

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Brustkrebs: Spezielle Situationen

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■ Versionen 2005-2017:

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

■ Version 2018:

Harbeck / Rody

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 2018, ASCO 2005 – 2017, SABCS 2005 – 2017, ECCO/ESMO (2005 – 2017), 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
- Angiosarkome
- 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 ≤ 35 Jahre

- Meist ungünstige Tumorbiologie mit schlechter Prognose
- Lokaltherapie wie bei ≥ 35 Jahre
- Leitliniengerechte (neo-)adjuvante Systemtherapie (siehe Therapiekapitel)
- GnRH zur ovariellen Protektion (siehe Kap. Gyn. Probleme)
- Angebot zur genetischen Beratung und Fertilitätsberatung
- Frühzeitige Beratung zur Verhütung

	Oxford		AGO
	LoE	GR	
2a		B	
2b		B	+
1b		A	++
1a		B	+
2b		B	++
2b		B	++

1. Paluch-Paluch-Shimon S, Pagani O, Partridge AH, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast. 2017 Oct;35:203-217.
2. 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.
3. 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
4. Partridge AH, Pagani O, Abulkhair O, et al. First international consensus guidelines for breast cancer in young women (BCY1). Breast. 2014 Jun;23(3):209-20.
5. Cardoso F, Loibl S, Pagani O, et al: European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012 Dec;48(18):3355-77

Prognosis in young women

1. 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.
2. 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.
3. Gonzalez-Angulo AM et al., Women age ≤ 35 years with primary breast carcinoma: Disease features at presentation. Cancer 2005;103: 2466-2472

4. 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.
5. 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.
6. 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.
7. 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.
8. 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. Aebi S. Special issues related to the adjuvant therapy in very young women. *Breast* 2005, 14: 594-599 (Review)
2. 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
3. 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.
4. 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.
5. 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):d1v064.

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, Necozione 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. 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.

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* 29 (17) 2334-2341 2011
3. 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
4. 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
5. Lee MC et al.: Fertility and reproductive considerations in premenopausal patients with breast cancer. *Cancer Control*. 2010 Jul;17(3):162-72.
6. Partridge AH EP. Gelber S, Peppercorn J et al. Fertility and menopausal outcomes in young breast cancer survivors. *Clin Breast Cancer* 2008; (:65-69
7. Hulvat MC, Jeruss JS. Maintaining fertility in young women with breast cancer. *Curr Treat Options Oncol*. 2009 Dec;10(5-6):308-17.
8. 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.
9. 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)	4	C	+
▪ SNB 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. Bock K. et al., Rationale for a diagnostic chain in gestational breast tumor diagnosis. Arch Gynecol Obstet 2005
2. Ahn BY et al., Pregnancy and lactation-associated breast cancer: mammographic and sonographic findings. J Ultrasound Med 2003, 491-497
3. Nicklas AH et al., Imaging strategies in the pregnant cancer patient. Semin Oncol 2000, 27: 623-632
4. Hogge JP et al., Imaging and management of breast masses during pregnancy and lactation. Breast J 1999, 5: 272-283.
5. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. Eur J Cancer 2010;46:3158-3168. doi:10.1016/j.ejca.2010.09.010.
6. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70

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

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

Statement: Whole Body MRI

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

Statement: Surgery like in non-pregnant patients

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

Statement: „Sentinel node biopsy“ during pregnancy

1. Han SN, Amant F, Cardonick EH, et al; International Network on Cancer, Infertility and Pregnancy. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel node biopsy. *Breast Cancer Res Treat*. 2017 Dec 12.
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. Sophie E. McGrath Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists
2. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. *Cancer*. 2006 Jan 15;106(2):237-46.
3. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy associated breast cancer. *Cancer* 1991, 67: 869-872
4. Talele AC, Slanetz PJ, Edmister WB, et al. The lactating breast: MRI findings and literature review. *Breast J* 2003, 9: 237-240
5. 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
6. 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
7. Ben Brahim E, Mrad K, Driss M, et al. Placental metastasis of breast cancer. *Gynecol Obstet Fertil* 2001, 29: 545-548
8. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5
9. 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 –

	Oxford		
	LoE	GR	AGO
▪ Bestrahlung während der Schwangerschaft	4	C	-
▪ (Neo-)adjuvante Chemotherapie ab dem zweiten Trimenon (Indikation wie bei Nicht-Schwangeren)			++
▪ Antrazykline: AC, EC	2b	B	++
▪ Taxane	2b	B	+
▪ Platinsalze (Carboplatin, Cisplatin)	4	C	+/-
▪ MTX (e.g. CMF)	4	D	--
▪ Endokrine Therapie	4	D	--
▪ Anti-HER2-Therapie	3a	C	--
▪ Bisphosphonate, Denosumab	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, De Laurentiis M, Boni C, Cavazzini G 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. 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.
3. 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

1. Cunha GR, Taguchi O, Namikawa R, et al. Teratogenic effects of clomiphene, tamoxifen, and diethylstilbestrol on the developing human female genital tract *Hum Pathol.* 1987;18:1132–1143.
2. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy — case report and literature review. *Gynecol Oncol.* 2001;80:405-408.
3. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381,805–816.

Statement Trastuzumab during pregnancy

1. Fanale MA et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clin Breast Cancer* 2005, 6: 354-356 (Case Report)
2. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. *Obstetrics and Gynecology* 2005, 105: 642-643 (Case Report)
3. Loibl S. New Therapeutic Options for Breast Cancer during Pregnancy. *Breast Care* 2008; 3:171-176. (table overview of trastuzumab cases)
4. Aebi S, Loibl S. Breast cancer during pregnancy: medical therapy and prognosis. *Recent Results Cancer Res.* 2008;178:45-55.
5. Clemons M, Goss P: Estrogen and the risk of breast cancer. *New Engl J Med* 2001, 344: 276-285
6. 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.

7. Zagouri F et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013 Jan;137(2):349-57.
8. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* 2013; 5(7):733-41.

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 ≤ 3 Wochen nach Chemotherapie sollte vermieden werden
- Sollte eine Systemtherapie nach der Entbindung fortgeführt werden müssen, kann Stillen evtl. kontraindiziert sein (cave: Toxizität !)

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

* Teilnahme an Registerstudie empfohlen

General principles

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

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

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

Statements: Delivery mode like in non-pregnant; Avoid delivery ≤ 3 weeks from prior chemotherapy

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

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

1. Williams Obstetrics lecture book
2. Pistilli B et al. Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: how should we counsel cancer patients about breastfeeding?
Cancer Treat Rev. 2013;39(3):207-11.

Brustkrebs und Schwangerschaft*

– Familienplanung –

	Oxford		
	LoE	GR	AGO
▪ Nach einer Mammakarzinomerkrankung kann mit Hilfe reproduktionsmedizinischer Verfahren eine Schwangerschaft angestrebt werden.	5	D	++
▪ Die Erfolgsaussichten für eine intakte Schwangerschaft bzw. ein Kind sind bei autologer Eizellverwendung bei Mammakarzinompatientinnen geringer als bei Nicht-Karzinompatientinnen.	5	D	++
▪ Mammakarzinompatientinnen im gebärfähigen Alter sollten eine Beratung über Fertilität und Fertilitätserhalt vor Therapiebeginn erhalten.	5	D	++
▪ Von einer Schwangerschaft soll nach einer Mammakarzinomerkrankung nicht abgeraten werden. Dies gilt grundsätzlich unabhängig vom Hormonrezeptorstatus.	5	D	++

* Teilnahme an Registerstudie empfohlen

Brustkrebs während Schwangerschaft*

– Prognose –

**Oxford
LoE**

- **Mammakarzinom während Schwangerschaft / Stillzeit**
 - Prognose wird nicht verschlechtert, wenn korrekte Behandlung
- **Schwangerschaft / Laktation nach Mammakarzinom**
 - Prognose wird nicht verschlechtert

3a

3a

* Teilnahme an Registerstudie empfohlen

General principles

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

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

1. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy associated breast cancer. Cancer 1991, 67: 869-872
2. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. Cancer. 2006 Jan 15;106(2):237-46
3. Rodriguez et al. Evidence of poorer survival in pregnancy-associated breast cancer. Obstet Gynecol. 2008 Jul;112(1):71-8
4. 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.

5. Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? *Breast J.* 2010 Jul-Aug;16(4):404-11.
6. Azim HA Jr, Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev* 2012;38:834-842.
7. 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.
8. Litton JK et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. *Oncologist.* 2013;18(4):369-76.

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

1. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5: IBCSG-participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).
2. Kroman N et al. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol.* 2008;47(4):545-9
3. Azim HA Jr et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013;31:73-79.

Review articles

1. Del Mastro et al, Infertility and pregnancy after breast cancer: current knowledge and future perspectives. *Cancer Treat Rev.* 2006 Oct;32(6):417-22. Epub 2006 Jul 13. Review.
Kroman N, et al. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *Breast.* 2003 Dec;12(6):516-21.
2. Kroman N, et al. Should women be advised against pregnancy after breast-cancer treatment? *Lancet.* 1997 Aug 2;350(9074):319-22.
3. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer.* 2011 Jan;47(1):74-83. Epub 2010 Oct 11. Review.
4. Pagani O, Azim H Jr. Pregnancy after Breast Cancer: Myths and Facts. *Breast Care (Basel).* 2012 Jun;7(3):210-214. Epub 2012 Jun 27.
5. Valachis A, Tsali L, Pesce LL, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. *Obstet Gynecol Surv.* 2010 Dec;65(12):786-93.
6. Azim HA Jr, Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev.* 2012

Nov;38(7):834-42. Epub 2012 Jul 9. Review.

7. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. *Lancet*. 2012 Feb 11;379(9815):570-9.
8. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi160-70

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 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 13 (4):e 148-e160
2. Charlson et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-383.
3. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006 295:801-08.
4. 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.
5. Aaldriks AA. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy et al. Breast 2013;22(5):753-60.
6. Bellera CA et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166-72
7. Aaldriks AA, Maartense E, Nortier HJ, et al. Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. Acta Oncol. 2016 Jan;55(1):15-23.

Behandlung der „rüstigen älteren“ Patientin (Lebenserwartung > 5 Jahre und akzeptable Komorbidität)

- **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 in 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

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. Bouchardy C et al., Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol. 2003;21(19):3580-7
2. Enger SM: Breast cancer treatment of older women in integrated health care settings. J Clin Oncol. 2006 Sep 20;24(27):4377-83
3. Mustacchi G, Breast cancer in elderly women: a different reality? Results from the NORA study. Ann Oncol. 2007 Jun;18(6):991-6.
4. Chagpar AB: Determinants of early distant metastatic disease in elderly patients with breast cancer. Am J Surg. 2006 Sep;192(3):317-21
5. Kemeny MM: Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003 Jun 15;21(12):2268-75
6. Giordano SH: Breast cancer treatment guidelines in older women. J Clin Oncol. 2005 Feb 1;23(4):783-91.
7. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg. 2008 Jan;206(1):66-75
8. 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

9. Luque M et al. Breast cancer management in the elderly. Clin Transl Oncol. 2013 epub

Statement: Surgery similar to „younger“ age

1. Swaminathan V. et al. Choices in Surgery for older women with breast cancer Breast Care 2012;7:445-451
2. 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
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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. 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
2. Muss H et al. Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. J Clin Oncol. 2008 Apr 20;26(12):1956-64
3. 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
4. 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
5. 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

6. 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 Sep;16(5):R77
2. Fisher B: Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials. *J Natl Cancer Inst*. 2004 Dec 15;96(24):1823-31.
3. Fargeot P: Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. *J Clin Oncol*. 2004 Dec 1;22(23):4622-30
4. Du XL: Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. *J Gerontol A Biol Sci Med Sci*. 2005 Sep;60(9):1137-44
5. De Maio E et al., Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: a single-center experience. *BMC Cancer* 2005 24: 30
Muss HB et al., Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 2005, 293:1073-81.
6. Chagpar AB: Determinants of early distant metastatic disease in elderly patients with breast cancer. *Am J Surg*. 2006 Sep;192(3):317-21.
7. Hurria A et al., Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat*. 2005 92:151-6.
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Statement: Chemotherapy in pts. > 70 years

1. Qin A, Thompson CL, Silverman P. Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. *J Cancer Surviv*. 2015 Jun;9(2):252-9.
2. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007 Sep 1;25(25):3808-15.
3. von Minckwitz G, Reimer T, Potenberg J, et al. The phase III ICE study: Adjuvant lbandronate with or without capecitabine in elderly patients with moderate or

high risk early breast cancer. SABCS 2014 (S3-04).

4. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients Breast Care 2012;7:439-444
5. Muss HB, Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med. 2009 May 14;360(20):2055-65.
6. Muss HB: CLGB: Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. J Clin Oncol. 2007 Aug 20;25(24):3699-704
7. Muss HB: Adjuvant treatment of elderly breast cancer patients. Breast. 2007 Nov;16 Suppl 2:159-65
8. Nuzzo F et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for elderly breast cancer patients: safety data from the multicentre phase 3 randomised ELDA trial. Crit Rev Oncol Hematol. 2008 May;66(2):171-80. Epub 2007 Dec 21.
9. Crivellari D et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a "standard chemotherapy regimen": the CASA randomized trial. Breast. 2013;22(2):130-7.

Statement: Radiotherapy


1. Kunkler I Radiotherapy issues in elderly breast cancer patients Breast Cancer Patients Breast Care 2012;7:453-459
2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control Strahlenther Onkol 2012 :1-5
3. Giordano SH Radiotherapy in older women with low-risk breast cancer: why did practice not change? 2012 J Clin Oncol 30 (14): 1577-1578
4. Prescott RJ: A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technol Assess. 2007 Aug;11(31):1-149, iii-iv
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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
3. Guarneri V: Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol*. 2006 Sep 1;24(25):4107-15.
4. Tan-Chiu E: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol*. 2005 Nov 1;23(31):7811-9
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6. Adamo V et al. The Risk of Toxicities from Trastuzumab, Alone or in Combination, in an Elderly Breast Cancer Population. *Oncology* 2013;86(1):16-21.
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



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 In der DGK e.V.
 Guidelines Breast
 Version 2018.1D

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FORSCHEN
 LEHREN
 HEILEN

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 (≥ 65 Jahre, pT1, pN0, Rez. pos.)	1b	B	++
▪ Hypofraktionierte Radiatio	2b	B	+
▪ Keine Chemotherapie ≥ 70 Jahre bei negativer Risiko-Nutzen-Abwägung	2b	C	+

- Walzer DE Measuring the value of radiotherapy in older women with breast cancer J Clin Oncol 2012 30 (23) 2809-2811
- Audisio RA et al When reporting on older patients with cancer , frailty information is needed Ann Surg Oncol 2011; 18: 4-5
- Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
- 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).
- 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)

- 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.
- 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
- 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. 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
2. 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-
3. 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
4. Fyles AW: Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70
5. Kunkler IH, Williams LJ, Jack WJ, et al: on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.

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. 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
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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.**

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

* Teilnahme an Registerstudie empfohlen

International registry

- Cardoso F, Bartlett J, Slaets L, et al: Characterization of male breast cancer: First results of the EORTC10085/TBCRC/BIG/NABCG International Male BC Program. SABCS 2014 (S6-05).

General

- Vetto J et al. Accurate and cost-effective evaluation of breast masses in males. Am J Surg 1998 175: 383
- 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
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- 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. Dershaw DD. et al. Mammographic findings in men with breast cancer. Am J Roentgenol 1993 160: 267
2. 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):902-5
2. Lanitis S et al. Diagnosis and management of male breast cancer, World J Surg. 2008 Nov;32(11):2471-6.
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5. Fields EC et al. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. J Radiat Oncol Biol Phys 2013;87(4):747-52
6. 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: 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 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
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6. Agrawal A, Ayantunde AA, Rampaul R et al. Male breast cancer: a review of clinical management. *Breast Cancer Res Treat*. 2006 Oct 11;
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8. Patten DK et al. New Approaches in the Management of Male Breast. *Cancer Clinical Breast Cancer* 2013;13(5) 309–314
9. Sousa B et al. An update on male breast cancer and future directions for research and treatment. *Eur J Pharmacol* 2013;717(1-3)
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: Systemtherapie

- **Adjuvante Chemotherapie wie bei Frauen**
- **HER2 zielgerichtete Therapie (bei HER2 pos)**
- **Endokrine Therapie bei HR pos.**
 - Tamoxifen
 - Aromataseinhibitoren (adjuvant)
 - Aromataseinhibitoren (metastasiert)
 - GnRHa + AI (metastasiert)
 - Fulvestrant (metastasiert)
- **Palliative Chemotherapie wie bei Frauen**

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

* Studienteilnahme wird 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 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

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

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.

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	+
▪ Neoadjuvante Chemotherapieregime (wie bei nicht inflammatorischem MaCA)	2c	B	++
▪ Leitliniengerechte Systemtherapie	2c	B	++
▪ Mastektomie nach Chemotherapie	2c	B	+
▪ Brusterhaltende Therapie im Fall von pCR (Individualfall)	2b	C	+/-
▪ Sentinel-Node-Biopsie	3b	C	-
▪ Radiotherapie der Brustwand	2c	B	++

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 1.2016. NCCN.org (Inflammatory Breast Cancer. IBC-1)

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

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

Statement: Staging

1. Yamauchi H et al. Inflammatory breast cancer: what we know and what we need to learn. *Oncologist*. 2012;17(7):891-9. doi: 10.1634/theoncologist.2012-0039. Epub 2012 May 14.
2. S. Dawood et al International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment *Ann Oncol*. 2011 March; 22(3): 515–523
3. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790

Statement: Preoperative chemotherapy

1. Ardavanis A: Multidisciplinary therapy of locally far-advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin, vinorelbine, and Fluorouracil chemotherapy, surgery, and radiotherapy: long-term results. *Oncologist*. 2006 Jun;11(6):563-73
2. S. Johnston (2008), *J. Clin. Oncol.* 26: 1066-1072
3. Mathew J et al. Neoadjuvant chemotherapy for locally advanced breast cancer : A review of the literature and future directions.
4. Schairer C et al. Risk factors for inflammatory breast cancer and other invasive breast cancers. *J Natl Cancer Inst* 2013;105:1373-84.
5. Van Laere et al. Uncovering the molecular secrets of inflammatory breast cancer biology: an integrated analysis of three distinct affymetrix gene expression datasets. *Clin Cancer Res* 2013;19:4685-96.

Statement: Regimens as in non-inflammatory BC

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

Statement: in HER2 positive disease addition of trastuzumab

1. Gianni L et al: Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomized controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; 375:377-384
2. Semiglazov V, Eiermann W, Zambetti M et al. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. *Eur J Surg Oncol*. 2011;37(10):856-6

Statement: in HER2 positive disease addition of trastuzumab and pertuzumab

1. Gianni L, Pienkowski T, Im YH, et al: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012 Jan;13(1):25-32. doi: 10.1016/S1470-2045(11)70336-9. Epub 2011 Dec 6.

Statement: in HER2 negative disease addition of bevacizumab

1. Pierga JY, Petit T, Delozier T, et al. Neoadjuvant bevacizumab, trastuzumab, and chemotherapy for primary inflammatory HER2-positive breast cancer (BEVERLY-2): an open-label, single-arm phase2 study. *Lancet Oncol* 2012;13(April (4)):375–84.

Statement: Mastectomy after chemotherapy

1. Chen H, Wu K, Wang M, et al: A standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: A large population-based study in the Surveillance, Epidemiology, and End results database 18. *Breast*. 2017 Oct;35:48-54.
2. Semiglazov V et al Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. *Eur J Surg Oncol*. 2011 Oct;37(10):856-63.
3. Kaufmann M, von Minckwitz G, Bear HD, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. *Ann Oncol*. 2007;18:1927–1934
4. Motwani SB, Strom EA, Schechter NR, et al. The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;66:76–82.
5. Hennessy BT: Disease-free and overall survival after pathologic complete disease remission of cytologically proven inflammatory breast carcinoma axillary lymph node metastases after primary systemic chemotherapy. *Cancer*. 2006 Mar 1;106(5):1000-6.
6. Curcio LD et al. Beyond palliative mastectomy in inflammatory breast cancer: A reassessment of margin status. *Ann Surg Oncol* 1999; 6: 249-254
7. Bristol IJ, Woodward WA, Strom EA, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer *Int J Radiat Oncol Biol Phys*. 2008 Oct 1;72(2):474-84. Epub 2008 Apr 24
8. Tsai CJ et al. Outcomes after multidisciplinary treatment of inflammatory breast cancer in the era of neoadjuvant HER2-directed therapy. *Am J Clin Oncol* 2013 [Epub ahead of print].

Statement: Sentinel lymph node

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

Statement: Radiotherapy


1. Chargari C, Kirova YM, Cottu P, et al: Progressive inflammatory breast cancer in patient receiving chemotherapy: The importance of radiotherapy as a part of locoregional treatment. *Radiother Oncol*. 2009 Jan;90(1):160-1. Epub 2008 Sep 2
2. Bristol IJ, Woodward WA, Strom EA, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys*. 2008;72:474–484

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
2. Low JA: Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. *J Clin Oncol*. 2004 Oct 15;22(20):4067-74.

Reviews

1. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790
2. Penn CL: Remembering inflammatory breast cancer. Are you up to date on management and treatment? *J Ark Med Soc*. 2007 Oct;104(4):80-2.
3. Cristofanilli M: Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. *Cancer*. 2007 Oct 1;110(7):1436-44
4. Brouwers B et al. Clinicopathological features of inflammatory versus noninflammatory locally advanced nonmetastatic breast cancer
5. Dawood S, Merajver SD, Viens P, et al: International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol*. 2011;22(3):515-23.
6. van Uden DJ, van Laarhoven HW, Westenberg AH, et al. Inflammatory breast cancer: An overview. *Crit Rev Oncol Hematol*. 2015 Feb;93(2):116-126. doi: 10.1016/j.critrevonc.2014.09.003. Epub 2014 Oct 16.
7. Bertucci F, Finetti P, Vermeulen P, et al. Genomic profiling of inflammatory breast cancer: a review. *Breast*. 2014 Oct;23(5):538-45. doi: 10.1016/j.breast.2014.06.008. Epub 2014 Jul 4.
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Guidelines Breast
Version 2018.1D

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FORSCHEN
LEHREN
HEILEN

Axilla-Metastase(n) bei okkultem Mammakarzinom (Cancer of unknown primary – axillary CUP)

- **Inzidenz: < 1% aller axillären Metastasen**
- **In > 95% okkultes Mamma-Ca, in < 5% anderer Primarius**
- **Immunhistologie**
ER-positiv: 55%
HER2 3+: 35%
Triple-negativ: 38%
- **Nodalstatus:**
1–3 Lk-Met. in 48%
> 3 Lk-Met. in 52%
- **Outcome ähnlich oder besser als beim Mammakarzinom mit entsprechender Tumorbilogie und Stadium**

Guidelines

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (2016). Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), 1–202.
2. NICE (2010). Metastatic malignant disease of unknown primary origin in adults: diagnosis and management. Retrieved January 5, 2017, <https://www.nice.org.uk/guidance/cg104/resources/metastatic-malignant-disease-of-unknown-primary-origin-diagnosis-and-management-of-metastatic-malignant-disease-of-unknown-primary-origin-35109328970437>
3. ESMO Guidelines Working Group. (2011) Aebi, S., Davidson, T., Gruber, G., et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. <http://doi.org/10.1093/annonc/mdr371>
4. DGHO (2014). (Hübner, G., Borner, M., Neben, K., & Stöger, H eds.). CUP-Syndrom - Krebserkrankungen mit unbekanntem Primärtumor. Retrieved January 3, 2017 <https://www.onkopedia.com/de/onkopedia/guidelines/cup-syndrom-krebserkrankungen-mit-unbekanntem-primartumor/@@view/html/index.html>

Reviews

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

009-0554-3

2. Lanitis, S., Behranwala, K. A., Al-Mufti, R., et al.(2009). Axillary metastatic disease as presentation of occult or contralateral breast cancer. *Breast (Edinburgh, Scotland)*, 18(4), 225–227. <http://doi.org/10.1016/j.breast.2009.07.002>
3. Galimberti, V., Bassani, G., Monti, S., et al. (2004). Clinical experience with axillary presentation breast cancer. *Breast Cancer Research and Treatment*, 88(1), 43–47. <http://doi.org/10.1007/s10549-004-9453-9>
4. Pentheroudakis, G., Briasoulis, E., & Pavlidis, N. (2007). Cancer of unknown primary site: missing primary or missing biology? *Oncologist*, 12(4), 418–425. <http://doi.org/10.1634/theoncologist.12-4-418>

Pathology

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

Outcome

1. Sohn, G., Son, B. H., Lee, S. J., et al. (2014). Treatment and survival of patients with occult breast cancer with axillary lymph node metastasis: a nationwide retrospective study. *Journal of Surgical Oncology*, 110(3), 270–274. <http://doi.org/10.1002/jso.23644>

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

	Oxford		
	LoE	GR	AGO
▪ Mammographie, Mamma-Ultraschall, Mamma-MRT	3	B	++
▪ Ausschluss eines kontralateralen Tumors	3	B	++
▪ Ausschluss eines anderen Organtumors insbes. bei TNBC (Haut, weibl. Genitaltrakt, Lunge, Schilddrüse, Magen)	5	D	++
▪ Staging (CT Thorax / Abdomen, 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>
2. Lalonde, L., David, J., & Trop, I. (2005). Magnetic resonance imaging of the breast: current indications. Can Assoc Radiol J, 56(5), 301–308.
3. Ko, E. Y., Han, B.-K., Shin, J. H., & Kang, S. S. (2007). Breast MRI for evaluating patients with metastatic axillary lymph node and initially negative mammography and sonography. Korean J Radiol, 8(5), 382–389. <http://doi.org/10.3348/kjr.2007.8.5.382>
4. Varadhachary, G. R., Abbruzzese, J. L., & Lenzi, R. (2004). Diagnostic strategies for unknown primary cancer. Cancer, 100(9), 1776–1785. <http://doi.org/10.1002/cncr.20202>
5. Foroudi, F., & Tiver, K. W. (2000). Occult breast carcinoma presenting as axillary metastases. International Journal of Radiation Oncology, Biology, Physics, 47(1), 143–147. <http://doi.org/10.1007/s10147-005-0485-x>

Statement: Staging

1. Steunebrink: Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. Breast. 2005 Apr;14(2):165-8
2. Jerusalem, G., Rorive, A., Ancion, G. et al. (2006). Diagnostic and therapeutic management of carcinoma of unknown primary: radio-imaging investigations. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO,

17 Suppl 10(suppl_10), x168–76. <http://doi.org/10.1093/annonc/mdl255>

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

Statement: PET

1. Jerusalem, G., Rorive, A., Ancion, G., et al. (2006). Diagnostic and therapeutic management of carcinoma of unknown primary: radio-imaging investigations. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 17 Suppl 10(suppl_10), x168–76. <http://doi.org/10.1093/annonc/mdl255>
2. Kwee, T. C., & Kwee, R. M. (2009). Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. *European Radiology*, 19(3), 731–744. <http://doi.org/10.1007/s00330-008-1194-4>
3. Varadhachary, G. R., Abbruzzese, J. L., & Lenzi, R. (2004). Diagnostic strategies for unknown primary cancer. *Cancer*, 100(9), 1776–1785. <http://doi.org/10.1002/cncr.20202>
4. Pelosi, E., Pennone, M., Deandreis, D., et al. (2006). Role of whole body positron emission tomography/computed tomography scan with 18F-fluorodeoxyglucose in patients with biopsy proven tumor metastases from unknown primary site. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*: 50(1), 15–22.

Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP)

Pathologie, Molekularpathologie

- **ER, PgR, HER2, GATA3**
- **Ausschluss anderer Primärtumoren**
bei TNBC oder ungewöhnlicher Histologie,
z. B. Lunge, weibl. Genitaltrakt, Kopf-Hals-Tumoren,
neuroendokrine Ca
- **Genexpressionsprofile zur Bestimmung
des Primarius**
(CUPprint, Pathwork, TOT, Theros CTID)
- **NGS, Epigenetik zur Bestimmung des Primarius**
(Panel-Sequenzierung, EPICup)
- **Prognostische Genexpressionstests**

Oxford		
LoE	GR	AGO
5	D	++
5	D	++
2c	B	+/-
2c	B	+/-
5	D	--

Immunohistochemistry

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gene expression signature for the identification of tumor tissue origin. *Modern Pathology*, 29(6), 546–556. <http://doi.org/10.1038/modpathol.2016.60>

Axilla-Metastasen bei okkultem Mammakarzinom (ax. CUP) Therapie

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

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

Guidelines

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2. Matsuoka, K., Ohsumi, S., Takashima, S., et al. (2003). Occult breast carcinoma presenting with axillary lymph node metastases: follow-up of eleven patients. *Breast Cancer (Tokyo, Japan)*, 10(4), 330–334.
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[http://doi.org/10.1016/S0959-8049\(03\)00547-1](http://doi.org/10.1016/S0959-8049(03)00547-1)
4. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. *Breast Cancer Research and Treatment*, 119(1), 1–11.
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Statement: Axillary dissection

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2. Steunebrink, M., Schnater, J. M., Storm, et al.(2005). Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. *Breast (Edinburgh, Scotland)*, 14(2), 165–168.
<http://doi.org/10.1016/j.breast.2004.06.001>
3. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. *Breast Cancer Research and Treatment*, 119(1), 1–11.
<http://doi.org/10.1007/s10549-009-0554-3>
4. Schmidt, T., & Ulrich, A. (2014). [Surgical options in cancer of unknown primary (CUP)]. *Der Radiologe*, 54(2), 140–144. <http://doi.org/10.1007/s00117-013-2549-7>

Statement: Mastectomy without (in-)breast tumor

References 1-4 (retrospective analysis , case reports)

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Statement: Breast irradiation if breast MRI is negative

1. Hessler LK, Molitoris JK, Rosenblatt PY et al. Factors Influencing Management and Outcome in Patients with Occult Breast Cancer with Axillary Lymph Node Involvement: Analysis of the National Cancer Database. *Surg Oncol* 2017 Oct;24(10):2907-2914.
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Statement: Systemic treatment according N+ tumor

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

M. Paget der Mamille

- Beim M. Paget der Mamille handelt es sich um eine intraepidermale Manifestation eines intraduktalen oder eines invasiven Mammakarzinoms. Selten und meist tumorbiologisch weniger aggressiv ist der isolierte M. Paget.

Merkmal	Häufigkeiten
Präsentation	M. Paget mit invasivem Ca. (37 – 58%) M. Paget mit DCIS (30 – 63%) Isolierter M. Paget (4 – 7%) Isolierter M. Paget mit Invasion (selten)
IHC	HER2-positiv (83 – 97%) ER-positiv (10 – 14%) AR-positiv (71 – 88%)

Clinical Presentation

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

Pathology and Immunohistochemistry

1. Chen, C.-Y., Sun, L.-M., & Anderson, B. O. (2006). Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer*, 107(7), 1448–1458. <http://doi.org/10.1002/cncr.22137>
2. Hanna, W., Alowami, S., & Malik, A. (2003). The role of HER-2/neu oncogene and vimentin filaments in the production of the Paget's phenotype. *The Breast Journal*, 9(6), 485–490.
3. Kothari, A. S., Beechey-Newman, N., Hamed, H., et al. (2002). Paget disease of the nipple: a multifocal manifestation of higher-risk disease. *Cancer*, 95(1), 1–7. <http://doi.org/10.1002/cncr.10638>
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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, PgR, 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>
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3. Capobianco, G., Spaliviero, B., Dessole, S., et al. (2006). Paget's disease of the nipple diagnosed by MRI. Archives of Gynecology and Obstetrics, 274(5), 316–318. <http://doi.org/10.1007/s00404-006-0160-0>
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Pathology

1. Sandoval-Leon, A. C., Drews-Elger, K., Gomez-Fernandez, C. R., et al. (2013). Paget's disease of the nipple. Breast Cancer Research and Treatment, 141(1), 1–12. <http://doi.org/10.1007/s10549-013-2661-4>
2. Saeed, D., & Shousha, S. (2014). Toker cells of the nipple are commonly associated with underlying sebaceous glands but not with lactiferous ducts. Journal of Clinical

Pathology, 67(11), 1010–1012. <http://doi.org/10.1136/jclinpath-2014-202280>

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Morbus Paget der Mamille Diagnostik

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

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

1. Bijker, N., Rutgers, E. J., Duchateau, L., EORTC Breast Cancer Cooperative Group et al. (2001). Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer*, 91(3), 472–477.
2. Caliskan, M., Gatti, G., Sosnovskikh, I., et al. (2008). Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. *Breast Cancer Research and Treatment*, 112(3), 513–521. <http://doi.org/10.1007/s10549-007-9880-5>
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7. Siponen, E., Hukkinen, K., Heikkilä, P., et al. (2010). Surgical treatment in Paget's disease of the breast. *American Journal of Surgery*, 200(2), 241–246.
<http://doi.org/10.1016/j.amjsurg.2009.07.044>

Treatment of isolated Paget's disease

1. Durkan, B., Bresee, C., Bose, S. et al. (2013). Paget's disease of the nipple with parenchymal ductal carcinoma in situ is associated with worse prognosis than Paget's disease alone. *The American Surgeon*, 79(10), 1009–1012.
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3. Mirer, E., Sayed, El, F., Ammourey, A., et al. (2006). Treatment of mammary and extramammary Paget's skin disease with topical imiquimod. *The Journal of Dermatological Treatment*, 17(3), 167–171.
<http://doi.org/10.1080/09546630600788877>

Statement: Sentinel-node excision (SNE)

1. Bijker, N., Rutgers, E. J., Duchateau, L EORTC Breast Cancer Cooperative Group et al. (2001). Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer*, 91(3), 472–477.

Borderline und maligner Phylloides tumor

- Differenzialdiagnose gegenüber anderen Läsionen an der Stanzbiopsie problematisch
- Intramammäres Rezidiv relativ häufig (10 – 30%)
- Fernmetastasierung insgesamt selten (< 10%) und fast ausschließlich beim malignen Phylloides tumor

Merkmal	Häufigkeiten
Grading	Benigne (75%) Borderline (16%) Maligne (9%)
Medianes Alter bei Diagnosestellung	Benigner PT: 39 J. Borderline PT: 45 J. Maligner PT: 47 J.
Lokalrezidive	Benigner PT: 10 – 17% Borderline PT: 14 – 25% Maligner PT: 23 – 30%

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., Lee, H.-Y., et al. (2005). Phyllodes tumors of the breast: the role of pathologic parameters. American Journal of Clinical Pathology, 123(4), 529–540. <http://doi.org/10.1309/U6DV-BFM8-1MLJ-C1FN>
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Journal of Clinical Pathology, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>

Borderline und maligner Phylloides tumor Diagnostik

	Oxford		
	LoE	GR	AGO
▪ Mammographie / Mamma-Ultraschall (MG / MS)	3	C	++
▪ Stanzbiopsische Diagnostik des PT, Dignitätsbeurteilung am Resektat	3	C	++
▪ Mamma-MR	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>
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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. Dillon, M., Quinn, C., McDermott, E., et al. (2006). Needle core biopsy in the diagnosis of phyllodes neoplasm. *Surgery*, 140(5), 779–784.
3. Jacobs, T., Chen, Y., Guinee, D., et al. (2005). Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision? *American Journal of Clinical Pathology*, 124(3), 342–354.

4. Jara-Lazaro, A. R., Akhilesh, M., Thike, A. A., et al. (2010). Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*, 57(2), 220–232. <http://doi.org/10.1111/j.1365-2559.2010.03607.x>
5. 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 Phylloidentumor

Operative Therapie

- R0-Resektion
- SNE / Axilladisektion bei cN0
- Therapie des Lokalrezidivs
 - R0-Resektion oder einfache Mastektomie

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

Statement: Complete (wide) local excision or MRM

Surgical margins

- Guillot, E., Couturaud, B., Rey, F., et al. (2011). Management of phyllodes breast tumors. Breast Journal, 17(2), 129–137. <http://doi.org/10.1111/j.1524-4741.2010.01045.x>
- Onkendi, E. O., Jimenez, R. E., Spears, G. M., et al. (2014). Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent of resection and tumor characteristics on patient outcome. Annals of Surgical Oncology, 21(10), 3304–3309. <http://doi.org/10.1245/s10434-014-3909-x>
- Lin, C.-C., Chang, H.-W., Lin, C.-Y., et al. (2013). The clinical features and prognosis of phyllodes tumors: a single institution experience in Taiwan. International Journal of Clinical Oncology, 18(4), 614–620. <http://doi.org/10.1007/s10147-012-0442-4>
- Yom, C. K., Han, W., Kim, S.-W., et al. (2015). Reappraisal of conventional risk stratification for local recurrence based on clinical outcomes in 285 resected phyllodes tumors of the breast. Annals of Surgical Oncology, 22(9), 2912–2918. <http://doi.org/10.1245/s10434-015-4395-5>
- 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>

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. Fou, A., Schnabel, F. R., Hamele-Bena, D., et al. (2006). Long-term outcomes of malignant phyllodes tumors patients: an institutional experience. *American Journal of Surgery*, 192(4), 492–495. <http://doi.org/10.1016/j.amjsurg.2006.06.017>
3. Cheng, S.-P., Chang, Y.-C., Liu, T.-P., Lee, J.-J., Tzen, C.-Y., & Liu, C.-L. et al (2006). Phyllodes tumor of the breast: the challenge persists. *World Journal of Surgery*, 30(8), 1414–1421. <http://doi.org/10.1007/s00268-005-0786-2>
4. Ben Hassouna, J., Damak, T., Gamoudi, A., et al. (2006). Phyllodes tumors of the breast: a case series of 106 patients. *American Journal of Surgery*, 192(2), 141–147. <http://doi.org/10.1016/j.amjsurg.2006.04.007>
5. Pezner, R. D., Schultheiss, T. E., & Paz, I. B. (2008). Malignant phyllodes tumor of the breast: local control rates with surgery alone. *International Journal of Radiation Oncology, Biology, Physics*, 71(3), 710–713. <http://doi.org/10.1016/j.ijrobp.2007.10.051>
6. 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>
7. 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>
8. 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>

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. Chen, W.-H., Cheng, S.-P., Tzen, C.-Y. et al. (2005). Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. *Journal of Surgical Oncology*, 91(3), 185–194. <http://doi.org/10.1002/jso.20334>
3. 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>

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. Chaney, A. W., Pollack, A., McNeese, M. D., et al. (2000). Primary treatment of cystosarcoma phyllodes of the breast. *Cancer*, 89(7), 1502–1511.
4. Chen, W.-H., Cheng, S.-P., Tzen, C.-Y., et al. (2005). Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. *Journal of Surgical Oncology*, 91(3), 185–194. <http://doi.org/10.1002/jso.20334>
5. 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>
6. Spitaleri, G., Toesca, A., Botteri, E. et al. (2013). Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. *Critical Reviews in Oncology/Hematology*, 88(2), 427–436. <http://doi.org/10.1016/j.critrevonc.2013.06.005>

Statement: Adjuvant radiotherapy, if T ≥2cm (BCT) or T ≥10cm (mastectomy)

1. Kim, Y.-J., & Kim, K. (2017). Radiation therapy for malignant phyllodes tumor of the breast: An analysis of SEER data. *Breast (Edinburgh, Scotland)*, 32, 26–32. <http://doi.org/10.1016/j.breast.2016.12.006>
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/s10434-013-3395-6>
3. 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>
4. 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>

5. Mituś, J., Reinfuss, M., Mituś, J. W., Jakubowicz, J., Blecharz, P., Wysocki, W. M., & Skotnicki, P. (2014). Malignant phyllodes tumor of the breast: treatment and prognosis. *Breast Journal*, 20(6), 639–644. <http://doi.org/10.1111/tbj.12333>

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/tbj.12333>

Statement: Radiotherapy, chemotherapy after R1 resection

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

1. Jardim, D. L. F., Conley, A., & Subbiah, V. (2013). Comprehensive characterization of malignant phyllodes tumor by whole genomic and proteomic analysis: biological implications for targeted therapy opportunities. *Orphanet Journal of Rare Diseases*, 8(1), 112. <http://doi.org/10.1186/1750-1172-8-112>
2. Wang, H., Wang, X., & Wang, C.-F. (2014). Comparison of clinical 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>

Borderline und maligner Phylloides tumor Adjuvante Therapie

	Oxford		
	LoE	GR	AGO
▪ Adjuvante Radiotherapie	4	C	--
bei T \geq 2 cm (BEO) oder T \geq 10 cm (Mastektomie)	2b	C	+/-
▪ Systemische adjuvante Therapie (Chemotherapie, endokrine Therapie)	4	C	--
▪ Therapie des Lokalrezidivs			
▪ R0-Resektion oder einfache Mastektomie	4	C	+
▪ Radiotherapie, Chemotherapie nach R1-Resektion	4	C	+/-
▪ Fernmetastasen (sehr selten)			
▪ Therapie wie bei Weichteilsarkomen	4	C	++

Sarkome der Mamma

- **Nicht selten assoziiert mit familiären Syndromen (Li-Fraumeni, Familiäre Adenomatöse Polyposis, Neurofibromatose Typ 1)**
- **Primäre Sarkome: Angiosarkom, undifferenziertes Sarkom, Leiomyosarkom, Liposarkom, Osteosarkom**
- **Sekundäre Malignome der Mamma:**
 - Radiotherapie-assoziierte Angiosarkome
 - Brust-Implantat-assoziierte großzellig-anaplastische Lymphome (BI-ALCL)
- **Selten: Intramammäre Sarkometastasen**
- **Staging: TNM (UICC) bzw. AJCC-Schema der Weichteilsarkome analog anwendbar für Sarkome der Mamma**
- **Grading: Analog zum FNCLCC-System für Sarkome bzw. nach Rosen (1988) für Angiosarkome**

Primäres Angiosarkom der Mamma

- Häufigstes primäres Sarkom der Mamma
- Junges Alter (Median: 24 – 46 J.)
- Unscharfe Raumforderung
- Großer Tumor (Median: 5 – 7 cm)
- Untypischer Mammographie- und Sonographiebefund
- Hohes Lokalrezidivrisiko, auch nach Mastektomie
- Ungünstigere Prognose als andere primäre Sarkome der Mamma

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>
4. Penel, N., Marréaud, S., Robin, Y.-M. et al. (2011). Angiosarcoma: state of the art and perspectives. *Critical Reviews in Oncology/Hematology*, 80(2), 257–263. <http://doi.org/10.1016/j.critrevonc.2010.10.007>
5. Shah, S., & Rosa, M. (2016). Radiation-Associated Angiosarcoma of the Breast: Clinical and Pathologic Features. *Archives of Pathology & Laboratory Medicine*, 140(5), 477–481. <http://doi.org/10.5858/arpa.2014-0581-RS>
6. Young, R. J., Brown, N. J., Reed, M. W., et al. (2010). Angiosarcoma. *The Lancet Oncology*, 11(10), 983–991. [http://doi.org/10.1016/S1470-2045\(10\)70023-1](http://doi.org/10.1016/S1470-2045(10)70023-1)
7. Vorburger, S., Xing, Y., Hunt, K., et al. (2005). Angiosarcoma of the breast. *Cancer*, 104(12), 2682–2688. <http://doi.org/10.1002/cncr.21531>

8. Hodgson, N. C., Bowen-Wells, C., Moffat, F. et al. (2007). Angiosarcomas of the breast: a review of 70 cases. *American Journal of Clinical Oncology*, 30(6), 570–573. <http://doi.org/10.1097/COC.0b013e3181131d62>

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	++

* Behandlung in spezialisierten Zentren empfohlen

Imaging

1. Glazebrook, K. N., Magut, M. J., & Reynolds, C. (2008). Angiosarcoma of the breast. American Journal of Roentgenology, 190(2), 533–538. <http://doi.org/10.2214/AJR.07.2909>
2. O'Neill, A. C., D'Arcy, C., McDermott, E., et al. (2014). Magnetic resonance imaging appearances in primary and secondary angiosarcoma of the breast. Journal of Medical Imaging and Radiation Oncology, 58(2), 208–212. <http://doi.org/10.1111/1754-9485.12100>
3. Chikarmane, S. A., Gombos, E. C., Jagadeesan, J., et al. (2015). MRI findings of radiation-associated angiosarcoma of the breast (RAS). J Magn Reson Imaging, 42(3), 763–770. <http://doi.org/10.1002/jmri.24822>
4. Yang, W. T., Hennessy, B. T. J., Dryden, M. J., et al. (2007). Mammary angiosarcomas: imaging findings in 24 patients. Radiology, 242(3), 725–734. <http://doi.org/10.1148/radiol.2423060163>

Pathology

1. Nascimento, A. F., Raut, C. P., & Fletcher, C. D. M. (2008). Primary angiosarcoma of the breast: clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic. The American Journal of Surgical Pathology, 32(12), 1896–1904. <http://doi.org/10.1097/PAS.0b013e318176dbc7>
2. Adem, C., Reynolds, C., Ingle, J. N., et al. (2004). Primary breast sarcoma:

clinicopathologic series from the Mayo Clinic and review of the literature. *British Journal of Cancer*, 91(2), 237–241. <http://doi.org/10.1038/sj.bjc.6601920>

3. Rosen, P., Kimmel, M., & Ernsberger, D. (1988). Mammary angiosarcoma. The prognostic significance of tumor differentiation. *Cancer*, 62(10), 2145–2151.
4. Udager, A. M., Ishikawa, M. K., Lucas, D. R., et al. (2016). MYC immunohistochemistry in angiosarcoma and atypical vascular lesions: practical considerations based on a single institutional experience. *Pathology*, 48(7), 697–704. <http://doi.org/10.1016/j.pathol.2016.08.007>

Prognostic Factors

1. Wang, L., Lao, I. W., Yu, L., et al. (2016). Primary Breast Angiosarcoma: A Retrospective Study of 36 Cases from a Single Chinese Medical Institute with Clinicopathologic and Radiologic Correlations. *Breast Journal*. <http://doi.org/10.1111/tbj.12731>
2. Wang, X. Y., Jakowski, J., Tawfik, O. W., et al. (2009). Angiosarcoma of the breast: a clinicopathologic analysis of cases from the last 10 years. *Annals of Diagnostic Pathology*, 13(3), 147–150. <http://doi.org/10.1016/j.anndiagpath.2009.02.001>
3. Vorburger, S., Xing, Y., Hunt, K., et al. (2005). Angiosarcoma of the breast. *Cancer*, 104(12), 2682–2688. <http://doi.org/10.1002/cncr.21531>

Primäres Angiosarkom der Brust*

Therapie

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

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

* Behandlung in spezialisierten Zentren empfohlen

Surgery

1. Hui, A., Henderson, M., Speakman, D., et al. (2012). Angiosarcoma of the breast: a difficult surgical challenge. Breast (Edinburgh, Scotland), 21(4), 584–589. <http://doi.org/10.1016/j.breast.2012.01.001>
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. Vorburger, S., Xing, Y., Hunt, K. et al. (2005). Angiosarcoma of the breast. Cancer, 104(12), 2682–2688. <http://doi.org/10.1002/cncr.21531>

Adjuvant Treatment (Chemotherapy, Radiotherapy)

1. Ghareeb, E. R., Bhargava, R., Vargo, J. A., et al. (2016). Primary and Radiation-induced Breast Angiosarcoma: Clinicopathologic Predictors of Outcomes and the Impact of Adjuvant Radiation Therapy. American Journal of Clinical Oncology, 39(5), 463–467. <http://doi.org/10.1097/COC.0000000000000077>
2. Young, R. J., Fernando, M., Hughes, D et al. (2014). Angiogenic growth factor expression in benign and malignant vascular tumours. Experimental and Molecular Pathology, 97(1), 148–153. <http://doi.org/10.1016/j.yexmp.2014.06.010>
3. Gatcombe, H. G., Olson, T. A., & Esiashvili, N. (2010). Metastatic primary angiosarcoma of the breast in a pediatric patient with a complete response to systemic chemotherapy and definitive radiation therapy: case report and review of the

literature. *Journal of Pediatric Hematology/Oncology*, 32(3), 192–194.
<http://doi.org/10.1097/MPH.0b013e3181ca9ed7>

4. Sher, T., Hennessy, B. T., Valero, V., et al. (2007). Primary angiosarcomas of the breast. *Cancer*, 110(1), 173–178. <http://doi.org/10.1002/cncr.22784>
5. Schlemmer, M., Reichardt, P., Verweij, J., et al. (2008). Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. *European Journal of Cancer* (Oxford, England : 1990), 44(16), 2433–2436. <http://doi.org/10.1016/j.ejca.2008.07.037>

Sekundäres (Radiotherapie-assoziiertes) Angiosarkom der Mamma

- **Kumulative Inzidenz des Radiotherapie-assoziierten Sarkoms:
3.2 per 1,000 nach 15 Jahren**
- **Klinische Präsentation**
 - > 5 Jahre nach BET oder Ablatio mit Nachbestrahlung
 - meist intrakutan oder subkutan im Bestrahlungsgebiet mit lividen Hauteffloreszenzen,
 - multiple Herde
 - häufig im fortgeschrittenen Stadien (II – III)
 - Metastasen meist pulmonal, Lymphknoten möglich
- **Prognose ungünstiger als bei Nicht-Radiotherapie assoziierten Sarkomen**
- **Überleben nach 5 Jahren: 15%**

1. Shah, S., & Rosa, M. (2016). Radiation-Associated Angiosarcoma of the Breast: Clinical and Pathologic Features. Archives of Pathology & Laboratory Medicine, 140(5), 477–481. <http://doi.org/10.5858/arpa.2014-0581-RS>
2. 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 (Oxford, England : 1990), 50(10), 1779–1788. <http://doi.org/10.1016/j.ejca.2014.03.002>
3. D'Angelo, S. P., Antonescu, C. R., Kuk, D., et al. (2013). High-risk features in radiation-associated breast angiosarcomas. British Journal of Cancer, 109(9), 2340–2346. <http://doi.org/10.1038/bjc.2013.590>
4. Seinen, J. M., Styring, E., Verstappen, V., et al. (2012). Radiation-associated angiosarcoma after breast cancer: high recurrence rate and poor survival despite surgical treatment with R0 resection. Annals of Surgical Oncology, 19(8), 2700–2706. <http://doi.org/10.1245/s10434-012-2310-x>
5. Sheth, G. R., Cranmer, L. D., Smith, B. D., et al. (2012). Radiation-induced sarcoma of the breast: a systematic review. The Oncologist, 17(3), 405–418. <http://doi.org/10.1634/theoncologist.2011-0282>
6. Scow, J. S., Reynolds, C. A., Degnim, A. C., et al. (2010). Primary and secondary angiosarcoma of the breast: the Mayo Clinic experience. Journal of Surgical Oncology, 101(5), 401–407. <http://doi.org/10.1002/jso.21497>
7. Mery, C. M., George, S., Bertagnolli, M. M. et al. (2009). Secondary sarcomas after radiotherapy for breast cancer. Cancer, 115(18), 4055–4063.

<http://doi.org/10.1002/cncr.24462>

8. Fodor, J., Orosz, Z., Szabó, É., et al. (2006). Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature. *Journal of the American Academy of Dermatology*, 54(3), 499–504. <http://doi.org/10.1016/j.jaad.2005.10.017>
9. Nestle-Krämling, C., Bölke, E., Budach, W., et al. (2011). Hämangiosarkom nach brusterhaltender Therapie beim Mammakarzinom: vier Fallbeispiele mit molekulargenetischer Diagnostik und Literaturübersicht. *Strahlenther Onkol*, 187(10), 656–664. <http://doi.org/10.1007/s00066-011-2251-5>

Sekundäres Angiosarkom der Brust Therapie

- Sekundäre Mastektomie
- Adjuvante Chemotherapie (Anthrazyklin/Taxan-basiert)
- Adjuvante Radiotherapie bei Hochrisiko (Größe > 5 cm, R1)
- Regionale Hyperthermie (Verbesserung lokale Kontrolle) plus Chemotherapie und/oder Radiotherapie

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

Surgery

1. Lindford, A., Böhling, T., Vaalavirta, L., et al. (2011). Surgical management of radiation-associated cutaneous breast angiosarcoma. Journal of Plastic, Reconstructive & Aesthetic Surgery : JPRAS, 64(8), 1036–1042. <http://doi.org/10.1016/j.bjps.2011.02.014>
2. Jallali, N., James, S., Searle, A., et al. (2012). Surgical management of radiation-induced angiosarcoma after breast conservation therapy. American Journal of Surgery, 203(2), 156–161. <http://doi.org/10.1016/j.amjsurg.2010.12.011>

Adjuvant Chemotherapy

1. Jallali, N., James, S., Searle, A., et al. (2012). Surgical management of radiation-induced angiosarcoma after breast conservation therapy. American Journal of Surgery, 203(2), 156–161. <http://doi.org/10.1016/j.amjsurg.2010.12.011>
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Adjuvant Radiotherapy

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Adjuvant Hyperthermia

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Angiosarkome der Brust

Therapie von Lokalrezidiven und Metastasen

Therapie des Lokalrezidivs:

- R0-Resektion
- Adjuvante Radiotherapie bei Hochrisiko (Größe > 5 cm, R1)

Fernmetastasierung / nicht resektable Tumoren:

- Therapie wie Weichteilsarkome
- Paclitaxel weekly / liposomales Doxorubicin (bei Angiosarkomen)
- Antiangiogene Therapie (z.B. bei Angiosarkom)

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

Treatment of local recurrences

1. Lahat, G., Dhuka, A. R., Lahat, S., et al. (2009). Outcome of Locally Recurrent and Metastatic Angiosarcoma. *Annals of Surgical Oncology*, 16(9), 2502–2509.
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Treatment of metastatic and non-resectable tumors

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4. Ray-Coquard IL, Domont J, Tresch-Bruneel E, et al: Paclitaxel Given Once Per Week With or Without Bevacizumab in Patients With Advanced Angiosarcoma: A Randomized Phase II Trial, J Clin Oncol. 2015 Sep 1;33(25):2797-802

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

- **Selten, geschätzte jährliche Inzidenz <1 je 100,000 Frauen mit Implantaten (medianes Patientenalter 54 J.)**
- **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%)
- **Histologisch: CD30+ / ALK-T-Zell-Lymphom**
- **Meldepflicht als SAE nach § 3 MPSV an das BfArM**

Reviews

1. Kim, B., Predmore, Z. S., Mattke, S., et al. (2015). Breast Implant-associated Anaplastic Large Cell Lymphoma: Updated Results from a Structured Expert Consultation Process. Plastic and Reconstructive Surgery. Global Open, 3(1), e296. <http://doi.org/10.1097/GOX.0000000000000268>
2. Eaves, F., & Nahai, F. (2011). Anaplastic large cell lymphoma and breast implants: FDA report. Aesthetic Surgery Journal, 31(4), 467–468. <http://doi.org/10.1177/1090820X11407872>
3. Rupani, A., Frame, J. D., & Kamel, D. (2015). Lymphomas Associated with Breast Implants: A Review of the Literature. Aesthetic Surgery Journal, 35(5), 533–544. <http://doi.org/10.1093/asj/sjv016>
4. Clemens, M. W., & Miranda, R. N. (2015). Commentary on: Lymphomas Associated With Breast Implants: A Review of the Literature. Aesthetic Surgery Journal, 35(5), 545–547. <http://doi.org/10.1093/asj/sjv056>
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Brust-Implantat-assoziiertes großzellig-anaplastisches Lymphom (BIA-ALCL) – Diagnostik –

	Oxford		
	LoE	GR	AGO
▪ Sonographie (Abklärung neu aufgetretener Serome 1 Jahr nach Implantateinlage, Herdbefund)	5	D	++
▪ Mamma-MRT bei Bestätigung der Diagnose	5	D	++
▪ Nodalstatus, PET-CT, Knochenmarksbiopsie	5	D	++
▪ Ergusszytologie (bei neu aufgetretenen Seromen 1 Jahr nach Implantateinlage) mit Fragestellung „Z.A. BIA-ALCL“	5	D	++
▪ Lymphomdiagnostik am Resektat und histologisches Staging (n. Clemens 2016)	5	D	++
▪ Dokumentation des Implantates (Hersteller, Größe, Füllung, Oberfläche, Batch-Nummer)	5	D	++

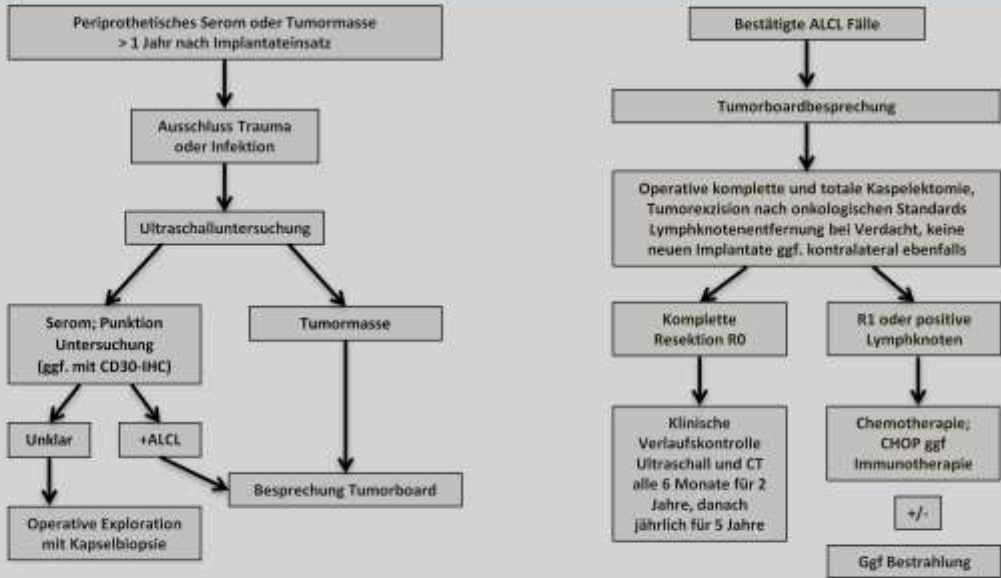
1. Clemens, M. W., Medeiros, L. J., Butler, C. E., et al. (2016). Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 34(2), 160–168. <http://doi.org/10.1200/JCO.2015.63.3412>
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5. Granados, R., Lumbreras, E. M., Delgado, M. C. et al (2016). Cytological Diagnosis of Bilateral Breast Implant-Associated Lymphoma of the ALK-Negative Anaplastic Large-Cell Type. *Clinical Implications of Peri-Implant Breast Seroma Cytological Reporting. Diagnostic Cytopathology*, 44(7), 623–627. <http://doi.org/10.1002/dc.23485>
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Brust-Implantat-assoziiertes großzellig-anaplastisches Lymphom (BIA-ALCL) – Therapie –

	Oxford		
	LoE	GR	AGO
▪ Implantatentfernung und vollständige Capsulektomie einschließlich Tumorentfernung	3a	C	++
▪ Entfernung suspekter Lymphknoten, keine routinemäßige Sentinel-Node Biospie, keine Axilladisektion	4	D	++
▪ Polychemotherapie (z.B. CHOP) bei extrakapsulärer Tumorausbreitung	4	D	+
▪ Radiatio bei unresektablen Tumoren oder R1	5	D	+/-
▪ Rekonstruktion nach 1 Jahr erscheinungsfreiem Intervall	5	D	+

1. Clemens, M. W., Medeiros, L. J., Butler, C. E., et al. (2016). Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 34(2), 160–168.
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3. Kim, B., Predmore, Z. S., Mattke, S., et al. (2015). Breast Implant-associated Anaplastic Large Cell Lymphoma: Updated Results from a Structured Expert Consultation Process. Plastic and Reconstructive Surgery. Global Open, 3(1), e296.
<http://doi.org/10.1097/GOX.0000000000000268>

Brust-Implantat-assoziiertes großzellig-anaplastisches Lymphom (BIA-ALCL) – Schemata zum Management (n. Noah 2017) –



Metaplastisches Mammakarzinom

	Oxford		
	LoE	GR	AGO
▪ Bildgebung und Histologie zur Diagnosesicherung nach üblichem Standard	5	D	++
▪ Staging mittels CT-Thorax/ -Abdomen (hämatogene Metastasierung)	4	C	++
▪ Operative Therapie nach den üblichen Grundsätzen (häufiger MRM aufgrund fortgeschrittenen Tumorstadiums, RR > 3 cm)	4	C	++
▪ SNB	4	C	+
▪ Adjuvante Chemotherapie (eher chemoresistent)	4	C	+
▪ Adjuvante endokrine Therapie nach Standard	4	C	+/-
▪ Adjuvante Strahlentherapie nach Standard	4	C	+

Imaging, Prognosis, Staging

1. Lakhani SR, Ellis IO, Schnitt SJ, et al. WHO classification of tumors of the breast. World Health Organization classification of tumours. 4th ed. Lyon: IARC Press; 2012. 48–52 pp.
2. Song Y, Liu X, Zhang G, et al. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. World J Surg Oncol. 2013; 11:129
3. Zhang Y, Lv F, Yang Y, et al. Clinicopathological Features and Prognosis of Metaplastic Breast Carcinoma: Experience of a Major Chinese Cancer Center, PLoS One. 2015 Jun 26;10(6):e0131409
4. Sinn HP, Kreipe H. A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. Breast Care (Basel) 2013; 8:149-54.

Surgical Therapy

1. Pezzi CM, Patel-Parekh L, Cole K, et al (2007). Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol, 14, 166-73.
2. J. D. Beatty, M. Atwood, R. Tickman, et al, “Metaplastic breast cancer: clinical significance,” American Journal of Surgery, vol. 191, no. 5, pp. 657–664, 2006.

Adjuvant chemotherapy

1. Reviewed in: Tzanninis IG et al., Management and Outcomes in Metaplastic Breast Cancer Clin Breast Cancer. 2016 Dec;16(6):437-443

Adjuvant endocrine therapy

1. Reviewed in: Tzanninis IG et al., Management and Outcomes in Metaplastic Breast Cancer Clin Breast Cancer. 2016 Dec;16(6):437-443

Adjuvant radiotherapy

1. Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol 2011; 18:94-103.

Metaplastisches Mammakarzinom

Häufigkeit: 0,2-5 % aller Mammakarzinome (1)
Histologie: epitheliale und mesenchymale Anteile mit zwei bis drei unterschiedlichen Komponenten innerhalb eines Tumors; hohe Proliferationsrate
Subtypen: nach WHO (4)

Metaplastic carcinoma of no special type	Low-grade adenosquamous carcinoma
Fibromatosis-like carcinoma	Squamous cell carcinoma
Spindle cell carcinoma	Metaplastic carcinoma with mesenchymal differentiation
Chondroid differentiation	Osseous differentiation
Other types of mesenchymal differentiation	Mixed metaplastic carcinoma
Myoepithelial carcinoma	

Molekularbiologie: > 90 % ER-, PR-, HER2-
in ca. 70 % Überexpression von HER1, CK 5/6-Expression
(stem-cell-like and BRCA-like)(2)
molekulares Profil hauptsächlich basal-like (3)
häufige Mutationen in PIK3CA und PTEN (mTOR-Überaktivität)

Klinik:

- große Tumore bei Erstmanifestation (> 5 cm)
- hohes hämatogenes Metastasierungspotenzial; Nodalbefall in ca. 20 % (kein Nodalbefall bei spindelzellförmigem Subtyp und Karzinosarkom)
- klinischer Verlauf ungünstiger als TNBC
- prognostisch ungünstiger bei asiatischen Patientinnen (häufiger MRM, schlechtes grading, häufig plattenepithelialer Subtyp, seltener spindelzellförmig)

Metaplastic breast cancer - Background

1. Lakhani SR, Ellis IO, Schnitt SJ, et al. WHO classification of tumors of the breast. World Health Organization classification of tumours. 4th ed. Lyon: IARC Press; 2012. 48–52 pp.
2. Song Y, Liu X, Zhang G, et al. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. World J Surg Oncol. 2013; 11:129
3. Zhang Y, Lv F, Yang Y, et al. Clinicopathological Features and Prognosis of Metaplastic Breast Carcinoma: Experience of a Major Chinese Cancer Center, PLoS One. 2015 Jun 26;10(6):e0131409
4. Sinn HP, Kreipe H. A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. Breast Care (Basel) 2013; 8:149-54.
5. Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol 2011; 18:94-103.