

Screened data bases: Pubmed 2007 - 2020, ASCO 2010 – 2020, SABCS 2010 – 2020, Cochrane Data Base (2017)

1. ABC Consensus Guidelines for Advanced Breast Cancer (ABC 1-4): Cardoso F, Costa A, Senkus E et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017 Jan 1;28(1):16-33.
2. Harbeck N, Lüftner D, Marschner N et al. ABC4 Consensus: assessment by a German Group of Experts. Breast Care (Basel). 2018 Mar;13(1):48-58.
3. ASCO (American Association of Clinical Oncology, Practice Guidelines, 2016) <http://www.asco.org>
4. American Society of Clinical Oncology Clinical Practice Survivorship Guidelines, Endorsements and Adaptations: <https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/Survivorship-Summary-of-Recs-Binder.pdf>
5. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology: <http://ascopubs.org/doi/pdfdirect/10.1200/JOP.2016.017905>
6. Hershman DL, Lacchetti C, Dworkin RH et al. American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67.
7. CMA (Canadian Medical Association , 2016): <http://www.cmaj.ca>
8. NCCN (National Comprehensive Cancer Network , 2018): <http://www.nccn.org>

9. NCI (National Cancer Institute , 2017): <http://www.cancer.gov>
10. S3 Leitlinie Supportive Therapie: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff 29. Januar 2018)



Brustkrebs: Spezielle Situationen

- **Versionen 2005–2020:**

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

- **Version 2021:**

Gluz / Sinn

Update January 2019 – Stickeler / Müller
Update January 2018 – Harbeck / Rody
Update January 2017 – Schütz / Sinn
Update January 2016 – Thomssen / Harbeck
Update January 2015 – Solomayer / Harbeck
Update January 2014 – Fehm/Schneeweiss
Update January 2013 – Fersis/Friedrich
Update January 2012 – Lux/Lück
Update February 2011 – Janni/Huober
Update January 2010 – Mundhenke/Rody

Screened data bases:

Pubmed 2000 – Jan 2019, ASCO 2005 – 2018, SABCS 2005 – 2018, ECCO/ESMO (2005 – 2018), EBCC (2005 – 2017), Cochrane data base (2012),

Screened for: Clinical Trials, Meta-Analyses, Practice Guidelines, Randomized Controlled Trial, Reviews

Screened guidelines

- NCCN: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

Brustkrebs: Spezielle Situationen

- „Junge“ Patientin
- Brustkrebs in der Schwangerschaft und Stillzeit
- „Ältere“ Patientin
- Mammakarzinom des Mannes
- Inflammatorisches Mammakarzinom
- Okkultes Karzinom CUP („Cancer of Unknown Primary“)
- Morbus Paget
- Maligner und Borderline Phylloides-Tumor
- Angiosarkom
- Brust-Implantat assoziiertes großzellig-anaplastisches Lymphom (BIA-ALCL)
- Metaplastisches Karzinom

1. Dietz JR, Partridge AH, Gemignani ML, et al.: Cancer Management Updates: Young and Older, Pregnant, or Male. Ann Surg Oncol. 2015 Oct;22(10):3219-24.

Brustkrebs bei der jungen Patientin ≤ 40 Jahre

	Oxford		
	LoE	GR	AGO
▪ Meist ungünstige Tumorbiologie mit schlechter Prognose	2a	B	
▪ Lokaltherapie altersunabhängig	2b	B	+
▪ Leitliniengerechte (neo-)adjuvante Systemtherapie (siehe Therapiekapitel)	1b	A	++
▪ GnRHa zur ovariellen Protektion (siehe Kap. Gyn. Probleme)	1a	B	+
▪ Angebot zur genetischen Beratung und Fertilitätsberatung	2b	B	++
▪ Frühzeitige Beratung zur Verhütung	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-Mitsunashi 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.
5. Liu Z, Sahli Z, Wang Y, Wolff AC et al. Young age at diagnosis is associated with worse prognosis in the Luminal A breast cancer subtype: a retrospective institutional cohort study. *Breast Cancer Res Treat* 2018;172(3):689-702.
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
8. Rapiti E, et al. Survival of young and older breast cancer patients in Geneva from 1990 to 2001. *Eur J Cancer* 2005;41(10):1446-52.
9. Oh JL, Bonnen M, Outlaw ED, et al . The impact of young age on locooregional recurrence after doxorubicin-based breast conservation therapy in patients 40 years old or younger: How young is "young"? *Int J Radiat Oncol Biol Phys* 2006;65:1345-52.
10. Anders CK, Hsu DS, Broadwater G, et al . Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol* 2008;26:3324-30.
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.
6. Huober J et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat. 2010;124:133–140.
7. Loibl S, Jackisch C, Lederer B et al. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials. Breast Cancer Res Treat. 2015 Jul;152(2):377-87.

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.
2. 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

3. Gray RG, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 2013; 31(suppl): abstr 5
4. Love RR, Laudico AV, Van Dinh N et al. Timing of adjuvant surgical oophorectomy in the menstrual cycle and disease-free and overall survival in premenopausal women with operable breast cancer. J Natl Cancer Inst. 2015 Mar 19;107(6):djv064.

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
4. S.M. Swain, J.H. Jeong, C.E. Geyer Jr., et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 2010 ; (362);2053–2065
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

6. 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;22(2):150-7.
7. Recchia F, Necozone S, Bratta M, et al. LH-RH analogues in the treatment of young women with early breast cancer: Long-term follow-up of a phase II study. Int J Oncol. 2015 Mar;46(3):1354-60.
8. Kim J, Kim M, Lee JH et al. Ovarian function preservation with GnRH agonist in young breast cancer patients: does it impede the effect of adjuvant chemotherapy? Breast. 2014 Oct;23(5):670-5.
9. Moore HCF, Unger JM, Phillips KA, et al Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance). J Clin Oncol 32:5s, 2014 (suppl; abstr LBA505)

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].
3. Mahmood U et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiat Oncol Biol Phys.2012;83(5):1387e93.

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.
6. Frandsen J, Ly D, Cannon G, et al. In the Modern Treatment Era, Is Breast Conservation Equivalent to Mastectomy in Women Younger Than 40 Years of Age? A Multi-Institution Study. *Int J Radiat Oncol Biol Phys*. 2015 Dec 1;93(5):1096-103.
7. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (≤ 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.
4. 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* 29 (17) 2334-2341 2011
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
6. Ruddy KJ et al. Menopausal symptoms and fertility concerns in premenopausal breast cancer survivors: A comparison to age- and

gravidity-matched controls. *Menopause*. 2011;18:105–108

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
9. Hulvat MC, Jeruss JS. Maintaining fertility in young women with breast cancer. *Curr Treat Options Oncol*. 2009 Dec;10(5-6):308-17.
10. Ruddy KJ, Gelber SI, Tamimi RM, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. *J Clin Oncol*. 2014 Apr 10;32(11):1151-6.
11. Lambertini M, Ceppi M, Poggio F, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. *Ann Oncol*. 2015 Dec;26(12):2408-19.

Brustkrebs in der Schwangerschaft*			
– Diagnostik und OP –			
	Oxford		
	LoE	GR	AGO
▪ Diagnostik wie außerhalb der Schwangerschaft (keine grundsätzliche MRT-Indikation)	4	C	++
▪ Staging: wenn indiziert (Knochenszintigraphie nach Entbindung)	5	D	+
▪ Ganzkörper MRT ohne Kontrastmittel	4	C	+/-
▪ OP wie bei Nicht-Schwangeren	4	C	++
▪ Sentinel-Node Biopsie (nur Technetium)	2b	B	+
▪ SLNE im 1. Trimester	5	D	+/-
▪ Sensitivität und Spezifität sind unklar (während Stillzeit); Stillen sollte für 24 Stunden vermieden werden	4	C	++
▪ Farbstoffblau (keine Studiendaten in der Schwangerschaft)	4	C	--
* Teilnahme an Registerstudie empfohlen			

Study link: <http://germanbreastgroup.de/studien/adjutant/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, Loibl S, Peccatori FA, Gheysens O, 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, Zagar TM, Faso A, Muss HB, 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.
7. Framarino-Dei-Malatesta M, Sammartino P, Napoli A. Does anthracycline-based chemotherapy in pregnant women with cancer offer safe cardiac and neurodevelopmental outcomes for the developing fetus? *BMC Cancer* 2017;17(1):777.
8. Scharl A, Ahr A, Göhring U-J: Malignome in der Schwangerschaft. In: Kaufmann M, Costa SD, Scharl A (eds) *Die Gynäkologie*. Springer, Heidelberg, 2002 pp 509
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

Brustkrebs in der Schwangerschaft – (Neo-)adjuvante Therapie –

- Bestrahlung während der Schwangerschaft
- (Neo-)adjuvante Chemotherapie ab dem zweiten Trimenon (Indikation wie bei Nicht-Schwangeren)
 - Anthrazykline: AC, EC
 - Taxane
 - Platinsalze (Carboplatin, Cisplatin)
 - MTX (e.g. CMF)
- Endokrine Therapie
- Anti-HER2-Therapie
- Bisphosphonate, Denosumab

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

Die Behandlung (Systemtherapie, Operation, RT) des Mammakarzinoms in der Schwangerschaft soll so nah wie möglich an der Standardbehandlung junger, nicht-schwangerer Patientinnen mit Mammakarzinom ausgerichtet sein.

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.

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, Feng S, Zheng C. 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.
4. Kong TW, Lee EJ, Lee Y, et al. Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy. *Obstet Gynecol Sci*. 2014 Nov;57(6):539-43.

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

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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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8. Azim HA Jr et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). Breast Cancer Res Treat. 2012;133(1):387-91.
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Statement Bisphosphonate during pregnancy

1. Levy S, Fayed I, Taguchi N et al. Pregnancy outcome following in utero exposure to bisphosphonates. Bone. 2009 Mar;44(3):428-30.
2. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9. Review.

General information: Chemotherapy during pregnancy

1. Murthy RK, Theriault RL, Barnett CM, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. Breast Cancer Res. 2014 Dec 30;16(6):3414.

Brustkrebs in der Schwangerschaft* – Entbindung und Stillen –

- Entbindung erst bei ausreichender kindlicher Reife
- Eine Beendigung der Schwangerschaft verbessert den mütterlichen Erkrankungsverlauf nicht
- Entbindungsmodus wie bei gesunden Schwangeren; Entbindung im Leukozytennadir nach Chemotherapie sollte vermieden werden
- Sollte eine Systemtherapie nach der Entbindung fortgeführt werden müssen, kann Stillen evtl. kontraindiziert sein (cave: Toxizität I)

Oxford		
LoE	GR	AGO
2b	C	++
3b	C	
4	C	++
5	D	++

* Teilnahme an Registerstudie empfohlen

General principles

- Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9.
- Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:87-896.
- 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.
- 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

- 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

- 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.



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Brustkrebs und Schwangerschaft*

– Familienplanung –

- Nach einer Mammakarzinomerkrankung kann mit Hilfe reproduktionsmedizinischer Verfahren eine Schwangerschaft angestrebt werden.
- Die Erfolgsaussichten für eine intakte Schwangerschaft bzw. ein Kind sind bei autologer Eizellverwendung bei Mammakarzinompatientinnen geringer als bei Nicht-Karzinompatientinnen.
- Mammakarzinompatientinnen im gebärfähigen Alter sollten eine Beratung über Fertilität und Fertilitätsverlust vor Therapiebeginn erhalten.
- Von einer Schwangerschaft soll nach einer Mammakarzinomerkrankung nicht abgeraten werden. Dies gilt grundsätzlich unabhängig vom Hormonrezeptorstatus.

* Teilnahme an Registerstudie empfohlen

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Brustkrebs während Schwangerschaft*

– Prognose –

Oxford
LoE

	<ul style="list-style-type: none"> ■ Mammakarzinom während Schwangerschaft / Stillzeit <ul style="list-style-type: none"> ▪ Prognose wird nicht verschlechtert, wenn korrekte Behandlung ■ Schwangerschaft / Laktation nach Mammakarzinom <ul style="list-style-type: none"> ▪ Prognose wird nicht verschlechtert 	<p style="color: green;">3a</p> <p style="color: green;">3a</p>	
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* Teilnahme an Registerstudie empfohlen

General principles

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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.
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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.
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8. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. *Cancer*. 2006 Jan 15;106(2):237-46
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.
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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.
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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

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Kroman N, et al. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *Breast.* 2003 Dec;12(6):516-21.
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Geriatrische Einschätzung

- Spezifische Algorithmen nicht existent
- Toleranz gegenüber onkologischen Behandlungen variiert erheblich („funktionelle Reserve“)
- Zur umfassenden geriatrischen Einschätzung (CGA) gehört die multidisziplinäre Auswertung der Prädiktoren für Morbidität und Mortalität älterer Menschen
 - Physische, mentale und psychosoziale Gesundheit
 - Basisaktivitäten des täglichen Lebens (Ankleiden, Körperpflege, Zubereiten des täglichen Essens, Medikamenteneinnahme, etc.)
 - Lebensumstände, soziales Netz, Verfügbarkeit von Hilfsdienstleistern
- Einschätzungsinstrumente:
 - Charlson Comorbidity Index (breit eingesetzt; verlässliche Prädiktion über 10 Jahre)
 - 12 Prognosefaktoren zur Abschätzung des 4-Jahre-Sterberisikos
 - Kurze Screening-Tests (eher zur qualitativen Bewertung geeignet)
 - IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale), G-8 Screening tool

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.
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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.

Behandlung der „rüstigen älteren“ Patientin

(Lebenserwartung > 5 Jahre und akzeptable Komorbidität)

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- Bestimmung des aktuellen Gesundheitszustandes

- Leitliniengerechte Behandlung

- Operation wie bei „jüngeren“ Patientinnen

- Hormontherapie (endokrin-sensibles Ca.)

- Chemotherapie (Standard Regime)

- < 70 Jahre

- > 70 Jahre

- Radiotherapie

- Verzicht auf Radiotherapie bei „low risk“, wenn eine endokrine Therapie geplant ist

- Trastuzumab

Oxford

LoE GR AGO

2b B ++

2a C ++

2b B ++

1a A ++

1a A +

2a C +*

1a A +

1b B +

2b C +

* Studienteilnahme wird empfohlen

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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 ≥ 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.
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10. Giordano SH: Breast cancer treatment guidelines in older women. *J Clin Oncol.* 2005 Feb 1;23(4):783-91.
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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.
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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
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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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Statement: Chemotherapy in pts. > 70 years

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4. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients *Breast Care* 2012;7:439-444
5. Muss HB, Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med.* 2009 May 14;360(20):2055-65.
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10. Tamirisa N, Lin H, Shen Y, et al. Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor-Positive, Node-Positive Breast Cancer. *JAMA Oncol* 2020;6:1548-54.

Statement: Radiotherapy

1. Kunkler I Radiotherapy issues in elderly breast cancer patients *Breast Cancer Patients Breast Care* 2012;7:453-459
2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control *Strahlenther Onkol* 2012 :1-5

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Statement: Trastuzumab

1. Freedman RA, Vaz-Luis I, Barry WT, et al. Patterns of chemotherapy, toxicity, and short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. Breast Cancer Res Treat. 2014 Jun;145(2):491-501.
2. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol. 2013 Nov 20;31(33):4222-8
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7. Albanell J et al. Trastuzumab in small tumours and in elderly women. Cancer Treat Rev. 2014;40(1):41-7.
8. Brollo J et al. Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. Cancer Treat Rev. 2013;39(1):44-50

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

	Oxford		
	LoE	GR	AGO
▪ Reduzierte Standardtherapie	2b	C	++
▪ Therapieoptionen abgeleitet aus Studien mit älteren Patientinnen:			
▪ Keine Brustoperation (endokrine Therapieoption erwägen)	2b	C	+
▪ Keine Axilla-Op. (≥ 60 Jahre, cN0, Rez. pos.)	2b	B	+
▪ Keine Radiatio (<3 cm, pN0, Rez. pos.)	1b	B	++
▪ Hypofraktionierte Radiatio	2b	B	+
▪ Keine Chemotherapie ≥ 70 Jahre bei negativer Risiko-Nutzen-Abwägung	2b	C	+

1. Walzer DE Measuring the value of radiotherapy in older women with breast cancer J Clin Oncol 2012 30 (23) 2809-2811
2. Audisio RA et al When reporting on older patients with cancer , frailty information is needed Ann Surg Oncol 2011; 18: 4-5
3. Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
4. Hughes KS et al Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer 2010 J Clin Oncol 28:69s (suppl 15, abstr 507).
5. Albrand G et al Early breast cancer: assessment and management considerations Drugs Aging 2008 25:35-45

Statement: Reduced standard treatment

Statement: No breast surgery (consider endocrine options)

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

4. de Haes JC, et al: Quality of life in breast cancer patients aged over 70 years, participating in the EORTC 10850 randomised clinical trial. Eur J Cancer. 2003 May;39(7):945-51. doi: 10.1016/j.ejca.2012.08.010. Epub 2012 Sep 6.
5. Balakrishnan A et al. Early operable breast cancer in elderly women treated with an aromatase inhibitor letrozole as sole therapy. Br J Cancer. 2011;105(12):1825-9.
6. Hamaker ME et al. Omission of surgery in elderly patients with early stage breast cancer. Eur J Cancer 2013;49(3):545-52.
7. Wink CJ et al. Hormone treatment without surgery for patients aged 75 years or older with operable breast cancer. Ann Surg Oncol. 2012;19(4):1185-91.

Statement: No axillary clearing (≥ 60 y, cN0, ER+)

1. Rudenstam CM, Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol. 2006 Jan 20;24(3):337-44.
2. Martelli G: A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. Ann Surg. 2005 Jul;242(1):1-6
3. Zurrida S: Axillary radiotherapy instead of axillary dissection: a randomized trial. Italian Oncological Senology Group. Ann Surg Oncol. 2002 Mar;9(2):156-60

Statement: No radiotherapy (≥ 70 y, pT1, pN0, ER+)

1. Kim YJ, Shin KH, Kim K. Omitting Adjuvant Radiotherapy for Hormone ReceptorPositive Early-Stage Breast Cancer in Old Age: A Propensity Score Matched SEER Analysis. Cancer research and treatment : official journal of Korean Cancer Association 2018.
2. Hannoun-Levi JM, et al. Breast cancer in elderly women: is partial breast irradiation a good alternative? Breast Cancer Res Treat. 2003 Oct;81(3):243-51
3. Hughes KS, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):971-
4. Kunkler I, et al. Postoperative breast irradiation: new trials needed in older patients. J Clin Oncol. 2003 May 1;21(9):1893; author reply 1893-4
5. Fyles AW: Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70
6. Kunkler IH, Williams LJ, Jack WJ, et al: on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.

7. Stueber TN, Diessner J, Bartmann C, et al. Effect of adjuvant radiotherapy in elderly patients with breast cancer. PLOS ONE 2020;15:e0229518.

Statement: Hypofractionated radiotherapy

1. Vaidya JS, 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.
2. Vaidya JS, Wenz F, Bulsara M, et al: TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2014 Feb 15;383(9917):603-13.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013 Dec;14(13):1269-77.
4. Ortholan C, et al. Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. Int J Radiat Oncol Biol Phys. 2005 Jan 1;61(1):154-62.
5. Kirova YM, Campana F, Savignoni A, et al: for the Institut Curie Breast Cancer Study Group Breast-Conserving Treatment in the Elderly: Long-Term Results of Adjuvant Hypofractionated and Normofractionated Radiotherapy. Int J Radiat Oncol Biol Phys. 2009 Jan 2

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

1. Du XL, Jones DV, Zhang D. Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. J Gerontol A Biol Sci Med Sci. 2005 Sep;60(9):1137-44.
2. Kehl KL, Niu J, Chavez-MacGregor M et al. Hospitalization by cytotoxic chemotherapy regimen among older women with stage IV breast cancer. Cancer 2018;124(24):4685-91.
3. 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 May 14-20;365(9472):1687-717
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. Lancet. 371;2008:1687-717

Mammakarzinom des Mannes: Diagnostik und lokale Therapie

• Diagnostische Aufarbeitung wie bei Frauen

- Mammographie
- Ultraschall

• Standard-Op: Mastektomie

- BET (Tumor-Brust-Relation!)
- Sentinel-Node Biopsie (SNE)

• Radiotherapie wie bei Frauen (beachte Tumor-Brust-Relation!)

• Genetische Beratung, falls ein weiterer Verwandter / Verwandte betroffen

• Krebsfrüherkennungsuntersuchungen gemäß Empfehlungen der DKG e.V.

* Teilnahme an Registerstudie empfohlen

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

International registry

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

General

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

7. Wang J, Sun Y, Qu J, et al. Survival analysis for male ductal and lobular breast cancer patients with different stages. Future Oncol 2018.
8. Gucalp A, Traina TA, Eisner JR, et al. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat 2018.
9. Wang K, Wang QJ, Xiong YF, et al. Survival Comparisons Between Early Male and Female Breast Cancer Patients. Scientific reports 2018;8(1):8900.
10. Heinig J: Clinical management of breast cancer in males: a report of four cases. Eur J Obstet Gynecol Reprod Biol. 2002 Apr 10;102(1):67-73
11. Thalib L ,Hall P. Survival of male breast cancer patients: Population-based cohort study. Cancer Sci. 2008
12. Dietz JR, Partridge AH, Gemignani ML, et al. Breast Cancer Management Updates: Young and Older, Pregnant, or Male. Ann Surg Oncol. 2015 Oct;22(10):3219-24.
13. Deb S, Lakhani SR, Ottini L, et al. The cancer genetics and pathology of male breast cancer. Histopathology. 2016 Jan;68(1):110-8.

Statement: Diagnostic work up as in women

Statement: Mammography

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

Statement: Ultrasound

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

Statement: Standard-surgery: Mastectomy – men

1. Shen. I et al Skin-sparing mastectomy: a survey based approach to defining standard of care. Am Surg. 2008 Oct;74(10):902-51.
2. Fentiman IS. Surgical options for male breast cancer. Breast Cancer Res Treat 2018;172(3):539-44.
3. Lanitis S et al. Diagnosis and management of male breast cancer, World J Surg. 2008 Nov;32(11):2471-6.
4. Kuo SH et al. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence, Int J

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

5. Fogh S et al. Therapy for Male Breast Cancer: Functional Advantages With Comparable Outcomes Using Breast Conservation. Clin Breast Cancer. 2013;13(5):344-9.
6. Fields EC et al. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. J Radiat Oncol Biol Phys 2013;87(4):747-52
7. Cloyd et al. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983-2009. Ann Surg Oncol. 2013;20:1545-50
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Statement: Surgery: BEO – men

1. Cloyd JM, Hernandez-Boussard T, Wapnir IL. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983–2009. Ann Surg Oncol. 2013;20(5):1545–50.
2. Bratman SV, Kapp DS, Horst KC. Evolving trends in the initial locoregional management of male breast cancer. Breast. 2012;21(3):296–302. <https://doi.org/10.1016/j.breast.2012.01.008>.
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4. Cutuli B, Lacroze M, Dilhuydy JM, Velten M, De Lafontan B, Marchal C, Resbeut M, Graic Y, Campana F, Moncho-Bernier V, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer. 1995;31A(12):1960–4.
5. Golshan M, Rusby J, Dominguez F, Smith BL. Breast conservation for male breast carcinoma. Breast. 2007;16(6):653–6.
6. Selcukbiricik F, Tural D, Aydog˘an F, Bes˘e N, Bu˘yu˘ku˘nal E, Serdengec˘ti S. Male breast cancer: 37-year data study at a single experience center in Turkey. J Breast Cancer. 2013;16(1):60–5. <https://doi.org/10.4048/jbc.2013.16.1.60>.
7. Serarslan A, Gursel B, Okumus NO, Meydan D, Sullu Y, Gonullu G. Male breast cancer: 20 years experience of a tertiary hospital from the Middle Black Sea Region of Turkey. Asian Pac J Cancer Prev. 2015;16(15):6673–9.
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):616-21
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!)

1. Ribeiro GG: A review of the management of the male breast carcinoma based on an analysis of 420 treated cases. Breast 1996; 5: 141-146
2. Schuchardt U et al. Adjuvant radiotherapy for breast carcinoma in men: a 20-year clinical experience. Am J Clin Oncol 1996 19:330
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
3. Basham VM: BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. Breast Cancer Res 2002; 4: R2
4. Thorlacius S, Sigurdson S, Bjanadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet 1997; 60: 1079-1084

Statement: Screening for 2nd malignancies according guidelines

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

Statement: Systemic therapy

1. Doyen J et al., Ann Oncol. 2009 Oct 27. [Epub ahead of print], Aromatase inhibition in male breast cancer patients: biological and

clinical implications.

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

Review articles

1. Donegan WL: Carcinoma of the breast in males. *Cancer* 1998; 83: 498-509
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
5. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. *Lancet.* 2006 Feb 18;367(9510):595-604. Review. Erratum in: *Lancet.* 2006 Jun 3;367(9525):1818
6. Agrawal A, Ayantunde AA, Rampaul R et al. Male breast cancer: a review of clinical management. *Breast Cancer Res Treat.* 2006 Oct 11;
7. Korde LA et al: Multidisciplinary meeting on male breast cancer; summary and research recommendations *J Clin Oncol* 28: 2114-2122, 2010
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)
10. Ruddy KJ et al. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann Oncol* 2013; 24(6):1434-43.

Mammakarzinom des Mannes: Prognosefaktoren

- Nodalstatus
- Alter
- Tumorgroße
- ER/PR Expression
- Ki-67 Expression
- Grading
- Genomische Signaturen (z.B. OncotypeDx)

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

Registries

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

Mammakarzinom des Mannes: Systemtherapie

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

* Studienteilnahme empfohlen

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.

Statement endocrine therapy

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
5. Goss PE: Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955–1996. Cancer 1999; 85: 629-639
6. Giordano SH: Efficacy of anastrozole in male breast cancer. Am J Clin Oncol 2002 25: 235-237
7. Agrawal A: Fulvestrant in advanced male breast cancer. Breast Cancer Res Treat. 2007 Jan;101(1):123. Epub 2006 Jun 29. No abstract available
8. Giordano SH: Leuprolide acetate plus aromatase inhibition for male breast cancer. J Clin Oncol. 2006 Jul 20;24(21):e42-3. No abstract available.
9. Nahleh ZA: Hormonal therapy for male breast cancer: A different approach for a different disease. Cancer Treatment Reviews 2006 32:101-105
10. Arriola E: Aromatase inhibitors and male breast cancer. Clin Transl Oncol. 2007 Mar;9(3):192-4
11. Eggemann H, Ignatov A, Smith BJ, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat. 2013 Jan;137(2):465-70.
12. 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
13. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. Br J Cancer. 2013;108(11):2259-63
14. Eggemann H, Brucker C, Schrauder M, et al. Survival benefit of tamoxifen in male breast cancer: prospective cohort analysis. British journal of cancer 2020;123:33-7.


Statement palliative chemotherapy

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

Benefit from Trimodal Treatment in Inflammatory Breast Cancer			
 <p> *AGO e. V. in der DGBC e. V. in der DGBC e. V. Guidelines Breast Version 2021.10 </p> <p> www.ago-online.de FÜR DIE FÜR DIE FÜR DIE </p>	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.



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Primäres inflammatorisches Mammakarzinom

	5yr- OS	
pCR	77%	p<0.0001
Non-pCR	54%	
TN-IBC	37%	p<0.0001
other biologic subtypes (HR+/HER2-, HR+/HER2+, HR-/HER2+)	60%	

- N=8.550
- On multivariable analysis, TNBC, positive margins, and not receiving either chemotherapy, hormonal therapy or radiotherapy were independently associated with poor 5-year survival (p < 0.0001).

1. Biswas T, Jindal C, Fitzgerald TL, et al.: Pathologic Complete Response (pCR) and Survival of Women with Inflammatory Breast Cancer (IBC): An Analysis Based on Biologic Subtypes and Demographic Characteristics. Int J Environ Res Public Health. 2019 Jan 4;16(1)

Primäres inflammatorisches Mammakarzinom (IBC, cT4d)

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

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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 3.2018. 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

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

Statement: Preoperative chemotherapy

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Statement: Regimens as in non-inflammatory BC

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Statement: in HER2 positive disease addition of trastuzumab

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Statement: in HER2 positive disease addition of trastuzumab and pertuzumab

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Statement: in HER2 negative disease addition of bevacizumab

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Statement: Sentinel lymph node

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Statement: Radiotherapy


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Statement: Postoperative systemic therapy as in non-inflammatory BC

1. Veyret C: Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: ten-year results from the French Adjuvant Study Group GETIS 02 Trial.Cancer. 2006 Dec 1;107(11):2535-44
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Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary – Axillary CUP)

- **Incidence:** < 1% of metastatic axillary disease
- **In > 95% occult breast cancer, < 5% other primary**
- **Immunhistology**
 - ER-positive: 55%
 - HER2 3+: 35%
 - Triple-negative: 38%
- **Nodal status:**
 - 1 - 3 Ln-Met. in 48%
 - > 3 Ln-Met in 52%
- **Outcome similar compared to breast cancer with similar tumor biology and tumor stage**

Guidelines

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Outcome

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Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP) Bildgebende Diagnostik			
	Oxford		
	LoE	GR	AGO
▪ Mammadiagnostik inkl. Mamma-MRT	3	B	++
▪ Ausschluss eines kontralateralen Tumors	3	B	++
▪ Ausschluss eines anderen Primarius insbes. bei TNBC (Haut, weibl. Genitaltrakt, Lunge, Schilddrüse, Magen, NEC)	5	D	++
▪ Staging (insbes. Thorax, Abdomen, Becken, ggf. auch Schilddrüsen-Sonographie, HNO-Untersuchung)	3	B	++
▪ PET/ PET-CT	3b	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>
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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

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Statement: PET

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Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP) Pathologie, Molekularpathologie			
	Oxford		
	LoE	GR	AGO
▪ Immunhistologie: ER, PR, HER2, GATA3 (ggf. auch Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, u.a.)	5	D	++
▪ Ausschluss anderer Primärtumoren bei TNBC oder ungewöhnlicher Histologie, z. B. Lunge, weibl. Genitaltrakt, Kopf-Hals-Tumoren, neuroendokrine Ca	5	D	++
▪ Genexpressionsprofile zur Bestimmung des Primarius (z.B. CUPprint, Pathwork, TOT, Theros CTID)	2c	B	+/-
▪ NGS, Epigenetik zur Bestimmung des Primarius (Panel-Sequenzierung, z.B. EPICup)	2c	B	+/-
▪ Prognostische Genexpressionstests	5	D	--

Immunohistochemistry

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Gene expression profiling and other molecular approaches in CUP disease

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Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP)

Therapie

Oxford		
LoE	GR	AGO
3a	C	++
3a	C	--
5	D	++
2c	B	+
3b	B	+

- Axilladisektion
- Mastektomie bei unauffälligem MRT
- Leitliniengerechte (neo-)adjuvante Systemtherapie
- Brust-Bestrahlung bei negativem Mamma-MRT
- Bestrahlung der regionären LK

Guidelines

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Statement: Axillary dissection

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Statement: Mastectomy without (in-)breast tumor

References 1-4 (retrospective analysis , case reports)

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<http://doi.org/10.1007/s00117-013-2549-7>

Statement: Breast irradiation if breast MRI is negative

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Statement: Systemic treatment according N+ tumor

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Paget's Disease of the Breast

- **Definition:** Paget's disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer.
- **Clinical presentation:** skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin

Feature	Frequency
Presentation	Paget's disease with invasive Ca. (37 - 58%) Paget's disease mit DCIS (30 - 63%) Isolated Paget's disease (4 - 7%) Isolated Paget's disease with invasion (rare)
IHC	HER2-positive (83 - 97%) ER-positive (10 - 14%) AR-positive (71 - 88%)
Prognosis and tumor biology	Better in isolated Paget's disease Worse if in combination with invasive breast cancer or DCIS compared to isolated Paget's disease

Review

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

Clinical Presentation

1. 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>

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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>
7. Schelfhout, V. R., Coene, E. D., Delaey, B., et al. (2000). Pathogenesis of Paget's disease: epidermal heregulin-alpha, motility factor, and the HER receptor family. *Journal of the National Cancer Institute*, 92(8), 622–628.



Morbus Paget der Mamille Diagnostik

- Stanzbiopsische histologische Sicherung
- Mammographie, Mammasonographie
- Mamma-MR (falls andere Bildgebung nicht aussagekräftig)
- Immunhistologie (ER, PR, HER2, Ck7) zur Abgrenzung benigner und HER2-negativer Befunde

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

Imaging

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>
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. Capobianco, G., Spaliviero, B., Dessole, S., et al. (2006). Paget's disease of the nipple diagnosed by MRI. *Archives of Gynecology and Obstetrics*, 274(5), 316–318.

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

immunohistochemical study. *Histopathology*, 57(4), 564–571.

<http://doi.org/10.1111/j.1365-2559.2010.03665.x>

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4. Raivoherivony TI, Feron J, Klijanienko J: MIAC1 he utility of nipple scraping in the diagnosis of Paget disease of the breast, Letter to the Editor; *Diagnostic Cytopathology*. 2019;47:249–250

Morbus Paget der Mamille Therapie

	Oxford		
	LoE	GR	AGO
▪ Morbus Paget mit Mamma-Tumor (invasives MaCa, DCIS)			
▪ Therapie entsprechend Standards der Grunderkrankung	5	D	++
▪ Operation mit R0 Resektion	1c	B	++
▪ Isolierter Morbus Paget des NAC:			
▪ R0-Resektion inkl. NAC	1c	B	++
▪ keine adjuvante Bestrahlung bei R0	4	D	++
▪ Sentinel-Lymphknoten-Exzision (SLNE)	2b	B	-

Surgical Treatment of Pagets'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>
3. Dominici, L. S., Lester, S. C., Liao, G.-S., et al. (2012). Current surgical approach to Paget's


Treatment of isolated Pagets'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)

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. Chaney, A. W., Pollack, A., McNeese, M. D., et al. (2000). Primary treatment of cystosarcoma phyllodes of the breast. Cancer, 89(7), 1502–1511.
3. Esposito, N. N., Mohan, D., Brufsky, A., et al. (2006). Phyllodes tumor: a clinicopathologic and immunohistochemical study of 30 cases. Archives of Pathology & Laboratory Medicine, 130(10), 1516–1521. [http://doi.org/10.1043/1543-2165\(2006\)130\[1516:PTACAI\]2.0.CO;2](http://doi.org/10.1043/1543-2165(2006)130[1516:PTACAI]2.0.CO;2)
4. Roa, J. C., Tapia, O., Carrasco, P., et al. (2006). Prognostic factors of phyllodes tumor of the breast. Pathology International, 56(6), 309–314. <http://doi.org/10.1111/j.1440-1827.2006.01965.x>
5. Tan, P. H., Jayabaskar, T., Chuah, K.-L. et al. (2005). Phyllodes tumors of the breast: the role of pathologic parameters. American

histological criteria and surgical margins. *Journal of Clinical Pathology*, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>

7. 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
8. 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.
9. 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
10. 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	
<p>AGO e. V. in der DGGG e. V. sowie in der DKG e. V.</p> <p>Guidelines Breast Version 2021.10</p> <p>www.ago-online.de</p> <p>FOURTH EDITION 1. EDITION 2017 2. EDITION 2018</p>	
<p>▪ Frequency 0.3 – 1% of all primary breast tumors</p>	
parameter	frequencies
Grading (3-STEP histological grading system)	Benign (75%) Borderline (16%) Malignant (9%)
Median age at time of diagnosis	Benign PT: 39 y Borderline PT: 45 y Malignant PT: 47 y
Local recurrence	Benign PT: 4 – 17% Borderline PT: 14 – 25% Malignant PT: 23 – 30%
Metastasis	Benign PT: <1% Borderline PT: 1.6% Malignant PT: 16–22%
<p>10y 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>

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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*.
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4. 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
5. Choi N, Kim K, Shin KH, et al.: The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and

6. 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
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Borderline und maligner Phylloides tumor - Diagnostik -

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

Borderline und maligner Phylloides tumor - Operative Therapie -

	Oxford		
	LoE	GR	AGO
▪ Borderline-/ maligner Phylloides tumor Komplettresektion mit ausreichendem und mind. > 1mm breitem Randsaum	2b	B	++
▪ SLNE / Axilladisektion	4	C	--
▪ Therapie des Lokalrezidivs ▪ RO-Resektion oder einfache Mastektomie	4	C	++

Statement: Complete (wide) local excision or MRM

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.

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>

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>

Systematic Reviews (2016 – 2021)

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

Borderline und maligner Phylloides tumor - Adjuvante Therapie -			
	Oxford		
	LoE	GR	AGO
Adjuvante Radiotherapie (jüngeres Alter, größeres Tumolvolumen >5cm, knapper Resektionsrand) <ul style="list-style-type: none"> Lokale Kontrolle Effekt aufs krankheitsfreie/Gesamtüberleben 	2B	B	+
	2B	B	-
Systemische adjuvante Therapie (Chemotherapie, endokrine Therapie)	4	C	--
Adjuvante Therapie des Lokalrezidivs <ul style="list-style-type: none"> Radiotherapie, Chemotherapie nach R1-Resektion 	4	C	+/-
Fernmetastasen (sehr selten) <ul style="list-style-type: none"> Therapie wie bei Weichteilsarkomen 	4	C	++

Statements: Systemic adjuvant therapy/ Chemotherapy and Endocrine therapy

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>
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>
3. Morales-Vásquez, F., Gonzalez-Angulo, A. M., Broglio, K., et al. (2007). Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. The Breast Journal, 13(6), 551–556. <http://doi.org/10.1111/j.1524-4741.2007.00510.x>

Statement: Adjuvant radiotherapy

1. Barth, R. J., Wells, W. A., Mitchell, S. E., et al. (2009). A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Annals of Surgical Oncology, 16(8), 2288–2294. <http://doi.org/10.1245/s10434-009-0489-2>
2. Gnerlich, J. L., Williams, R. T., Yao, K., et al. (2014). Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer Data Base. 1998-2009. Annals of Surgical Oncology, 21(4), 1222–1230. <http://doi.org/10.1245/s10434-013->

Journal, 20(6), 639–644. <http://doi.org/10.1111/tbj.12333>

4. 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>
5. Choi, N., Kim, K., Shin, K.H., et al. (2018). Malignant and borderline phyllodes tumors of the breast: a multicenter study of 362 patients (KROG 16-08). *Breast Cancer Res Treat.* 2018 Sep;171(2):335-344. doi: 10.1007/s10549-018-4838-3. Epub 2018 May 28.
6. 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.
7. 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.
8. 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.

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>
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>
3. 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/tbi.12333>

characteristics between benign borderline and malignant phyllodes tumors of the breast. Asian Pacific Journal of Cancer Prevention : APJCP, 15(24), 10791–10795.
<http://doi.org/10.7314/APJCP.2014.15.24.10791>

3. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2016;14(6):758-786.



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FINDEN
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TEILEN

Sarcomas of the Breast

- Not infrequently associated with familial syndromes (Li-Fraumeni, familial adenomatous polyposis, neurofibromatosis type 1)
- Primary sarcomas: angiosarcoma, undifferentiated sarcoma, leiomyosarcoma, liposarcoma, osteosarcoma
- Secondary malignancies of the breast:
 - Radiotherapy-Associated Angiosarcoma
 - Breast Implant Associated Large-Cell Anaplastic Lymphoma (BI-ALCL)
- Rare: intramammary sarcoma metastases
- Staging: TNM (UICC) or AJCC scheme of the soft tissue sarcoma analogous to sarcoma of the breast
- Grading: Analogous to the FNCLCC system for sarcoma or according to Rosen (1988) for angiosarcomas



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Primary Angiosarcoma of the Breast

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

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>
2. Kaklamanos, I. G., Birbas, K., Syrigos, K. N., et al. (2011). Breast angiosarcoma that is not related to radiation exposure: a comprehensive review of the literature. *Surgery Today*, 41(2), 163–168. <http://doi.org/10.1007/s00595-010-4341-x>
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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Primäres Angiosarkom der Brust*			
Diagnostik			
	Oxford		
	LoE	GR	AGO
▪ MG/MS zur Bestimmung der Tumorausdehnung	3a	C	--
▪ Präop. MRT zur Bestimmung der Tumorausdehnung	3a	C	++
▪ Diagnose durch Stanzbiopsie	3a	C	++
▪ Diagnose durch Feinnadelbiopsie	3a	C	--
▪ Staging (CT Thorax, Abd.; bei Angiosarkom MRI Kopf)	4	D	++
▪ Prognostische Faktoren: Größe, Grading, Tumorränder	3a	C	++

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* Behandlung in spezialisierten Zentren empfohlen

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Primäres Angiosarkom der Brust Therapie


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

- Operation mit weiten freien Tumorrändern,
i.d.R. Mastektomie
 - Brusterhaltende Therapie
- SLNE oder axilläre Dissektion im Falle cN0
- Adjuvante Chemotherapie
(Anthrazyklin/Taxan-basiert)
- Adjuvante Radiotherapie, wenn high risk
(Größe > 5 cm, R1)

• Behandlung in spezialisierten Zentren empfohlen

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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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Sekundäres Angiosarkom der Brust Therapie			
	Oxford		
	LoE	GR	AGO
▪ Sekundäre Mastektomie	3a	C	++
▪ Adjuvante Chemotherapie (Anthrazyklin/Taxan-basiert)	2b	B	+/-
▪ Adjuvante Radiotherapie bei Hochrisiko (Größe > 5 cm, R1)	2b	B	+/-
▪ Regionale Hyperthermie (Verbesserung lokale Kontrolle) plus Chemotherapie und/oder Radiotherapie	2b	B	+/-

Surgery

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Adjuvant Hyperthermia

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Angiosarkome der Brust			
Therapie von Lokalrezidiven und Metastasen			
	Oxford		
	LoE	GR	AGO
<u>Therapie des Lokalrezidivs:</u>			
• R0-Resektion	4	C	++
• Adjuvante Radiotherapie bei Hochrisiko (Größe > 5 cm, R1)	4	C	+/-
<u>Fernmetastasierung / nicht resektable Tumoren:</u>			
• Therapie wie Weichteilsarkome	4	C	++
• Paclitaxel weekly / liposomales Doxorubicin (bei Angiosarkomen)	2b	B	+
• Antiangiogene Therapie (z.B. bei Angiosarkom)	4	C	+/-

Treatment of local recurrences

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Treatment of metastatic and non-resectable tumors

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Brust-Implantat-assoziiertes großzellig-anaplastisches Lymphom (BIA-ALCL)

- Etwa 10.000.000 Implantatträgerinnen weltweit
- Selten, 3% aller Non-Hodgkin-Lymphome, 0,04–0,5% aller malignen Brusterkrankungen
- geschätzte jährliche Inzidenz 0,6–1,2 je 100.000 Frauen mit Implantaten (medianes Patientenalter 54 J.)
- 1:3.000-30.000 bei Frauen mit texturierten Implantaten (CAVE: Underreporting!)
- Auftreten überwiegend bei texturierten Implantaten
- 5-Jahres-OAS 89%
- Intervall zur Lymphomdiagnose: 8 Jahre (Median)
- Klinische Präsentation
 - Schwellung und Serom (60%)
 - Tumoröse Raumforderung (17%)
 - Serom und Raumforderung (20%)
 - Axilläre Lymphadenopathie (20%)
- Histologisch: CD30+ / ALK- T-Zell-Lymphom
- Meldepflicht als SAE nach §3 MPVS an das BfArM

Reviews

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12. Cordeiro PG, Ghione P, Ni A, et al. Risk of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) in a cohort of 3546 women prospectively followed long term after reconstruction with textured breast implants. *J Plast Reconstr Aesthet Surg.* 2020 May;73(5):841-846. doi: 10.1016/j.bjps.2019.11.064. Epub 2020 Jan 20. PMID: 32008941
13. Clemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). *Aesthet Surg J.* 2019 Jan 31;39(Suppl_1):S3-S13. doi: 10.1093/asj/sjy331. PMID: 30715173
14. BfArm recommendations
<https://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/Br>

	<h2>BIA-ALCL - Implantatoberflächen</h2>					
<small> © AGO e. V. in der DGOP e. V. sowie in der DGBR e. V. Guidelines Breast Version 2021.10 </small>	<ul style="list-style-type: none"> The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface. The risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces. 					
Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/ Nano
Surface Area	high	intermediate	intermediate	low	low	minimal
Roughness	high	intermediate	low	low	low	minimal
SURFACE TYPE	4	3	3	2	2	1

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BIA-ALCL– Diagnostik			
	Oxford		
	LoE	GR	AGO
■ Sonographie (Abklärung neu aufgetretener Serome 1 Jahr nach Implantateinlage, Herdbefund (Sensitivität: 84%, Spezifität: 75%))	3a	D	++
■ Mamma-MRT bei Bestätigung Verdachtsdiagnose	3a	D	++
■ Staging (Bildgebung, z.B. CT, PET-CT)	3a	D	++
■ Erguss-Zytologie bei Späterom <ul style="list-style-type: none"> ■ Untersuchung von mind. 50ml ■ komplette Aufarbeitung ■ Flowzytometrie (T-Zell-Klon) ■ BIA-ALCL spezifische zytol. Diagnostik (CD 30+) 	3a	D	++
■ Stanzbiopsie bei soliden Herdbefunden	3a	D	++
■ Lymphomdiagnostik am Resektat und histologisches Staging			
■ Dokumentation des Implantates (Hersteller, Größe, Füllung, Oberfläche, Batch-Nummer) und Einlage in Register	5	D	++

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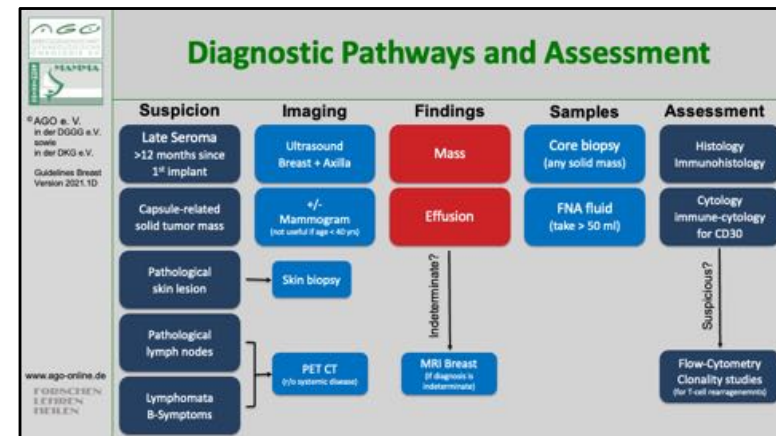
BIA-ALCL – Therapie			
	Oxford		
	LoE	GR	AGO
▪ Implantatentfernung und vollständige Kapsulektomie einschließlich Tumorentfernung	3a	C	++
▪ Entfernung suspekter Lymphknoten, keine routine-mäßige Sentinel-Node Biopsie, keine Axilladisektion	4	D	++
▪ Polychemotherapie (z.B. CHOP) bei extrakapsulärer Tumorausbreitung	4	D	+
▪ Radiotherapie bei unresektablen Tumoren oder R1	5	D	+/-
▪ Vorstellung im interdisziplinären Tumorboard (inkl. Lymphonspezialist)	5	D	++

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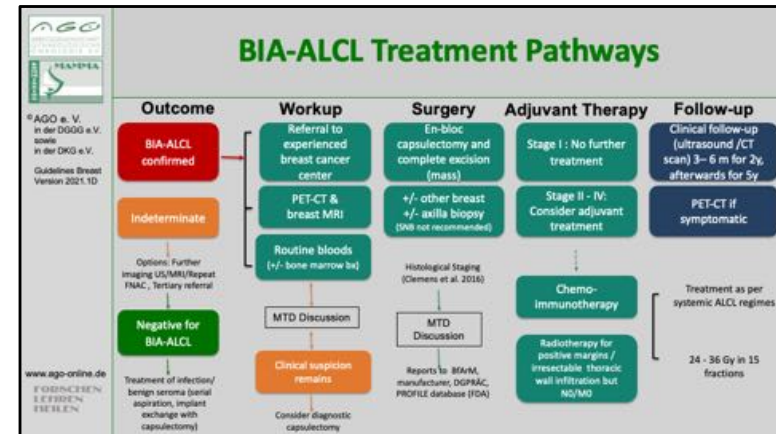
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TNM Staging of BIA-ALCL (proposed)				
	TNM-Kategorie	Definition	Stage	Definition
Tumor extent (cT/pT)	T1	Confined to seroma or a layer on luminal side of capsule	IA	T1 N0 M0
	T2	Early capsule infiltration	TB	T2 N0 M0
	T3	Cell aggregates or sheets infiltrating the capsule	TC	T3 N0 M0
	T4	Lymphoma infiltrates beyond the capsule	IIA	T4 N0 M0
Regional lymph nodes (cN/pN)	N0	No lymph node involvement	IIB	T1-3 N1 M0
	N1	One regional lymph node positive	III	T4 N1-2 M0
	N2	Multiple regional lymph nodes positive	IV	T any N any M1
Metastasis (cM/pM)	M0	No distant spread		
	M1	Spread to other organs or distant sites		


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3. NCCN Guidelines Version 1.2020 Breast implant-associated ALCL, <https://biaalcl.com/wp-content/uploads/NCCN-G>



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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Cardoso MJ et al EUSOMA position regarding breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and Breast. 2019 Apr;44:90-93. doi: 10.1016/j.breast.2019.01.011.



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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 adenosquamöser oder Fibromatose-ähnliche Differenzierung

Background

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28689362

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Metaplastisches Mammakarzinom - high-grade -			
	Oxford		
	LoE	GR	AGO
▪ Operative Therapie und axilläres Staging nach Standard	4	C	++
▪ Adjuvante Chemotherapie (eher chemoresistent)	4	C	++
▪ Neoadjuvante Chemotherapie (eher chemoresistent)	4	C	+/-
▪ Adjuvante endokrine Therapie, wenn Rezeptor-positiv	4	C	+
▪ Adjuvante Radiotherapie nach Standard	4	C	++

Therapy review:

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Axilla

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Adjuvant chemotherapy

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Neoadjuvant chemotherapy

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Adjuvant endocrine therapy

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Metaplastisches Mammakarzinom mit unsicherem malignen Potential (fibromatoseartiges und adenosquamöses Ca.)*			
	Oxford		
	LoE	GR	AGO
▪ Operative Therapie und axilläres Staging nach Standard	4	C	++
▪ Adjuvante Chemotherapie	4	C	-
▪ Neoadjuvante Chemotherapie	4	C	--
▪ Adjuvante endokrine Therapie (entfällt, da triple-negative Tumoren)	4	C	-
▪ Adjuvante Radiotherapie nach Standard	4	C	+

Fibromatose-ähnliches Mammakarzinom (low-grade)

1. Takano EA, Hunter SM, Campbell IG, Fox SB. Low-grade fibromatosis-like spindle cell carcinomas of the breast are molecularly exiguous. *SciMed Central. BMJ Publishing Group*; 2015 May;68(5):362–367. PMID: 25713418
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Adenosquamoses metaplastisches Karzinom (low grade)

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