenberg E, et al. No increased risk of relapse of breast cancer for women who give birth after assisted conceptionHum Reprod Open. 2019 Dec 18;2019(4):hoz039. doi: 10.1093/hropen/hoz039
2. Condorelli M, et al. Safety of assisted reproductive techniques in young women harboring germline pathogenic variants in BRCA1/2 with a pregnancy after prior history of breast cancer. ESMO Open. 2021 Dec;6(6):100300.
3. Lambertini M, et al., Pregnancy After Breast Cancer in Patients With Germline *BRCA* Mutations. J Clin Oncol. 2020;38:3012–3023
4. Oktay K et al. Increased chemotherapy-induced ovarian reserve loss in women with germline BRCA mutations due to oocyte deoxyribonucleic acid double strand break repair deficiency. Fertil Steril 2020;113:1251–1260
5. Turan V, et al. The impact of malignancy on response to ovarian stimulation for fertility preservation: a meta-analysis. Fertil Steril 2018 Dec;110(7):1347–1355. doi: 10.1016/j.fertnstert.2018.08.013
6. Grynberg M et al. *BRCA1/2* gene mutations do not affect the capacity of oocytes from breast cancer candidates for fertility preservation to mature in vitro. Hum Reprod 2019 ;34(2):374–379
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8. Turan V, et al. Association of Germline BRCA Pathogenic Variants With Diminished Ovarian Reserve: A Meta-Analysis of Individual Patient-Level Data. J Clin Oncol. 2021 Jun 20;39(18):2016-2024.

| Breast Cancer During Pregnancy and Lactation*<br>- Outcome -           |                       |
|--|-----------------------|
|  | <b>Oxford<br/>LoE</b> |
| ■ <b>BC during pregnancy</b>   |                       |
| ■ Prognosis is not worse if adequately treated                         | <b>3a</b>             |
| ■ <b>BC during lactation and within the first year after pregnancy</b> | <b>3a</b>             |
| ■ Prognosis worse than in BCP and if unrelated to pregnancy            |                       |
| ■ <b>Pregnancy / lactation after BC</b>                                |                       |
| ■ Outcome not compromised  | <b>3a</b>             |

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\* Participation in register study recommended

### General principles

1. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9.
2. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.
3. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. Cancer biology & medicine 2018;15(1):6-13.
4. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70.
5. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

### Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately

1. Gerstl B, Sullivan E, Ives A et al. Pregnancy Outcomes After a Breast Cancer Diagnosis: A Systematic Review and Meta-analysis. Clin Breast Cancer 2018;18(1):e79-e88.
2. Lambertini M, Kroman N, Ameye L et al. Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status. J Natl Cancer Inst 2018;110(4):426-29.

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5. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. *Cancer biology & medicine* 2018;15(1):6-13.
6. de Haan J, Verheecke M, Van Calsteren K et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol* 2018;19(3):337-46.
7. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy associated breast cancer. *Cancer* 1991, 67: 869-872
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9. Rodriguez et al. Evidence of poorer survival in pregnancy-associated breast cancer. *Obstet Gynecol*. 2008 Jul;112(1):71-8
10. Stensheim H, Møller B, van Dijk T et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009;27:45-51. doi:10.1200/JCO.2008.17.4110.
11. Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? *Breast J*. 2010 Jul-Aug;16(4):404-11.
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13. Amant F et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study *J Clin Oncol*. 2013;31(20):2532-9.
14. Litton JK et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. *Oncologist*. 2013;18(4):369-76.
15. Iqbal J, Amir E, Rochon PA, et al. Association of the Timing of Pregnancy With Survival in Women With Breast Cancer *JAMA Oncol* 2017;3(5):659–665
16. O'sullivan et al. Clinico-pathologic features, treatment and outcomes of breast cancer during pregnancy or the post-partum period. *Breast Cancer Res Treat* 2020;180(3):695–706
17. Lefrère H, et al. Breast cancer diagnosed in the post-weaning period. *Lancet Oncol*. 2021: 22:1139-50

Statement: Pregnancy and lactation after breast cancer: Outcome not compromised


1. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5: IBCSG-

participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).

2. Kroman N et al. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol.* 2008;47(4):545-9
3. Azim HA Jr et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013;31:73-79.

#### Review articles

1. Del Mastro et al, Infertility and pregnancy after breast cancer: current knowledge and future perspectives. *Cancer Treat Rev.* 2006 Oct;32(6):417-22. Epub 2006 Jul 13. Review.  
Kroman N, et al. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *Breast.* 2003 Dec;12(6):516-21.
2. Kroman N, et al. Should women be advised against pregnancy after breast-cancer treatment? *Lancet.* 1997 Aug 2;350(9074):319-22.
3. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer.* 2011 Jan;47(1):74-83. Epub 2010 Oct 11. Review.
4. Pagani O, Azim H Jr. Pregnancy after Breast Cancer: Myths and Facts. *Breast Care (Basel).* 2012 Jun;7(3):210-214. Epub 2012 Jun 27.
5. Valachis A, Tsali L, Pesce LL, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. *Obstet Gynecol Surv.* 2010 Dec;65(12):786-93.
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8. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi160-70
9. Lambertini M, et al. Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis.. *J Clin Oncol.* 2021;39:3293-3305.



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## Geriatric Assessment

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

1. 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.
2. 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.
3. Charlson et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987 40:373-383.
4. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006 295:801-08.
5. 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.
6. Aaldriks AA. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy et al. *Breast* 2013;22(5):753-60.
7. Bellera CA et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol.* 2012;23(8):2166-72
8. 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.





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## Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

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

\* Study participation recommended

1. 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.

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. Chagpar AB: Determinants of early distant metastatic disease in elderly patients with breast cancer. Am J Surg. 2006 Sep;192(3):317-21
9. Kemeny MM: Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003 Jun 15;21(12):2268-75
10. Giordano SH: Breast cancer treatment guidelines in older women. J Clin Oncol. 2005 Feb 1;23(4):783-91.
11. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg. 2008 Jan;206(1):66-75
12. Wildiers H: Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 2007 Dec;8(12):1101-15
13. 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. Fentiman IS: 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 Feb;39(3):309-16
3. Fentiman IS: 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. 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.
5. 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.
6. 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
7. 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.
8. 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.

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. Crivellari D, Sun Z, Coates AS, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 Trial. J Clin Oncol 2008; 26:1972-79
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4. Lash TL: Physicians' assessments of adjuvant tamoxifen's effectiveness in older patients with primary breast cancer. J Am Geriatr Soc. 2005 Nov;53(11):1889-96
5. 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
6. 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
7. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381, 805–816

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. Fargeot P: Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. J Clin Oncol. 2004 Dec 1;22(23):4622-30
4. 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
5. De Maio E et al., Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: a single-center experience. BMC Cancer 2005 24: 30  
Muss HB et al., Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 2005, 293:1073-81.

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7. Hurria A et al., Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat*. 2005 92:151-6.
8. 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. 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.
2. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007 Sep 1;25(25):3808-15.
3. 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)*.
4. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients *Breast Care* 2012;7:439-444
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Statement: Radiotherapy

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2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control *Strahlenther Onkol* 2012 :1-5

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#### Statement: Trastuzumab

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| <div>  <h2>Treatment for Frail Patients</h2> <p>(Life Expectancy &lt; 5 yrs., Substantial Comorbidities)</p> </div>  |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
|  | 2b     | C  | ++  |
| <ul style="list-style-type: none"> <li>Reduced standard treatment</li> <li>Options extrapolated from trials in elderly: <ul style="list-style-type: none"> <li>No breast surgery (consider endocrine options)</li> <li>No axillary clearing (≥ 60 y, cN0, HR-pos)</li> <li>No radiotherapy (Tumor size &lt; 3 cm, pN0, HR-pos)</li> <li>Hypofractionated radiotherapy</li> <li>No chemotherapy if &gt; 70 yrs. and negative risk-benefit analysis</li> </ul> </li> </ul> | 2b     | C  | +   |
|  | 2b     | B  | +   |
|  | 1b     | B  | ++  |
|  | 2b     | B  | +   |
|  | 2b     | C  | +   |

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- Audisio RA et al When reporting on older patients with cancer , frailty information is needed Ann Surg Oncol 2011; 18: 4-5
- Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
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#### Statement: Reduced standard treatment

#### Statement: No breast surgery (consider endocrine options)

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

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Statement: Hypofractionated radiotherapy

1. Vaidya JS, Joseph DJ, Tobias JS et al: Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010 Jul 10;376(9735):91-102.
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Statement: No chemotherapy > 70 years and negative risk benefit analysis

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

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

### International registry

- 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.
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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.
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Radiat Oncol Biol Phys. 2008 Dec 1;72(5):1456-64. Epub 2008 Aug 7

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8. Yildirim E, Berberog˘lu U. Male breast cancer: a 22-year experience. Eur J Surg Oncol. 1998;24(6):548–52.

#### Statement: Sentinel-node excision (SNE)

1. Port ER et al. Sentinel lymph node biopsy in patients with male breast carcinoma. Cancer 2001 91:319-323
2. 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-

3. 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
4. De Cicco C: Sentinel node biopsy in male breast cancer. Nucl Med Commun 2004; 25: 139-143
5. Albo D et al. Evaluation of lymph node status in male breast cancer patients: a role for sentinel lymph node biopsy. Breast Cancer Res Treat 2003 77:9-14

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

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3. Eggemann H et al. Male breast cancer: 20-year survival data for post-mastectomy radiotherapy. Breast Care (Basel). 2013;8(4):270-5.

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

1. Ottini L et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Res Treat. 2008 Sep 26
2. Friedman LS, Gayther SA, Kurosaki T, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet 1997; 60: 313-319
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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


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4. 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
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#### Review articles

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2. Borgen PI et al. Current management of male breast cancer. A review of 104 cases. *Ann Surg* 1992 215:451
3. Erlichman C et al. Male breast cancer: a 13- year review of 89 patients. *J Clin Oncol* 1984 2: 903
4. Cutuli B, Lacroze M, Dilhuydy JM, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. *Eur J Cancer* 1995; 31A: 1960-1964
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8. Patten DK et al. New Approaches in the Management of Male Breast. *Cancer Clinical Breast Cancer* 2013;13(5) 309–314
9. Sousa B et al. An update on male breast cancer and future directions for research and treatment. *Eur J Pharmacol* 2013;717(1-3)
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## Male Breast Cancer-Prognostic Factors

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

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

### Registries

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## Male Breast Cancer: Systemic Therapy

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

### Statement: Adjuvant Chemotherapy

1. Patel HZ et al. Role of adjuvant chemotherapy in male breast cancer. Cancer 1989 64: 1583
2. Bagley CS et al. Adjuvant Chemotherapy in males with cancer of the breast. Am J Clin Oncol 1987; 2:903
3. Giordano SH, Perkins GH, Broglio K, et al. Adjuvant systemic therapy for male breast cancer. Cancer 2005; 104: 235-264
4. 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.

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1. Ribeiro G et al. Adjuvant tamoxifen for male breast cancer (MBC). Br J Cancer 1992 65: 252
2. Anelli TF et al. Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. Cancer 1994 74: 74
3. Agrawal: Fulvestrant in advanced male breast cancer. Breast Cancer Res Treat. 2007 Jan;101(1):123. Epub 2006 Jun 29.
4. 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
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#### Statement palliative chemotherapy

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and/or taxane therapy. Gan To Kagaku Ryoho. 2006 Jun;33(6):761-6



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# Benefit from Trimodal Treatment in Inflammatory Breast Cancer

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

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

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

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

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

1. 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.

| Inflammatory Breast Cancer (IBC, cT4d)  |        |    |     |
|---|--------|----|-----|
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| <ul style="list-style-type: none"> <li>Invasive BC and clinical signs of inflammation (e.g. <math>\geq 1/3</math> of the breast affected) determine stage cT4d</li> </ul> |        |    | ++  |
| <ul style="list-style-type: none"> <li>Staging</li> </ul>   | 2c     | B  | ++  |
| <ul style="list-style-type: none"> <li>Skin punch biopsy (at least 2; detection rate &lt; 75%)</li> </ul>   | 2c     | B  | +   |
| <ul style="list-style-type: none"> <li>Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)</li> </ul>   | 2c     | B  | ++  |
| <ul style="list-style-type: none"> <li>Mastectomy after chemotherapy</li> </ul>   | 2c     | B  | +   |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Breast conserving therapy in case of pCR (individual)</li> </ul> </li> </ul>               | 2b     | C  | +/- |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Delayed breast reconstruction</li> </ul> </li> </ul>                                       | 3b     | C  | +   |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Sentinel excision only</li> </ul> </li> </ul>  | 3b     | C  | -   |
| <ul style="list-style-type: none"> <li>Radiotherapy of the chest wall including regional lymph nodes independent of therapy response</li> </ul>                           | 2c     | B  | ++  |

## General

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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

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 2.2022. NCCN.org (Inflammatory Breast Cancer. IBC-1)

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

1. 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

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.
2. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790

Statement: Regimens as in non-inflammatory BC

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 2.2022. NCCN.org (Inflammatory Breast Cancer. IBC-1)

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.
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Statement: Immediate breast reconstruction:

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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. Hidar S et al Sentinel lymph node biopsy after neoadjuvant chemotherapy in inflammatory breast cancer. Int J Surg. 2009 Jun;7(3):272-5. doi: 10.1016/j.ijsu.2009.04.012. Epub 2009 May 3.
2. 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

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Research and Treatment, 88(1), 43–47. <http://doi.org/10.1007/s10549-004-9453-9>


4. Pentheroudakis, G., Briasoulis, E., & Pavlidis, N. (2007). Cancer of unknown primary site: missing primary or missing biology? *Oncologist*, 12(4), 418–425. <http://doi.org/10.1634/theoncologist.12-4-418>

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1. Montagna, E., Bagnardi, V., Rotmensz, et al. (2011). Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation. *Breast Cancer Research and Treatment*, 129(3), 867–875. <http://doi.org/10.1007/s10549-011-1697-6>

### Outcome

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

|  | Oxford    |          |           |
|--|-----------|----------|-----------|
|  | LoE       | GR       | AGO       |
| ▪ <b>Breast imaging incl. Breast-MRI</b>   | <b>3</b>  | <b>B</b> | <b>++</b> |
| ▪ <b>Exclude contralateral cancer</b>  | <b>3</b>  | <b>B</b> | <b>++</b> |
| ▪ <b>Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)</b> | <b>5</b>  | <b>D</b> | <b>++</b> |
| ▪ <b>Staging (CT thorax / abdomen, pelvis, in certain circumstances also thyroid sonography, HNT-exam)</b>                         | <b>3</b>  | <b>B</b> | <b>++</b> |
| ▪ <b>PET / PET-CT</b>  | <b>3b</b> | <b>B</b> | <b>+</b>  |

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

1. 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>
2. 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>
3. 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: 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>
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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 (ex. CUP)  |        |    |     |
|--|--------|----|-----|
| Pathology, Molecular Pathology   |        |    |     |
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ▪ ER, PR, HER2, GATA3 (in some cases Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, and others)  | 5      | D  | ++  |
| ▪ Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca. | 5      | D  | ++  |
| ▪ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)   | 2c     | B  | +/- |
| ▪ NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)   | 2c     | B  | +/- |
| ▪ Prognostic gene expression tests   | 5      | D  | --  |

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### Immunohistochemistry

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2. <http://doi.org/10.1016/j.humpath.2012.09.005>
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5. Oien, K. A. (2009). Pathologic evaluation of unknown primary cancer. Seminars in Oncology, 36(1), 8–37. <http://doi.org/10.1053/j.seminoncol.2008.10.009>
6. Ordonez, N. G. (2013). Value of GATA3 immunostaining in tumor diagnosis: a review. Advances in Anatomic Pathology, 20(5), 352–360. <http://doi.org/10.1097/PAP.0b013e3182a28a68>
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breast cancers enriched for triple-negative tumours. *Histopathology*, 68(3), 367–377. <http://doi.org/10.1111/his.12765>

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1. Ades, F., De Azambuja, E., Daugaard, G., et al. (2013). Comparison of a gene expression profiling strategy to standard clinical work-up for determination of tumour origin in cancer of unknown primary (CUP). *Journal of Chemotherapy (Florence, Italy)*, 25(4), 239–246. <http://doi.org/10.1179/1973947813Y.0000000085>
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## Axillary Metastasis in Occult Breast Cancer (Axillary CUP): Therapy

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

### Guidelines

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1. 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: Mastectomy without (in-)breast tumor

1. Khandelwal, A. K., & Garguilo, G. A. (2005). Therapeutic options for occult breast cancer: a survey of the American Society of Breast Surgeons and review of the literature. *The American Journal of Surgery*, 190(4), 609–613. <http://doi.org/10.1016/j.amjsurg.2005.06.026>
2. 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. [http://doi.org/10.1016/S0959-8049\(03\)00547-1](http://doi.org/10.1016/S0959-8049(03)00547-1)
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Statement: Breast irradiation if breast MRI is negative

1. Hessler LK, Molitoris JK, Rosenblatt PY et al. Factors Influencing Management and Outcome in Patients with Occult Breast Cancer with Axillary Lymph Node Involvement: Analysis of the National Cancer Database. *Surg Oncol* 2017 Oct;24(10):2907-2914.
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3. Masinghe, S. P., Faluyi, O. O., Kerr, G. R., et al. (2011). Breast Radiotherapy for Occult Breast Cancer with Axillary Nodal Metastases -

Does it Reduce the Local Recurrence Rate and Increase Overall Survival? Clinical Oncology (Royal College of Radiologists (Great Britain)), 23(2), 95–100. <http://doi.org/10.1016/j.clon.2010.10.001>

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..

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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|   |   |   |
|---|---|---|
|   | <h2 style="text-align: center;">Paget's Disease of the Breast</h2>  |   |
| <p>© AGO e. V.<br/>in der DGGG e. V.<br/>sowie<br/>in der DKG e. V.</p> <p>Guidelines Breast<br/>Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN<br/>LEHREN<br/>HEILEN</p> | <ul style="list-style-type: none"> <li>▪ <b>Definition:</b> Paget's disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer.</li> <li>▪ <b>Clinical presentation:</b> skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin</li> </ul> |   |
|   | Feature   | Frequency   |
|   | Presentation  | Paget's disease with invasive Ca. (37-58%)<br>Paget's disease mit DCIS (30-63%)<br>Isolated Paget's disease (4-7%)<br>Isolated Paget's disease with invasion (rare) |
|   | IHC   | HER2-positive (83-97%)<br>ER-positive (10-14%)<br>AR-positive (71-88%)  |
|   | Prognosis and tumor biology   | Better in isolated Paget's disease<br>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. Günhan-Bilgen, I., & Oktay, A. (2006). Paget's disease of the breast: clinical, mammographic, sonographic and pathologic findings in 52 cases. *European Journal of Radiology*, 60(2), 256–263. <http://doi.org/10.1016/j.ejrad.2006.06.010>
3. Kothari, A. S., Beechey-Newman, N., Hamed, H., et al. (2002). Paget disease of the nipple: a multifocal manifestation of higher-risk disease. *Cancer*, 95(1), 1–7. <http://doi.org/10.1002/cncr.10638>
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5. 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. Chen, C.-Y., Sun, L.-M., & Anderson, B. O. (2006). Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer*, 107(7), 1448–1458. <http://doi.org/10.1002/cncr.22137>
2. Hanna, W., Alowami, S., & Malik, A. (2003). The role of HER-2/neu oncogene and vimentin filaments in the production of the Paget's phenotype. *The Breast Journal*, 9(6), 485–490.
3. Kothari, A. S., Beechey-Newman, N., Hamed, H., et al. (2002). Paget disease of the nipple: a multifocal manifestation of higher-risk disease. *Cancer*, 95(1), 1–7. <http://doi.org/10.1002/cncr.10638>
4. 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.
5. 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>
6. 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>
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## Paget's Disease of the Breast Diagnosis

- **Histological verification by skin biopsy**
- **Mammography, sonography**
- **MRI of the breast if other imaging negative**
- **Immunohistochemistry (ER, PR, HER2, CK7) to detect benign and HER2-negative cases**

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

### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (2.2022). Paget Disease (PAGET-1)

### maging

1. 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>
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## 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>

| Paget's Disease of the Breast - Therapy   |         |        |                                |
|---|---------|--------|--------------------------------|
|   | Oxford  |        |                                |
|   | LoE     | GR     | AGO                            |
| <ul style="list-style-type: none"> <li>■ <b>Paget's disease with underlying disease (invasive breast cancer, DCIS)</b> <ul style="list-style-type: none"> <li>■ Therapy according to standard of underlying disease</li> <li>■ Surgery must achieve R0</li> </ul> </li> <li>■ <b>Isolated Paget's disease of the NAC:</b> <ul style="list-style-type: none"> <li>■ Surgery must achieve R0</li> <li>■ Surgical resection only, no adjuvant radiotherapy</li> <li>■ Sentinel-node excision (SLNE)</li> </ul> </li> </ul> | 5<br>1c | D<br>B | ++<br>++<br><br>++<br>++<br>-- |

#### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (2.2022). Paget Disease (PAGET-1)

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


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. Caliskan, M., Gatti, G., Sosnovskikh, I., et al. (2008). Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. Breast Cancer Research and Treatment, 112(3), 513–521. <http://doi.org/10.1007/s10549-007-9880-5>
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### 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.

### 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>



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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. Barrio, A., Clark, B., Goldberg, J. et al. (2007). Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. *Annals of Surgical Oncology*.
2. 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>
3. 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
4. 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.

5. 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
6. 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>

| Phyllodes Tumor   |   |           |             |  |  |                                 |  |                  |   |            |  |
|---|---|-----------|-------------|--|--|---------------------------------|--|------------------|---|------------|--|
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| <p>Frequency 0.3 – 1% of all primary breast tumors</p> <table> <tr> <th>parameter</th><th>frequencies</th></tr> <tr> <td>Grading (3-STEP histological grading system)</td><td>Benign (75%)<br/>Borderline (16%)<br/>Malignant (9%)</td></tr> <tr> <td>Median age at time of diagnosis</td><td>Benign PT: 39 y<br/>Borderline PT: 45 y<br/>Malignant PT: 47 y</td></tr> <tr> <td>Local recurrence</td><td>Benign PT: 4 – 17%<br/>Borderline PT: 14 – 25%<br/>Malignant PT: 23 – 30%</td></tr> <tr> <td>Metastasis</td><td>Benign PT: &lt; 1%<br/>Borderline PT: 1.6%<br/>Malignant PT: 16-22%</td></tr> </table> |   | parameter | frequencies | Grading (3-STEP histological grading system) | Benign (75%)<br>Borderline (16%)<br>Malignant (9%) | Median age at time of diagnosis | Benign PT: 39 y<br>Borderline PT: 45 y<br>Malignant PT: 47 y | Local recurrence | Benign PT: 4 – 17%<br>Borderline PT: 14 – 25%<br>Malignant PT: 23 – 30% | Metastasis | Benign PT: < 1%<br>Borderline PT: 1.6%<br>Malignant PT: 16-22% |
| parameter   | frequencies   |           |             |  |  |                                 |  |                  |   |            |  |
| Grading (3-STEP histological grading system)  | Benign (75%)<br>Borderline (16%)<br>Malignant (9%)                      |           |             |  |  |                                 |  |                  |   |            |  |
| Median age at time of diagnosis   | Benign PT: 39 y<br>Borderline PT: 45 y<br>Malignant PT: 47 y            |           |             |  |  |                                 |  |                  |   |            |  |
| Local recurrence  | Benign PT: 4 – 17%<br>Borderline PT: 14 – 25%<br>Malignant PT: 23 – 30% |           |             |  |  |                                 |  |                  |   |            |  |
| Metastasis  | Benign PT: < 1%<br>Borderline PT: 1.6%<br>Malignant PT: 16-22%          |           |             |  |  |                                 |  |                  |   |            |  |
| <p>10 y OS: 86–90% (range: 57–100%) depending on subtype and unfavorable histological criteria</p>  |   |           |             |  |  |                                 |  |                  |   |            |  |

## 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. Barrio, A., Clark, B., Goldberg, J. et al. (2007). Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. Annals of Surgical Oncology.
2. 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>
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4. 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.



5. 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
6. 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 and Malignant Phyllodes Tumor Diagnosis                    |        |    |     |
|---|--------|----|-----|
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| ▪ Mammography, sonography   | 3      | C  | ++  |
| ▪ Diagnosis on core biopsy, grade determination on resection specimen | 3      | C  | ++  |
| ▪ Breast MRI  | 3      | C  | +/- |
| ▪ Staging only malignant PT (CT thorax, skeletal system)              | 5      | D  | ++  |

### 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 Surgery

|   | Oxford<br>LoE | GR       | AGO       |
|---|---------------|----------|-----------|
| ▪ <b>Borderline / malignant phyllodes tumor: Complete resection with adequate margins, min. &gt; 1 mm</b> | <b>2b</b>     | <b>B</b> | <b>++</b> |
| ▪ <b>SLNE / Axillary dissection</b>   | <b>4</b>      | <b>C</b> | <b>--</b> |
| ▪ <b>Treatment of local recurrence</b>  |               |          |           |
| ▪ R0 resection or simple mastectomy   | <b>4</b>      | <b>C</b> | <b>++</b> |

### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (2.2022). Phyllodes Tumor (Phyll-1)

### Surgical margins: Systematic review

1. 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.
2. 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.
3. Rosenberger LH, Thomas SM, Nimbkar SN, et al.. Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines. *J Clin Oncol*. 21 Jan 20;39(3):178-189.

### Operative management and prognosis of Phyllodes Tumors



1. 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>
2. Mituś, J., Reinfuss, M., Mituś, J. W., et al. (2014). Malignant phyllodes tumor of the breast: treatment and prognosis. *Breast Journal*, 20(6), 639–644. <http://doi.org/10.1111/tbj.12333>
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>
4. 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>

|  <b>Systematic Reviews (2016-2021)</b><br><b>Optimal Surgical Margins for Phyllodes and Borderline Tumors</b>  |  |   |
|---|--|---|
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|   | Thind A, et al. Ann R Coll Surg Engl. 102(3):165-173, 2020. PMID 31918563  | Surgical margins for borderline and malignant phyllodes tumours. (10 studies, 456 cases, 1990 – 2019).  |
|   | Lu Y, et al. Ann Surg Oncol. 90:342–13, 2019. PMID 30617873.               | Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. (54 studies, 9234 cases, 1995 – 2018). |
|   | Tan BY, et al. Histopathology. 2016;68(1):5-21. PMID: 26768026             | Phyllodes tumours of the breast: a consensus review.  |
| Local recurrence (all PT grades) was not reduced with wider negative margin width ( $\leq 2$ mm v. $> 2$ mm); or final margin status (positive v negative).<br><br>No statistically significant difference between $<1$ cm and $\geq 1$ cm margins in terms of local recurrence rates or distant metastasis.<br><br>A positive margin and BCS both were significantly correlated with a higher LR risk for malignant PTs but not for benign and borderline PTs.<br><br>Tumour on ink, or $<1$ mm, should be considered as a positive margin. Excision with negative margins should be achieved for recurrent and malignant phyllodes tumours. |  |   |

1. Rosenberger LH, Thomas SM, Nimbkar SN, et al. Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines. J Clin Oncol. 2021 Jan 20;39(3):178-189. doi: 10.1200/JCO.20.02647. Epub 2020 Dec 10. PMID: 33301374; PMCID: PMC8462612.
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.
4. Tan BY, Acs G, Apple SK, et al. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016 Jan;68(1):5-21. doi: 10.1111/his.12876. PMID: 26768026; PMCID: PMC5027876.

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

#### General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (2.2022). Phyllodes Tumor (Phyll-1)
2. [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) Version 2.2022

#### Statements: Systemic adjuvant therapy/ Chemotherapy and Endocrine therapy

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2. Tan, E. Y., Tan, P. H., Hoon, T. P., et al. (2006). Recurrent phyllodes tumours of the breast: pathological features and clinical implications. ANZ J Surg, 76(6), 476–480. <http://doi.org/10.1111/j.1445-2197.2006.03754.x>
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review and meta-analysis. BMC Cancer. 2019;19(1):372. Published 2019 Apr 23. doi:10.1186/s12885-019-5585-5

Statement: Adjuvant radiotherapy

1. 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>
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Statement: Treatment of local recurrence => R0 Resection: References (retrospective analysis , case reports)

1. Soumarová, R., Šeneklová, Z., Horová, H. et al. (2004). Retrospective analysis of 25 women with malignant cystosarcoma phyllodes--treatment results. Archives of Gynecology and Obstetrics, 269(4), 278–281. <http://doi.org/10.1007/s00404-003-0593-7>
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Statement: Distant metastases (very rare) => Treatment like soft tissue sarcomas

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<http://doi.org/10.7314/APJCP.2014.15.24.10791>
3. [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) Version 2.2022





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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. Depla, A. L., Scharloo-Karels, C. H., de Jong, M. A. A., et al. (2014). Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review. *European Journal of Cancer*, 50(10), 1779–1788. <http://doi.org/10.1016/j.ejca.2014.03.002>
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3. Lim, S. Z., Ong, K. W., Tan, B. K. T., et al. (2016). Sarcoma of the breast: an update on a rare entity. *Journal of Clinical Pathology*, 69(5), 373–381. <http://doi.org/10.1136/jclinpath-2015-203545>
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8. Kunkiel, M., Maczkiewicz



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## Primary Angiosarcoma of the Breast

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

### Reviews

1. Depla, A. L., Scharloo-Karels, C. H., de Jong, M. A. A., et al. (2014). Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review. *European Journal of Cancer*, 50(10), 1779–1788. <http://doi.org/10.1016/j.ejca.2014.03.002>
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| Primary Angiosarcoma of the Breast*                      |        |    |     |
|--|--------|----|-----|
| Diagnosis  |        |    |     |
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ■ Mammography, sonography to determine extent of disease | 3a     | C  | --  |
| ■ Preoperative MRI to determine the extent of disease    | 3a     | C  | ++  |
| ■ Diagnosis by core biopsy                               | 3a     | C  | ++  |
| ■ Diagnosis by FNB                                       | 3a     | C  | --  |
| ■ Staging (CT thorax & abd.; angiosarcoma: MRI brain)    | 4      | D  | ++  |
| ■ Prognostic factors: size, grade, margins               | 3a     | C  | ++  |

\* Therapy in specialized centers recommended



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## Imaging

1. Glazebrook, K. N., Magut, M. J., & Reynolds, C. (2008). Angiosarcoma of the breast. American Journal of Roentgenology, 190(2), 533–538. <http://doi.org/10.2214/AJR.07.2909>
2. O'Neill, A. C., D'Arcy, C., McDermott, E., et al. (2014). Magnetic resonance imaging appearances in primary and secondary angiosarcoma of the breast. Journal of Medical Imaging and Radiation Oncology, 58(2), 208–212. <http://doi.org/10.1111/1754-9485.12100>
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## Pathology

1. Nascimento, A. F., Raut, C. P., & Fletcher, C. D. M. (2008). Primary angiosarcoma of the breast: clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic. The American Journal of Surgical Pathology, 32(12), 1896–1904.

<http://doi.org/10.1097/PAS.0b013e318176dbc7>

2. Adem, C., Reynolds, C., Ingle, J. N., et al. (2004). Primary breast sarcoma: clinicopathologic series from the Mayo Clinic and review of the literature. *British Journal of Cancer*, 91(2), 237–241. <http://doi.org/10.1038/sj.bjc.6601920>
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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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3. Vorburger, S., Xing, Y., Hunt, K., et al. (2005). Angiosarcoma of the breast. *Cancer*, 104(12), 2682–2688. <http://doi.org/10.1002/cncr.21531>
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| Primary Angiosarcoma of the Breast*   |        |    |     |
|---|--------|----|-----|
| Therapy   |        |    |     |
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| <ul style="list-style-type: none"> <li>■ <b>Surgery with wide clear margins, mostly as mastectomy</b> <ul style="list-style-type: none"> <li>■ Breast-conserving therapy</li> </ul> </li> <li>■ <b>SLNE or axillary dissection if cN0</b></li> <li>■ <b>Adjuvant chemotherapy (anthracycline / taxane-based)</b></li> <li>■ <b>Adjuvant radiotherapy if high risk (size &gt; 5 cm, R1)</b></li> </ul> | 2b     | C  | ++  |
|   | 3a     | C  | -   |
|   | 3a     | C  | --  |
|   | 4      | C  | +/- |
|   | 4      | C  | +/- |

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\* Therapy in specialized centres recommended


### Surgery

1. 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.000000000000077>

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| Secondary Angiosarcoma<br>of the Breast Therapy   |        |    |     |
|---|--------|----|-----|
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| <div>  <p>© AGO e. V.<br/>in der DGGG e.V.<br/>sowie<br/>in der DKG e.V.<br/>Guidelines Breast<br/>Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN<br/>LEHREN<br/>HEILEN</p> </div> <ul style="list-style-type: none"> <li>▪ <b>Tumor resection (BCT / mastectomy)</b><br/><b>Radical surgery ist not associated with better outcome</b></li> <li>▪ <b>(Neo-)adjuvant chemotherapy</b></li> <li>▪ <b>Adjuvant radiotherapy if high risk (size &gt; 5 cm, R1)</b></li> <li>▪ <b>Regional hyperthermia (to improve local control) plus chemotherapy and / or radiotherapy</b></li> </ul> | 3a     | C  | +   |
|   | 3a     | C  | +/- |
|   | 2b     | B  | +/- |
|   | 2b     | B  | +/- |

### Surgery (BEO/mastectomy)

1. Lindford, A., Böbling, T., Vaalavirta, L., et al. (2011). Surgical management of radiation-associated cutaneous breast angiosarcoma. Journal of Plastic, Reconstructive & Aesthetic Surgery : JPRAS, 64(8), 1036–1042. <http://doi.org/10.1016/j.bjps.2011.02.014>
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### (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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#### 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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### Adjuvant Hyperthermia

1. Lim, S. Z., Ong, K. W., Tan, B. K. T., et al. (2016). Sarcoma of the breast: an update on a rare entity. *Journal of Clinical Pathology*, 69(5), 373–381. <http://doi.org/10.1136/jclinpath-2015-203545>
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## Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

- **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%**

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| Angiosarcoma of the Breast<br>Treatment of Local Recurrence and Metastases |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| <b><u>Treatment of Local Recurrence:</u></b>                               |        |    |     |
| ▪ R0 resection   | 4      | C  | ++  |
| ▪ Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)     | 4      | C  | +/- |
| <b><u>Distant Metastases / Unresectable Tumors:</u></b>                    |        |    |     |
| ▪ Treatment like as for soft tissue sarcomas (according to S3 guideline)   | 4      | C  | ++  |
| ▪ Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)           | 2b     | B  | +   |
| ▪ Antiangiogenic treatment (e.g. in angiosarcoma)                          | 4      | C  | +/- |

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


- **Aproximately 10.000.000 implant carrier**
- **Rare disease, 3% of T-cell Non-Hodgkin Lymphomas, 0.04-0.5% of all malignant breast diseases**
- **1:3.000 – 30.000 in women with textured implants (caveat: underreporting!)**
- **Estimated incidence 0.6-1.2/100.000 women with implants (median age: 54 y)**
- **Mainly associated with textured implants (1:300 women)**
- **Interval to diagnosis: 8 years (median)**
- **Clinical symptoms**
  - Erythema, swelling and seroma. (60%)
  - Solid tumor (17%)
  - Seroma and solid tumor (20%)
  - Axillary lymphadenopathia (20%)
- **Histology: CD30+ / ALK-T-Cell Lymphoma**
- **Compulsory registration as SAE (§3 MPSV to BfArM)**  
(<https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html>)

### Reviews

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## BIA-ALCL - Surfaces of Breast Implants

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

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

1. Jones P, Mempin M, Hu H et al. The functional influence of breast implant outer shell morphology on bacterial attachment and growth. *Plast Reconstr Surg.* 2018;142:837–849
2. Collett DJ, Rakhorst H, Lennox P et al.: Current Risk Estimate of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants. *Plast Reconstr Surg.* 2019 Mar;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):30S-40S. doi: 10.1097/PRS.0000000000005567.
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| BIA-ALCL– Diagnosis  |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ▪ Breast US (assessment of new seromas > 1 year after implant insert, solid lesion (sensitivity: 84%, specificity: 75%)) | 3a     | D  | ++  |
| ▪ Mamma-MRT in confirmed cases   | 3a     | D  | ++  |
| ▪ Staging (Imaging, e.g. CT, PET-CT)   | 3a     | D  | ++  |
| ▪ Cytology of late seromas   | 3a     | D  | ++  |
| ▪ - > 50 ml  |        |    |     |
| ▪ - Complete assessment  |        |    |     |
| ▪ - flow-cytology (T-cell clone)   |        |    |     |
| ▪ - BIA-ALCL specific cytologic diagnostic (e.g. CD 30+)   |        |    |     |
| ▪ Core needle biopsy in solid lesions  | 3a     | D  | ++  |
| ▪ Lymphoma assessment of resected tissue and histologic staging  |        |    |     |
| ▪ Documentation of the implant and enter in registry   | 5      | D  | ++  |

### BIA-ALCL-Work-up

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| BIA-ALCL – Therapy  |        |    |     |
|---|--------|----|-----|
|   | Oxford |    |     |
|   | LoE    | GR | AGO |
| ▪ <b>Implant resection and complete capsulectomy including tumorectomy</b>  | 3a     | C  | ++  |
| ▪ <b>Contralateral implant resection including capsulectomy in case of bilateral implants (2-4% BIA-ALCL bilateral)</b>       | 4      | D  | +/- |
| ▪ <b>Resection of suspicious lymph nodes, no routine use of Sentinel-Node-Biopsy, no axillary dissection</b>                  | 4      | D  | ++  |
| ▪ <b>Polychemotherapy (e.g. CHOP / CHOEP) in cases of extra capsular extension, Brentuximab-Vedotin-CHP as an alternative</b> | 4      | D  | +   |
| ▪ <b>Radiotherapy in unresectable tumors</b>  | 5      | D  | +/- |
| ▪ <b>Case discussion in an interdisciplinary tumor board in the presence of a specialist for lymphomas</b>                    | 5      | D  | ++  |

#### BIA-ALCL-Treatment:

1. Clemens MW, Medeiros LJ, Butler CE, et al. Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. J Clin Oncol. 2016;34(2):160-168. doi:10.1200/JCO.2015.63.3412.
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# TNM Staging of BIA-ALCL (proposed)

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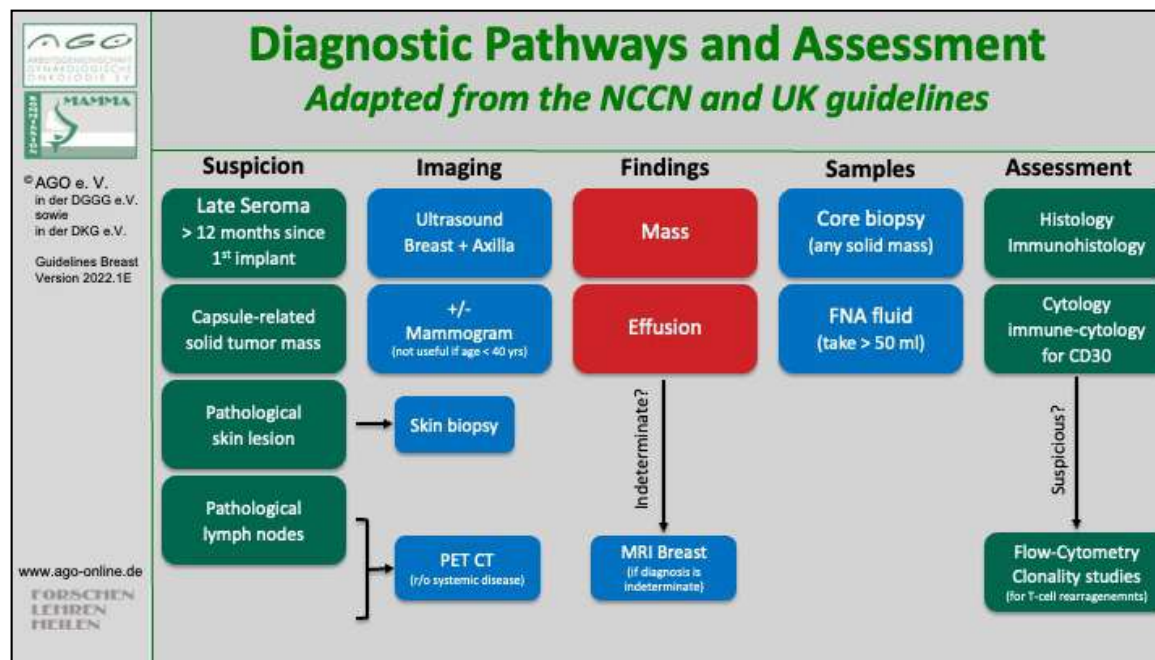
|                              | TNM-Kategorie | Definition   |
|------------------------------|---------------|--|
| Tumor extent (cT/pT)         | T1            | Confined to seroma or a layer on luminal side of capsule |
|                              | T2            | Early capsule infiltration 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

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

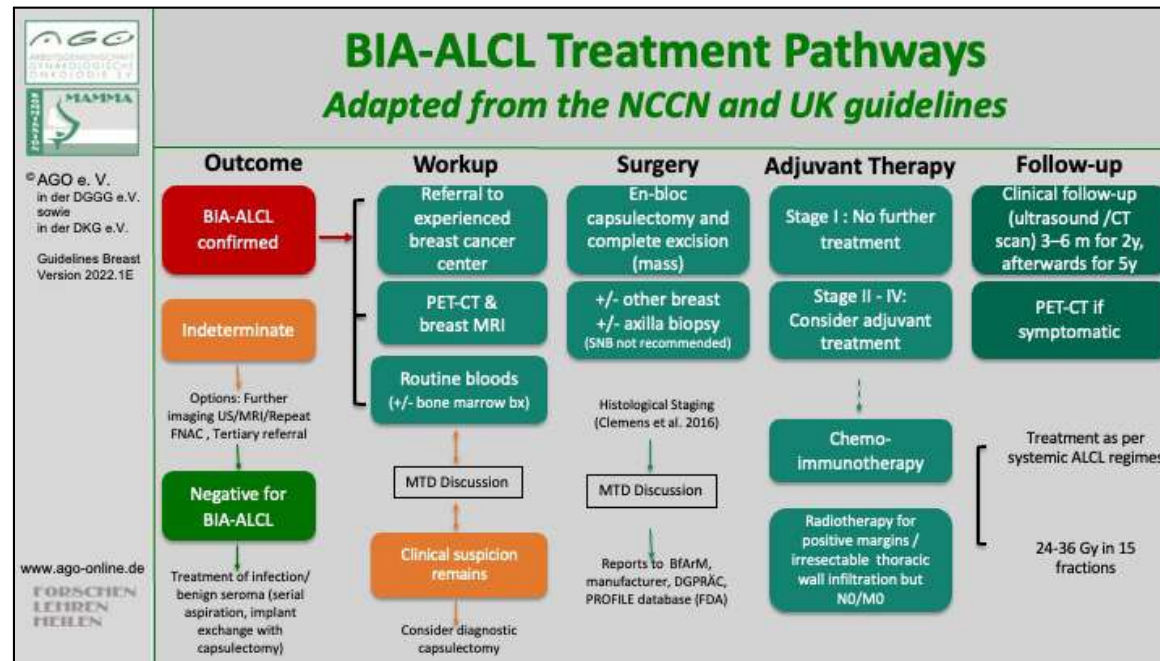
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2. NCCN Guidelines Version 1.2020 Breast implant-associated ALCL, <https://biaalcl.com/wp-content/uploads/NCCN-Guidelines-January-2020.pdf>
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## BIA-ALCL – EUSOMA-Recommendation

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

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

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## Metaplastisches Mammakarzinom

**Definition: Metaplastische Transformation der glandulären Tumorzellen**

- Bei epithelialer Differenzierung: Plattenepithelkarzinom, Spindelzellkarzinom
- Bei heterologer (mesenchymaler) Differenzierung: chondroides, ossäres oder rhabdoides metaplastisches Mammakarzinom

**Klinisch-pathologische Charakteristika:**

- < 1 % der Malignome der Mamma
- Gleiche Altersgruppe wie NST-Karzinome
- Umschrieben, tastbar
- Schnell wachsend, schlechtes Ansprechen auf Chemotherapie
- > 90 % triple-negativ

**Aggressivität:**

- Hoch maligne bei heterologer (mesenchymaler), plattenepithelialer oder high-grade spindelzelliger Differenzierung
- Unsicheres malignes Potential (low-grade) bei adenosquämöser oder Fibromatose-ähnliche Differenzierung

**Frequent mutations:**

- TP53, EGFR, PIK3CA, PTEN

### Background

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| Metaplastic breast carcinoma*<br>- high-grade -                        |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ▪ Operative therapy surgery and axillary staging according to standard | 4      | C  | ++  |
| ▪ Adjuvant chemotherapy (rather chemoresistant)                        | 4      | C  | +/- |
| ▪ Neoadjuvant chemotherapy (rather chemoresistant)                     | 4      | C  | -   |
| ▪ Adjuvant endocrine therapy if HR-positive                            | 4      | C  | +   |
| ▪ Adjuvant radiotherapy according to standard                          | 4      | C  | ++  |
| * Reference pathology recommended                                      |        |    |     |

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| Metaplastic Breast Carcinoma with Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)* |        |    |     |
|--|--------|----|-----|
|  | Oxford |    |     |
|  | LoE    | GR | AGO |
| ▪ Operative therapy and axillary staging according to standard                                       | 4      | C  | ++  |
| ▪ Adjuvant chemotherapy  | 4      | C  | -   |
| ▪ Neoadjuvant chemotherapy   | 4      | C  | --  |
| ▪ Adjuvant endocrine therapy (not applicable, since triple-negative tumors)                          | 4      | C  | -   |
| ▪ Adjuvant radiotherapy according to standard  | 4      | C  | +   |

\* Reference pathology recommended



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HEILEN

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