

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer: Specific Situations



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Brustkrebs: Spezielle Situationen

- **Versions 2005–2018:**
**Dall / Fehm / Fersis / Friedrich / Gerber / Göhring /
Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass /
Mundhenke / Oberhoff / Rody / Scharl / Schneeweiss /
Schütz / Sinn / Solomayer / Thomssen**
- **Version 2019:**
Stickeler / Müller

Update January 2018 – Harbeck / Rody

Update January 2017 – Schütz / Sinn

Update January 2016 – Thomssen / Harbeck

Update January 2015 – Solomayer / Harbeck

Update January 2014 – Fehm/Schneeweiss

Update January 2013 – Fersis/Friedrich

Update January 2012 – Lux/Lück

Update February 2011 – Janni/Huober

Update January 2010 – Mundhenke/Rody

Screened data bases:


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

base (2012),

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

Screened guidelines

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



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Breast Cancer: Specific Situations

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

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.



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Breast Cancer in Young Women ≤ 40 Years

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

- **Aggressive biological behavior with worse prognosis**
- **Local therapy independent of young age**
- **Guidelines adapted (neo-)adjuvant systemic treatment (see chapters there)**
- **GnRHa as ovarian protection (see chapter gyn. problems)**
- **Genetic and fertility counseling**
- **Contraception counseling**

1. Poggio F, Lambertini M, Bighin C et al. Management of young women with early breast cancer. ESMO open 2018;3(Suppl 1):e000458.
2. 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.
3. 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.
4. 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
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. Shoemaker ML, White MC, Wu M et al. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013. *Breast Cancer Res Treat* 2018;169(3):595-606.
2. Ann H. Partridge et al. Model Program to Improve Care for a Unique Cancer Population: Young Women With Breast Cancer *J Oncol Pract*. 2012; 8(5): e105–e110.
3. Hironaka-Mitsuhashi A, Tsuda H, Yoshida M et al. Invasive breast cancers in adolescent and young adult women show more aggressive immunohistochemical and clinical features than those in women aged 40-44 years. *Breast Cancer* 2018.
4. Johansson ALV, Trewin CB, Hjerkind KV et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. *Int J Cancer* 2018.
5. Liu Z, Sahli Z, Wang Y, Wolff AC et al. Young age at diagnosis is associated with worse prognosis in the Luminal A breast cancer subtype: a retrospective institutional cohort study. *Breast Cancer Res Treat* 2018;172(3):689-702.
6. Kroman N. et al, Factors influencing the effect of age on prognosis in breast cancer: population based study. *BMJ*. 2000 Feb 19;320(7233):474-8.
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9. Oh JL, Bonnen M, Outlaw ED, et al . The impact of young age on locooregional recurrence after doxorubicin-based breast conservation therapy in patients 40 years old or younger: How young is "young"? *Int J Radiat Oncol Biol Phys* 2006;65:1345-52.

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12. Tichy JR et al. Breast cancer in adolescents and young adults: a review with a focus on biology. J Natl Compr Canc Netw. 2013;11(9):1060-9.

Chemotherapy in young women

1. Passildas J, Collard O, Savoye AM et al. Impact of Chemotherapy-induced Menopause in Women of Childbearing Age With Non-metastatic Breast Cancer - Preliminary Results From the MENOCOR Study. Clin Breast Cancer 2018.
2. Oktay K, Harvey BE, Partridge AH et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36(19):1994-2001.
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Endocrine therapy in young women

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

1. Smith I, HERA study team: 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet.* 2007;369(9555):29-36
2. A.H. Partridge et al. The effect of age on breast cancer outcomes in women with her-2 positive breast cancer: results from the

HERA trial J Clin Oncol 2013;44,2692–2698

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

1. M. Gnant et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360 (7) 679–691
2. Gerber B et al. Effect of Luteinizing Hormone-Releasing Hormone Agonist on ovarian function after adjuvant breast cancer chemotherapy: by the GBG 37 ZORO study. J. Clin Oncol 2011;29 (17) 2334-2341
3. Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial J Natl Cancer Inst 2007 ;99:516–525
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5. Del Mastro L et al. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: Systematic review and meta-analysis of randomized trials. Cancer Treat Rev 2013 in press
6. Yang B et al. Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials Breast 2013;22(2):150-7.
7. Recchia F, Necozone S, Bratta M, et al. LH-RH analogues in the treatment of young women with early breast cancer: Long-term follow-up of a phase II study. Int J Oncol. 2015 Mar;46(3):1354-60.
8. Kim J, Kim M, Lee JH et al. Ovarian function preservation with GnRH agonist in young breast cancer patients: does it impede the

effect of adjuvant chemotherapy? Breast. 2014 Oct;23(5):670-5.

9. Moore HCF, Unger JM, Phillips KA, et al Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance). J Clin Oncol 32:5s, 2014 (suppl; abstr LBA505)

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

1. de Bock GH et al., Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy; Long-term results of European Organisation for Research and Treatment of Cancer Studies. Eur J Cancer 2005, 25.
2. Garg AK et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys. 2007 Dec 1;69(5):1478-83. – Radiation boost therapy can reduce in-breast recurrence [Bartelink H, Horiot JC, Poortmans PM, Struikmans H, et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10 year results of the EORTC trial 22881-10882. Br Cancer Res Treat 2006;100:S8-10].
3. Mahmood U et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2012;83(5):1387e93.
4. Cao JQ et al. Comparison of recurrence and survival rates after breast-conserving therapy and mastectomy in young women with breast cancer. Curr Oncol. 2013;20(6):e593-e601. Review.
5. Recio-Saucedo A, Gerty S, Foster C, et al. Information requirements of young women with breast cancer treated with mastectomy or breast conserving surgery: A systematic review. Breast. 2016 Feb;25:1-13.

6. Frandsen J, Ly D, Cannon G, et al. In the Modern Treatment Era, Is Breast Conservation Equivalent to Mastectomy in Women Younger Than 40 Years of Age? A Multi-Institution Study. *Int J Radiat Oncol Biol Phys*. 2015 Dec 1;93(5):1096-103.
7. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (≤ 40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *Breast*. 2015 Jun;24(3):175-81.

Genetic and fertility counselling

1. Copson ER, Maishman TC, Tapper WJ et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol* 2018;19(2):169-80.
2. Engel C, Rhiem K, Hahnen E et al. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. *BMC Cancer* 2018;18(1):265.
3. Yang B et al: Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: A meta-analysis of randomized controlled trials. *Breast* 2013 Jan 5. pii: S0960-9776(12)00252-4.
4. Gerber B. et al. Effect of Luteinizing Hormone-Releasing Hormone Agonist on ovarian function after adjuvant breast cancer chemotherapy: by the GBG 37 ZORO study. *J. Clin Oncol* 29 (17) 2334-2341 2011
5. Del Mastro L et al: Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer *JAMA* 306 (3); 269-276 2011
6. Ruddy KJ et al. Menopausal symptoms and fertility concerns in premenopausal breast cancer survivors: A comparison to age- and gravidity-matched controls. *Menopause*. 2011;18:105–108

7. Lee MC et al.: Fertility and reproductive considerations in premenopausal patients with breast cancer. *Cancer Control*. 2010 Jul;17(3):162-72.
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9. Hulvat MC, Jeruss JS. Maintaining fertility in young women with breast cancer. *Curr Treat Options Oncol*. 2009 Dec;10(5-6):308-17.
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11. Lambertini M, Ceppi M, Poggio F, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. *Ann Oncol*. 2015 Dec;26(12):2408-19.

Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery			
	Oxford		
	LoE	GR	AGO
▪ Breast imaging & biopsy like in non-pregnant	4	C	++
▪ Staging if indicated (Bone scan after delivery)	5	D	+
▪ Full body MRI (without contrast agent)	4	C	+/-
▪ Surgery like in non-pregnant patients	4	C	++
▪ Sentinel node excision (technetium only)	4	C	+
▪ SLNE during 1st trimester	5	D	+/-
▪ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
▪ Blue dye (has not been tested in pregnant animals or humans)	4	C	--

* Participation in register study recommended



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

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

Outcome information (e.g. GBG registry)

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

literature. Curr Oncol. 2015 Mar;22(Suppl 1):S8-S18

Statement: Breast imaging & biopsy like in non-pregnant

1. diFlorio-Alexander RM, Slanetz PJ, Moy L et al. ACR Appropriateness Criteria((R)) Breast Imaging of Pregnant and Lactating Women. Journal of the American College of Radiology : JACR 2018;15(11s):S263-s75.
2. Bock K. et al., Rationale for a diagnostic chain in gestational breast tumor diagnosis. Arch Gynecol Obstet 2005
3. Ahn BY et al., Pregnancy and lactation-associated breast cancer: mammographic and sonographic findings. J Ultrasound Med 2003, 491-497
4. Nicklas AH et al., Imaging strategies in the pregnant cancer patient. Semin Oncol 2000, 27: 623-632
5. Hogge JP et al., Imaging and management of breast masses during pregnancy and lactation. Breast J 1999, 5: 272-283.
6. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70

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

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

Statement: Whole Body MRI

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

Statement: Surgery like in non-pregnant patients

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

Statement: „Sentinel node biopsy“ during pregnancy


1. Han SN, Amant F, Cardonick EH, Loibl S, Peccatori FA, Gheysens O, et al. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. Breast Cancer Res Treat 2018;168(2):551-57.
2. Gropper AB, Calvillo KZ, Dominici L, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. Ann Surg Oncol. 2014 Aug;21(8):2506-11.
3. Khara SY, Kiluk JV, Hasson DM et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. Breast J. 2008 May-Jun;14(3):250-4

Reviews

1. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. Cancer. 2006 Jan 15;106(2):237-46.
2. Shachar SS, Gallagher K, McGuire K, Zagar TM, Faso A, Muss HB, et al. Multidisciplinary Management of Breast Cancer During Pregnancy. Oncologist 2017;22(3):324-34.
3. Lee GE, Mayer EL, Partridge A. Prognosis of pregnancy-associated breast cancer. Breast Cancer Res Treat 2017;163(3):417-21.
4. Ruiz R, Herrero C, Strasser-Weippl K, Touya D, St Louis J, Bukowski A, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review. Breast 2017;35:136-41.
5. Talele AC, Slanetz PJ, Edmister WB, et al. The lactating breast: MRI findings and literature review. Breast J 2003, 9: 237-240
6. Shachar SS, Gallagher K, McGuire K et al. Multidisciplinary Management of Breast Cancer During Pregnancy. Oncologist

2017;22(3):324-34.

7. Framarino-Dei-Malatesta M, Sammartino P, Napoli A. Does anthracycline-based chemotherapy in pregnant women with cancer offer safe cardiac and neurodevelopmental outcomes for the developing fetus? BMC Cancer 2017;17(1):777.
8. Scharl A, Ahr A, Göhring U-J: Malignome in der Schwangerschaft. In: Kaufmann M, Costa SD, Scharl A (eds) Die Gynäkologie. Springer, Heidelberg, 2002 pp 509
9. Gadducci A, Cosio S, Fanuchi A, et al; Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and a review of the literature. Anticancer Res 2003; 23: 5225-5229
10. Ben Brahim E, Mrad K, Driss M, et al. Placental metastasis of breast cancer. Gynecol Obstet Fertil 2001, 29: 545-548
11. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. JCO 2001; 19: 1671-5
12. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70



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

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

- Radiation therapy during pregnancy
- (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)
 - Anthracyclines: AC, EC
 - Taxanes
 - Platin salts (carboplatin, cisplatin)
 - MTX (e.g. CMF)
- Endocrine treatment
- HER2-neu targeted treatment
- Bisphosphonates, denosumab

General principles

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

Statement: Radiotherapy during pregnancy

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

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

1. Loibl S, Han S, Mayer K, et al. Neoadjuvant chemotherapy for patients with breast cancer during pregnancy (BCP). J Clin Oncol 32:5s, 2014 (suppl; abstr 1071)
2. Ring et al, Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. J Clin

Oncol 2005, 23: 4192-4197

3. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2008 Apr;19(4):607-13.

Statement: Anthracyclines: AC, EC

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

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

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

Statement: Taxanes

1. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2008 Apr;19(4):607-13.
2. Gadducci A, Cosio S, Fanuchi A, et al; Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and a review of the literature. Anticancer Res 2003; 23: 5225-5

3. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012;13:887-896.
4. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer* 2013;13:16-23.
5. Cardonick E et al. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012;23:3016-3023.

Statement: Platinum salts

1. Köhler C, Oppelt P, Favero G, et al. How much platinum passes through the placental barriers? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. *Am J Obstet Gynecol*. 2015 Aug;213(2):206.
2. Zheng X, Zhu Y, Zhao Y, Feng S, Zheng C. Taxanes in combination with platinum derivatives for the treatment of ovarian cancer during pregnancy: A literature review. *International journal of clinical pharmacology and therapeutics* 2017;55(9):753-60.
3. Calsteren KV, Verbesselt R, Devlieger R, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. *Int J Gynecol Cancer* 2010 Dec;20(9):1456-64.
4. Kong TW, Lee EJ, Lee Y, et al. Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy. *Obstet Gynecol Sci*. 2014 Nov;57(6):539-43.

Statement: MTX (e.g. CMF)

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

Statement: Endocrine treatment

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. Lambertini M, Martel S, Campbell C et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Cancer 2018.
2. Yildirim N, Bahceci A. Use of pertuzumab and trastuzumab during pregnancy. Anticancer Drugs 2018;29(8):810-13.
3. Fanale MA et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. Clin Breast Cancer 2005, 6: 354-356 (Case Report)
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5. Loibl S. New Therapeutic Options for Breast Cancer during Pregnancy. Breast Care 2008; 3:171-176. (table overview of trastuzumab cases)
6. Aebi S, Loibl S. Breast cancer during pregnancy: medical therapy and prognosis. Recent Results Cancer Res. 2008;178:45-55.
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Statement Bisphosphonate during pregnancy

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

General information: Chemotherapy during pregnancy

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



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Breast Cancer During Pregnancy*

– Delivery and Breast-Feeding –

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

- **Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)**
- **Termination of pregnancy does not improve maternal outcome**
- **Delivery mode like in healthy women; avoid delivery during chemotherapy induced leucocyte nadir**
- **If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities**

* Participation in register study recommended

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 in leucocyte nadir


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

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

1. Williams Obstetrics lecture book
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Breast Cancer and Pregnancy – Family Planning –

	Oxford		
	LoE	GR	AGO
▪ After breast cancer diagnosis reproductive techniques can be used to induce pregnancy	5	D	++
▪ Success rates for getting pregnant and for deliver a child are lower in breast cancer patients in comparison to non-cancer patients	5	D	++
▪ Breast cancer patients of reproductive age should be offered a fertility counseling before starting any kind of treatment	5	D	++
▪ Breast cancer patients should not be advised against getting pregnant regardless of tumor's hormone receptor status	5	D	++

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2>Pregnancy Associated Breast Cancer*: Outcome</h2>	
		Oxford LoE
	<ul style="list-style-type: none"> ■ BC during pregnancy / lactation <ul style="list-style-type: none"> ■ Adequate treatment is essential 	3a
	<ul style="list-style-type: none"> ■ Pregnancy and lactation after BC <ul style="list-style-type: none"> ■ Outcome not compromised 	3a
	<p>* Participation in register study recommended</p>	

General principles

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

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

1. Gerstl B, Sullivan E, Ives A et al. Pregnancy Outcomes After a Breast Cancer Diagnosis: A Systematic Review and Meta-analysis. Clin

Breast Cancer 2018;18(1):e79-e88.

2. Lambertini M, Kroman N, Ameye L et al. Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status. *J Natl Cancer Inst* 2018;110(4):426-29.
3. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. *Cancer biology & medicine* 2018;15(1):6-13.
4. Ploquin A, Pistilli B, Tresch E et al. 5-year overall survival after early breast cancer diagnosed during pregnancy: A retrospective case-control multicentre French study. *Eur J Cancer* 2018;95:30-37.
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13. Amant F et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study *J Clin Oncol*. 2013;31(20):2532-9.
14. Litton JK et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. *Oncologist*. 2013;18(4):369-76.


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

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

Review articles

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


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

1. Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 2012;13(4):e148-60.
2. Overcash J. Comprehensive Geriatric Assessment: Interprofessional Team Recommendations for Older Adult Women With Breast Cancer. Clinical journal of oncology nursing 2018;22(3):304-15.
3. Charlson et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987 40:373-383.
4. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006 295:801-08.
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8. Aaldriks AA, Maartense E, Nortier HJ, et al. Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. *Acta Oncol.* 2016 Jan;55(1):15-23.



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Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

	Oxford		
	LoE	GR	AGO
■ Clinical geriatric assessment	2b	B	++
■ Treatment according to guidelines	2a	C	++
■ Surgery similar to „younger“ age	2b	B	++
■ Endocrine treatment (endocrine resp.)	1a	A	++
■ Chemotherapy (standard regimens)			
■ < 70 years	1a	A	+
■ > 70 years (especially N+, ER/PgR-)	2a	C	+*
■ Radiotherapy	1a	A	+
■ Omit radiotherapy after BCT in low risk with endocrine treatment	1b	B	+
■ Trastuzumab	2b	C	+

* Study participation recommended

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

Statement: Treatment according to standard

1. Shachar SS, Jolly TA, Jones E et al. Management of Triple-Negative Breast Cancer in Older Patients: How Is It Different? Oncology (Williston Park) 2018;32(2):58-63.
2. Bouchardy C et al., Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol. 2003;21(19):3580-71.
3. Quinten C, Kenis C, Hamaker M et al. The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged ≥70 with early stage invasive breast cancer. Journal of geriatric oncology 2018;9(2):152-62.
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cancer has an adverse impact on breast cancer-specific survival. Br J Surg 2018;105(11):1454-63.

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9. Kemeny MM: Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003 Jun 15;21(12):2268-75
10. Giordano SH: Breast cancer treatment guidelines in older women. J Clin Oncol. 2005 Feb 1;23(4):783-91.
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12. Wildiers H: Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 2007 Dec;8(12):1101-15
13. Luque M et al. Breast cancer management in the elderly. Clin Transl Oncol. 2013 epub

Statement: Surgery similar to „younger“ age

1. Swaminathan V. et al. Choices in Surgery for older women with breast cancer Breast Care 2012;7:445-451
2. Fentiman IS: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. Eur J Cancer. 2003 Feb;39(3):309-16
3. Fentiman IS: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen. Eur J Cancer. 2003 Feb;39(3):300-8
4. Hind D: Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. Br J Cancer 2007 Apr 10;96(7):1025-9.
5. Rudenstam CM Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol. 2006 Jan 20;24(3):337-44.
6. Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol. 2011;18(1):125-33

7. Johnston SJ et al. A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up. *Ann Oncol* 2012;9:2296-300.
8. Chakrabarti J et al. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up. *Crit Rev Oncol Hematol*. 2011;78(3):260-4.

Statement: Endocrine treatment (endocrine resp.)

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2. Crivellari D, Sun Z, Coates AS, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 Trial. *J Clin Oncol* 2008; 26:1972-79
3. 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
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5. Silliman RA: Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer. *J Clin Oncol*. 2002 Jun 1;20(11):2680-8
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7. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381, 805–816

Statement: Chemotherapy in pts. < 70 years

1. Loibl S, von Minckwitz G, Harbeck N, et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. *Breast Cancer Res*. 2008 Sep16;10(5):R77

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

1. Qin A, Thompson CL, Silverman P. Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. *J Cancer Surviv.* 2015 Jun;9(2):252-9.
2. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol.* 2007 Sep 1;25(25):3808-15.
3. von Minckwitz G, Reimer T, Potenberg J, et al. The phase III ICE study: Adjuvant Ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. *SABCS 2014 (S3-04).*


4. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients Breast Care 2012;7:439-444
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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
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Statement: Radiotherapy

1. Kunkler I Radiotherapy issues in elderly breast cancer patients Breast Cancer Patients Breast Care 2012;7:453-459
2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control Strahlenther Onkol 2012 :1-5
3. Giordano SH Radiotherapy in older women with low-risk breast cancer: why did practice not change? 2012 J Clin Oncol 30 (14): 1577-1578
4. Prescott RJ: A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technol Assess. 2007 Aug;11(31):1-149, iii-iv
5. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg. 2008 Jan;206(1):66-75
6. Hughes KS et al: Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382-7
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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.
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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.
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Treatment for Frail Patients

(Life Expectancy <5 yrs, Substantial Comorbidities)

	Oxford		
	LoE	GR	AGO
■ Reduced standard treatment	2b	C	++
■ Options extrapolated from trials in elderly:			
■ No breast surgery (consider endocrine options)	2b	C	+
■ No axillary clearing (≥ 60 y, cN0, rec.-pos)	2b	B	+
■ No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)	1b	B	++
■ Hypofractionated radiotherapy	2b	B	+
■ No chemotherapy if >70 years and negative risk-benefit analysis	2b	C	+

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

Statement: Reduced standard treatment

Statement: No breast surgery (consider endocrine options)

1. Hind D: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004272.
2. Fentiman IS, et al. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing

tamoxifen alone with modified radical mastectomy. Eur J Cancer (2003) 39(3):309-16

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

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

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Statement: Hypofractionated radiotherapy


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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

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Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy			
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	LoE	GR	AGO
	4	C	+
	3b	C	+/-
	2b	B	++
	4	C	++*
	4	C	++*
	2b	B	+
	4	C	+
	2b	B	++
<p>GCP</p> <p>++</p>			

■ Diagnostic work-up as in women

- Mammography
- Ultrasound

■ Standard-surgery: Mastectomy

- BCT is an option (tumor breast relation)
- Sentinel-node excision (SNE)

■ Radiotherapy as in women

(consider tumor breast relation!)

■ Genetic counselling if one additional relative affected (breast/ovarian cancer)

■ Screening for 2nd malignancies according to guidelines

* Participation in register study recommended

International registry

- Cardoso F, Bartlett JMS, Slaets L et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018;29(2):405-17.
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General

- Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, Park BH, et al. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat 2018.
- Fentiman IS. Unmet needs of men with breast cancer. Eur J Surg Oncol 2018;44(8):1123-26.

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13. Deb S, Lakhani SR, Ottini L, et al. The cancer genetics and pathology of male breast cancer. Histopathology. 2016 Jan;68(1):110-8.

Statement: Diagnostic work up as in women

Statement: Mammography

1. Chesebro AL, Rives AF, Shaffer K. Male Breast Disease: What the Radiologist Needs to Know. Current problems in diagnostic radiology 2018.
2. Dershaw DD. et al. Mammographic findings in men with breast cancer. Am J Roentgenol 1993 160: 267

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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

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

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2. Schuchardt U et al. Adjuvant radiotherapy for breast carcinoma in men: a 20-year clinical experience. Am J Clin Oncol 1996 19:330
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Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer)

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2. Friedman LS, Gayther SA, Kurosaki T, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet 1997; 60: 313-319
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Statement: Screening for 2nd malignancies according guidelines

1. Wernberg JA. Multiple primary tumors in men with breast cancer diagnoses: a SEER database review. J Surg Oncol. 2009 Jan

1;99(1):16-9

Statement: Systemic therapy


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.
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4. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer Breast Cancer Res Treat. 2013;141(1):119-23
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Review articles

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Male Breast Cancer: Systemic Therapy

	Oxford		
	LoE	GR	AGO
■ Adjuvant chemotherapy as in women	2a	B	++
■ HER2-targeted therapy (if HER2 pos.)	5	D	++
■ Endocrine therapy	4	D	++
■ Tamoxifen	2b	B	++
■ Aromatase inhibitors (adjuvant)	2b	B	-*
■ Aromatase inhibitors (metastatic BC)	4	C	+/-
■ GnRHa and AI (metastatic BC)	4	C	+*
■ Fulvestrant (metastatic BC)	4	C	+/-
■ Palliative chemotherapy as in women	4	C	++

Statement: Adjuvant Chemotherapy

1. Patel HZ et al. Role of adjuvant chemotherapy in male breast cancer. Cancer 1989 64: 1583
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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

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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

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Benefit from Trimodal Treatment in Inflammatory Breast Cancer

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


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

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

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

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

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



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Inflammatory Breast Cancer (IBC, cT4d)

	Oxford		
	LoE	GR	AGO
■ Invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d			++
■ Staging	2c	B	++
■ Skin punch biopsy (at least 2; detection rate < 75%)	2c	B	+
■ Neoadjuvant chemotherapy (regimens as in noninflammatory BC)	2c	B	++
■ Adjuvant systemic treatment according to guidelines	2c	B	++
■ Mastectomy after chemotherapy	2c	B	+
■ Breast conserving therapy in case of pCR (individual)	2b	C	+/-
■ Sentinel excision only	3b	C	-
■ Radiotherapy (PMRT)	2c	B	++

General

- 1.Ueno NT, Espinosa Fernandez JR, Cristofanilli M et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. Journal of Cancer 2018;9(8):1437-47. 1.
- 2.Audisio RA. Inflammatory Breast Cancer: Updates on diagnosis and treatment options. Eur J Surg Oncol 2018;44(8):1127.
- 3.Copson E, Shaaban AM, Maishman T et al. The presentation, management and outcome of inflammatory breast cancer cases in the UK: Data from a multi-centre retrospective review. Breast 2018;42:133-41.
- 4.Copson E, Shaaban AM, Maishman T et al. The presentation, management and outcome of inflammatory breast cancer cases in the UK: Data from a multi-centre retrospective review. Breast 2018;42:133-41.
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- 6.Wu SG, Zhang WW, Wang J et al. Inflammatory breast cancer outcomes by breast cancer subtype: a population-based study. Future Oncol 2018.
- 7.Brzezinska M, Williams LJ, Thomas J et al. Outcomes of patients with inflammatory breast cancer treated by breast-conserving

surgery. Breast Cancer Res Treat 2016;160(3):387-91.

8. Boudin L, Goncalves A, Sfumato P et al. Prognostic impact of hormone receptor- and HER2-defined subtypes in inflammatory breast cancer treated with high-dose chemotherapy: a retrospective study. Journal of Cancer 2016;7(14):2077-84.
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10. van Uden DJ, Bretveld R, Siesling S et al. Inflammatory breast cancer in the Netherlands; improved survival over the last decades. Breast Cancer Res Treat 2017;162(2):365-74.

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

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 3.2018. NCCN.org (Inflammatory Breast Cancer. IBC-1)

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

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

Statement: Staging

1. Ueno NT, Espinosa Fernandez JR, Cristofanilli M et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. Journal of Cancer 2018;9(8):1437-47.
2. 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.

3. 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
4. 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. Johnston S (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 bevazizumab

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 phase 2 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.
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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.
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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.ijssu.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

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

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

Guidelines

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

	Oxford		
	LoE	GR	AGO
▪ Mammography, Breast-ultrasound, Breast-MRI	3	B	++
▪ Exclude contralateral cancer	3	B	++
▪ Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)	5	D	++
▪ Staging (CT thorax / abdomen, thyroid scintigraphy, HNT-exam)	3	B	++
▪ PET / PET-CT	3b	B	+

Statement: Mammography / Breast ultrasound/ Breast MRI


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Statement: Staging

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Statement: PET

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Axillary Metastasis in Occult Breast Cancer (ex. CUP)

Pathology, molecular pathology

	Oxford		
	LoE	GR	AGO
▪ ER, PgR, HER2, GATA3	5	D	++
▪ Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.	5	D	++
▪ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, Theros CTID)	2c	B	+/-
▪ NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)	2c	B	+/-
▪ Prognostic gene expression tests	5	D	--

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Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Therapy

	Oxford		
	LoE	GR	AGO
■ Axillary dissection	3a	C	++
■ Mastectomy if breast MRI is negative	3a	C	-
■ (Neo-) adjuvant systemic therapy according to breast cancer guidelines (AGO)	5	D	++
■ Breast irradiation if breast MRI is negative	2c	B	+
■ Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)	3b	B	+

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Statement: Axillary dissection

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Statement: Mastectomy without (in-)breast tumor

References 1-4 (retrospective analysis , case reports)

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Statement: Breast irradiation if breast MRI is negative

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Statement: Systemic treatment according N+ tumor

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Paget's Disease of the Breast

- **Paget's disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer. Isolated Paget's disease of the nipple is more rarely seen, and less aggressive.**


Feature	Frequency
Presentation	Paget's disease with invasive Ca. (37 - 58%) Paget's disease mit DCIS (30 - 63%) Isolated Paget's disease (4 - 7%) Isolated Paget's disease with invasion (rare)
IHC	HER2-positive (83 - 97%) ER-positive (10 - 14%) AR-positive (71 - 88%)

Clinical Presentation

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Paget's Disease of the Breast Diagnosis

- **Histological verification by skin biopsy**
- **Mammography, sonography**
- **MRI of the breast if other imaging negative**
- **Immunhistology (ER, PgR, HER2, Ck7)
to detect benign and HER2-negative cases**

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

Imaging

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Pathology

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Paget's Disease of the Breast Therapy

	Oxford		
	LoE	GR	AGO
■ Paget's disease with underlying disease (invasive breast cancer, DCIS)			
■ Therapy according to standard of the underlying disease	5	D	++
■ Surgery must achieve R0	1c	B	++
■ Isolated Paget's disease of the NAC:			
■ Surgery must achieve R0	1c	B	++
■ Surgical resection only, no adjuvant radiotherapy	4	D	++
■ Sentinel-node excision (SNE)	2b	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.
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Surgery, 192(4), 481–483. <http://doi.org/10.1016/j.amjsurg.2006.06.023>


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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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.



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Borderline and Malignant Phyllodes Tumor

- **Differential diagnosis may be problematic on core biopsy**
- **In-Breast recurrence relatively frequently seen (10 - 30%)**
- **Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.**

Feature	Frequency
Grading	Benign PT (75%) Borderline PT (16%) Malignant PT (9%)
Median age on diagnosis	Benign PT: 39 J. Borderline PT: 45 J. Malignant PT: 47 J.
Local recurrence	Benign PT: 10 - 17% Borderline PT: 14 - 25% Malignant 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.
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Borderline and Malignant Phyllodes Tumor Diagnosis

	Oxford		
	LoE	GR	AGO
■ Mammography, sonography	3	C	++
■ Diagnosis on core biopsy, grading on resection specimen	3	C	++
■ Breast MRI	3	C	+/-
■ Staging only malignant PT (CT thorax, skeletal system)	5	D	++


Imaging

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



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Borderline and Malignant Phyllodes Tumor Surgery

- **R0-Excision with at least 5mm margin irrespective of grading**
- **SNE / Axillary dissection when cN0**
- **Treatment of local recurrence**
 - R0 resection or simple mastectomy

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

Statement: Complete (wide) local excision or MRM

Surgical margins

1. 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>
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3. 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>
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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>

6. Co M., Chen C., Tsang JY., et al. (2018). Mammary phyllodes tumour: a 15 year multicentre clinical review. *J Clin Pathol.* , 71(6):493-497. doi: 10.1136/jclinpath-2017-204827.

7. Adam MJ, Bendifallah S, Kalhorpour N et al. (2018). Time to revise classification of phyllodes tumor of the breast? Results of a French multicentric study. *Eur J Surg Oncol*, 44(11), 1743-1749. doi: 10.1016/j.esjo.2018.08.007

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>

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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 cNO

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

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 and Malignant Phyllodes Tumor Adjuvant Therapy

	Oxford		
	LoE	GR	AGO
▪ Adjuvant radiotherapy	4	C	--
▪ If T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy)	2b	C	+/-
▪ Systemic adjuvant therapy (chemo, endocrine)	4	C	--
▪ Treatment of local recurrence			
▪ R0 resection or simple mastectomy	4	C	+
▪ Radiotherapy, chemotherapy after R1 resection	4	C	+/-
▪ Distant metastasis (very rare)			
▪ Treatment like soft tissue sarcomas	4	C	++

Sarcomas of the Breast

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



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Primary Angiosarcoma of the Breast

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

Reviews

1. Depla, A. L., Scharloo-Karels, C. H., de Jong, M. A. A., et al. (2014). Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review. *European Journal of Cancer*, 50(10), 1779–1788. <http://doi.org/10.1016/j.ejca.2014.03.002>
2. Kaklamanos, I. G., Birbas, K., Syrigos, K. N., et al. (2011). Breast angiosarcoma that is not related to radiation exposure: a comprehensive review of the literature. *Surgery Today*, 41(2), 163–168. <http://doi.org/10.1007/s00595-010-4341-x>
3. Lim, S. Z., Ong, K. W., Tan, B. K. T., et al. (2016). Sarcoma of the breast: an update on a rare entity. *Journal of Clinical Pathology*, 69(5), 373–381. <http://doi.org/10.1136/jclinpath-2015-203545>
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)

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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>
9. Kunkiel, M., Maczkiewicz, M., Jagiello-Grusfeld, A., et al. (2018). Primary angiosarcomas of the breast-series of 11 consecutive cases-a single centre experience. [Curr Oncol.](#), 25(1):e50-e53. doi: 10.3747/co.25.3816. Epub 2018 Feb 28.

Primary Angiosarcoma of the Breast*			
Diagnosis			
	Oxford		
	LoE	GR	AGO
■ Mammography, sonography to determine extent of disease	3a	C	--
■ Preoperative MRI to determine the extent of disease	3a	C	++
■ Diagnosis by core biopsy	3a	C	++
■ Diagnosis by FNB	3a	C	--
■ Staging (CT thorax & abd.; angiosarcoma: MRI brain)	4	D	++
■ Prognostic factors: size, grade, margins	3a	C	++

* Therapy in specialized centers recommended



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Imaging

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Primary Angiosarcoma of the Breast*

Therapy

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

- **Surgery with wide clear margins, mostly as mastectomy**
 - Breast-conserving therapy
- **SNB or axillary dissection if cNO**
- **Adjuvant chemotherapy (anthracycline/taxane-based)**
- **Adjuvant radiotherapy if high risk (size > 5 cm, R1)**

* Therapy in specialized centres recommended


Surgery

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Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

- **Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years**
- **Clinical presentation**
 - > 5 years after BCT or mastectomy with irradiation
 - usually intracutaneously or subcutaneously in the irradiation area with livid discoloration
 - multiple foci
 - most often in advanced stages (II - III)
 - metastasis mostly pulmonary
 - lymph node metastasis possible
- **Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma**
- **Survival after 5 years: 15%**

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Secondary Angiosarcoma of the Breast Therapy

	Oxford		
	LoE	GR	AGO
▪ Secondary mastectomy	3a	C	++
▪ Adjuvant chemotherapy (anthracycline/taxane-based)	2b	B	+/-
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	2b	B	+/-
▪ Regional hyperthermia (to improve local control) plus chemotherapy and/or radiotherapy	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>
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Adjuvant Radiotherapy

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Adjuvant Hyperthermia

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



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Treatment of local recurrences


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Treatment of metastatic and non-resectable tumors

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

- **Rare, 3% of all Non-Hodgkin-lymphomas, 0.04–0.5% of all malignant breast diseases**
- **estimated annual incidence 0.6–1.2 per 100,000 women with implants (median age 54 years)**
- **Occurrence predominantly of textured implants**
- **5-year OAS 89%**
- **Interval for lymphoma diagnosis: 8 years (median)**
- **Clinical presentation**
 - Effusion only (60%)
 - Mass only (17%)
 - Effusion and mass (20%)
- **Histological: CD30 + / ALK-T cell lymphoma**
- **Reporting obligation as SAE according to § 3 MPSV to the 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>
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in Response to the call for Data on the Safety of PIP Silicone Breast Implants and the Possible Association between Breast Implants and ALCL by the Scientific Committee on Health, Environmental and Emerging
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Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Diagnosis –

	Oxford		
	LoE	GR	AGO
▪ Sonography (for newly occurring seromas 1 year after implant placement, tumor mass)	5	D	++
▪ Breast MRI on confirmation of the diagnosis	5	D	++
▪ Nodal status, PET-CT, bone marrow biopsy	5	D	++
▪ Cytology of effusion (for newly occurring seromas 1 year after implant placement) with requisition "r/o BIA-ALCL"	5	D	++
▪ Lymphoma diagnosis on resection specimen and histological staging (acc. to Clemens 2016)	5	D	++
▪ Documentation of the implant (manufacturer, size, filling, surface, batch number)	5	D	++

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Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Treatment –			
	Oxford		
	LoE	GR	AGO
■ Implant removal and complete capsulectomy including tumor removal	3a	C	++
■ Removal of suspicious lymph nodes, no routine sentinel-node biopsy, no axillary dissection	4	D	++
■ Polychemotherapy (e.g., CHOP) when extracapsular tumor infiltration	4	D	+
■ Radiation for unresectable tumors or R1	5	D	+/-
■ Reconstruction after 1 year disease-free interval	5	D	+

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Guidelines Breast
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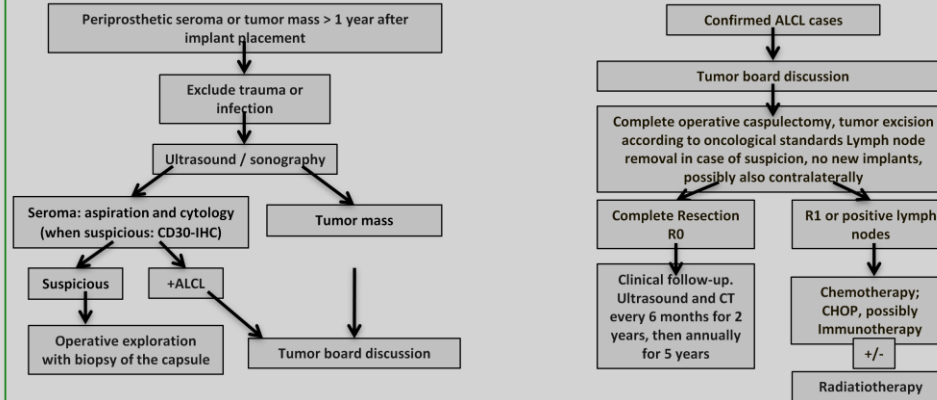
Management Implant reconstruction


- **Risk disclosure for BIA-ALCL upfront implant reconstruction**
- **Clinical examinations twice a year for the first 5 years**
- **Ultrasound examinations for the first 2 years**
- **In case of late seroma and surgically resected implant capsular histological exclusion of ALCL**

Blohmer, J.-U., Sinn, H.P., (2017). 243rd Statement by the German Society of Gynecology and Obstetrics (DGGG). Geburtshilfe Frauenheilkd, 77(06):617, doi:10.1055/s-0043-106280.

1. Blohmer, J.-U., Sinn, H.P., (2017). Zum möglichen Zusammenhang von Brustsilikonimplantaten und dem Auftreten von Lymphomen. 243rd Statement by the German Society of Gynecology and Obstetrics (DGGG) in Response to the call for Data on the Safety of PIP Silicone Breast Implants and the Possible Association between Breast Implants and ALCL by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) of the European Commission. Geburtshilfe Frauenheilkd, 77(06):617, doi:10.1055/s-0043-106280.
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Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Summary of the Management (acc. to Noah 2017) -



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	Oxford		
	LoE	GR	AGO
	5	D	++
	4	C	++
	4	C	++
	4	C	+
<p>Adjuvant chemotherapy (tumors more chemoresistant)</p> <p>Adjuvant endocrine standard therapy</p> <p>Adjuvant standard radiotherapy</p>	4	C	+
	4	C	+/-
	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.

Therapy review:

Ong, C.T., Campbell, B.M., Thomas, S.M., et al. (2018). Metaplastic breast cancer treatment and outcomes in 2500 patients: a retrospective analysis of a national oncology database. Ann Surg Oncol. 24:2249-2260.

Doi.org/10.1245/s10434-018-6533-3.

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.



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Metaplastic Breast Cancer

Incidence:: 0,2-5 % of all breast cancers (1)
Histology: epithelial and mesenchymal components with two to three different components within a tumor; high proliferation rate
subtypes: according to 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	

Molecular biology: > 90 % ER-, PR-, HER2-
~ 70 % overexpression of HER1, CK 5/6-expression (stem-cell-like and BRCA-like)(2)
molecular profile mostly basal-like (3)
frequent mutations in PIK3CA and PTEN (mTOR-overactivity)

Clinical features:

- Large tumors at diagnosis (> 5 cm)
- Frequent hematogenous metastases; nodal involvement in ~ 20 % (no nodal involvement in spindle cell carcinoma carcinosarcoma)
- Poor clinical course compared to TNBC
- Impaired prognosis in asian women (MRM more frequently, poor grading, more often squamous cell carcinoma, spindle cell carcinoma less frequent)

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
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7. [Budzik, M.P.](#), [Patera, J.](#), [Sobol, M.](#), et al. (2018). Clinicopathological characteristics of metaplastic breast cancer - analysis of the basic immunohistochemical profile and comparison with other invasive breast cancer types. Breast 43:135-141. doi:

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