



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

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

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



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

Screened data bases:

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

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

Screened guidelines

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



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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

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- Malignant and Borderline Phyllodes Tumor
- Angiosarcoma
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- 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.

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

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

Prognosis in young women

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

3. Hironaka-Mitsubishi A, Tsuda H, Yoshida M et al. Invasive breast cancers in adolescent and young adult women show more aggressive immunohistochemical and clinical features than those in women aged 40-44 years. *Breast Cancer* 2018.
4. Johansson ALV, Trewin CB, Hjerkind KV et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. *Int J Cancer* 2018.
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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8. Rapiti E, et al. Survival of young and older breast cancer patients in Geneva from 1990 to 2001. *Eur J Cancer* 2005;41(10):1446-52.
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10. Anders CK, Hsu DS, Broadwater G, et al . Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol* 2008;26:3324-30.
11. Freedman RA et al. Management of breast cancer in very young women. *Breast*. 2013;22 Suppl 2:S176-9. *J Natl Compr Canc Netw*. 2013;11(9):1060-9.
12. Tichy JR et al. Breast cancer in adolescents and young adults: a review with a focus on biology. *J Natl Compr Canc Netw*. 2013;11(9):1060-9.

Chemotherapy in young women

1. Passildas J, Collard O, Savoye AM et al. Impact of Chemotherapy-induced Menopause in Women of Childbearing Age With Non-metastatic Breast Cancer - Preliminary Results From the MENOCOR Study. *Clin Breast Cancer* 2018.

2. Oktay K, Harvey BE, Partridge AH et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2018;36(19):1994-2001.
3. Aebi S. Special issues related to the adjuvant therapy in very young women. *Breast* 2005, 14: 594-599 (Review)
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365: 1687–1717
5. M. De Laurentiis et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2008;26 (1),44–53.
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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.
8. Partridge AH EP. Gelber S, Peppercorn J et al. Fertility and menopausal outcomes in young breast cancer survivors. *Clin Breast Cancer* 2008; (:65-69
9. Hulvat MC, Jeruss JS. Maintaining fertility in young women with breast cancer. *Curr Treat Options Oncol*. 2009 Dec;10(5-6):308-17.
10. Ruddy KJ, Gelber SI, Tamimi RM, et al. Prospective study of fertility concerns and preservation strategies in young women with breast

cancer. J Clin Oncol. 2014 Apr 10;32(11):1151-6.

11. Lambertini M, Ceppi M, Poggio F, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015 Dec;26(12):2408-19.

Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery			
	Oxford		
	LoE	GR	AGG
• Breast imaging and 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)	2b	B	+
• SLNE during 1 st trimester	5	D	+/-
• Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
• Blue dye (not tested in pregnant animals or humans)	4	C	++

* Participation in register study recommended

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

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

Outcome information (e.g. GBG registry)

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

Statement: Breast imaging & biopsy like in non-pregnant

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

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

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

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

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

Statement: Whole Body MRI

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

Statement: Surgery like in non-pregnant patients

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

Statement: „Sentinel node biopsy“ during pregnancy

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

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

Reviews

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

Breast Cancer During Pregnancy - (Neo-)adjuvant Therapy -			
	Oxford LoE GR AGO		
• Radiation therapy during pregnancy	4	C	-
• (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
+ Anthracyclines: AC, EC	2b	B	++
+ Taxanes	2b	B	+
+ Platinum salts (carboplatin, cisplatin)	4	C	+/
+ MTH (e.g. CMF)	4	D	-
• Endocrine treatment	4	D	-
• HER2-targeted treatment	1a	C	-
• Bisphosphonates, denosumab	4	D	-

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

General principles

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

Statement: Radiotherapy during pregnancy

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

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

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

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)
4. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. *Obstetrics and*

Gynecology 2005, 105: 642-643 (Case Report)

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6. Aebi S, Loibl S. Breast cancer during pregnancy: medical therapy and prognosis. Recent Results Cancer Res. 2008;178:45-55.
7. Clemons M, Goss P: Estrogen and the risk of breast cancer. New Engl J Med 2001, 344: 276-285
8. Azim HA Jr et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). Breast Cancer Res Treat. 2012;133(1):387-91.
9. Zagouri F et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013 Jan;137(2):349-57.
10. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? Immunotherapy 2013; 5(7):733-41.
11. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Lambertini M, et al. Cancer. 2019

Statement 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.

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

* Participation in register study recommended

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;13:87-896.
3. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4). Annals of Oncology 2020;31:674-96.
4. Loibl S, Schmidt A, Gentilini O et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

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

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

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

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

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

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



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Breast Cancer and Pregnancy – Family Planning –

- After breast cancer diagnosis, reproductive techniques can be used to induce pregnancy
- Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients
- Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment
- Breast cancer patients should not be advised against getting pregnant independent of their tumor's hormone receptor status

Oxford		
LoE	GR	AGO
S	D	++
S	D	++
S	D	++
S	D	++

Pregnancy Associated Breast Cancer*: Outcome	
<ul style="list-style-type: none"> • BC during pregnancy / lactation <ul style="list-style-type: none"> • Adequate treatment is essential • Pregnancy and lactation after BC <ul style="list-style-type: none"> • Outcome not compromised 	Oxford LoiI
	3a
	3a
* Participation in register study recommended	

General principles

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

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

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

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.
5. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. *Cancer biology & medicine* 2018;15(1):6-13.
6. de Haan J, Verheecke M, Van Calsteren K et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol* 2018;19(3):337-46.
7. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy associated breast cancer. *Cancer* 1991, 67: 869-872
8. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. *Cancer*. 2006 Jan 15;106(2):237-46
9. Rodriguez et al. Evidence of poorer survival in pregnancy-associated breast cancer. *Obstet Gynecol*. 2008 Jul;112(1):71-8
10. Stensheim H, Møller B, van Dijk T et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009;27:45-51. doi:10.1200/JCO.2008.17.4110.
11. Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? *Breast J*. 2010 Jul-Aug;16(4):404-11.
12. 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.
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.
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

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 (which each good predictor over a 10 year period)
 - 11 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), CG
 - Geriatric Prognostic Index (GPI), 9 parameters in oncological patients (psychological distress or acute illness, >5 prescribed drugs, neuropsychological problems)

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1. Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13(4):e148-60.
2. Overcash J. Comprehensive Geriatric Assessment: Interprofessional Team Recommendations for Older Adult Women With Breast Cancer. *Clinical journal of oncology nursing* 2018;22(3):304-15.
3. Charlson et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987 40:373-383.
4. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006 295:801-08.
5. Wildes TM et al. Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer. *J Geriatr Oncol.* 2013;4(3):227-34.
6. Aaldriks AA. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy et al. *Breast* 2013;22(5):753-60.
7. Bellera CA et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol.* 2012;23(8):2166-72
8. Aaldriks AA, Maartense E, Nortier HJ, et al. Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. *Acta Oncol.* 2016 Jan;55(1):15-23.

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 responsive)	1a	A	++
• Chemotherapy (standard regimen)			
• < 70 years	1a	B	+
• < 70 years (especially fit, fit/fr)	1a	C	++
• Radiotherapy	1a	A	+
• Omit radiotherapy after BCS if low-risk and endocrine treatment	2b	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.
4. Schuil H, Derks M, Liefers GJ et al. Treatment strategies and survival outcomes in older women with breast cancer: A comparative study between the FOCUS cohort and Nottingham cohort. Journal of geriatric oncology 2018;9(6):635-41.
5. Ward SE, Richards PD, Morgan JL, Holmes GR, Broggio JW, Collins K, et al. Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival. Br J Surg 2018;105(11):1454-63.
6. Enger SM: Breast cancer treatment of older women in integrated health care settings. J Clin Oncol. 2006 Sep 20;24(27):4377-83

7. Mustacchi G, Breast cancer in elderly women: a different reality? Results from the NORA study. *Ann Oncol.* 2007 Jun;18(6):991-6.
8. Chagpar AB: Determinants of early distant metastatic disease in elderly patients with breast cancer. *Am J Surg.* 2006 Sep;192(3):317-21
9. Kemeny MM: Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol.* 2003 Jun 15;21(12):2268-75
10. Giordano SH: Breast cancer treatment guidelines in older women. *J Clin Oncol.* 2005 Feb 1;23(4):783-91.
11. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. *J Am Coll Surg.* 2008 Jan;206(1):66-75
12. Wildiers H: Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol.* 2007 Dec;8(12):1101-15
13. Luque M et al. Breast cancer management in the elderly. *Clin Transl Oncol.* 2013 epub

Statement: Surgery similar to „younger“ age

1. Swaminathan V. et al. Choices in Surgery for older women with breast cancer *Breast Care* 2012;7:445-451
2. Fentiman IS: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. *Eur J Cancer.* 2003 Feb;39(3):309-16
3. Fentiman IS: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen. *Eur J Cancer.* 2003 Feb;39(3):300-8
4. Hind D: Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. *Br J Cancer* 2007 Apr 10;96(7):1025-9.
5. Rudenstam CM Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol.* 2006 Jan 20;24(3):337-44.
6. Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. *Ann Surg Oncol.* 2011;18(1):125-33
7. Johnston SJ et al. A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up. *Ann Oncol* 2012;9:2296-300.
8. Chakrabarti J et al. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up. *Crit Rev Oncol Hematol.* 2011;78(3):260-4.

Statement: Endocrine treatment (endocrine resp.)

1. Rugo HS, Turner NC, Finn RS et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. *Eur J Cancer* 2018;101:123-33.
2. Crivellari D, Sun Z, Coates AS, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 Trial. *J Clin Oncol* 2008; 26:1972-79
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
4. Lash TL: Physicians' assessments of adjuvant tamoxifen's effectiveness in older patients with primary breast cancer. *J Am Geriatr Soc*. 2005 Nov;53(11):1889-96
5. Silliman RA: Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer. *J Clin Oncol*. 2002 Jun 1;20(11):2680-8
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-717
7. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381, 805–816

Statement: Chemotherapy in pts. < 70 years

1. Loibl S, von Minckwitz G, Harbeck N, et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. *Breast Cancer Res*. 2008 Sep16;10(5):R77
2. Fisher B: Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials. *J Natl Cancer Inst*. 2004 Dec 15;96(24):1823-31.
3. Fargeot P: Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. *J Clin Oncol*. 2004 Dec 1;22(23):4622-30
4. Du XL: Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. *J Gerontol A Biol Sci Med Sci*. 2005 Sep;60(9):1137-44
5. De Maio E et al., Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: a single-center experience. *BMC Cancer* 2005 24: 30
Muss HB et al., Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 2005, 293:1073-81.

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.
8. Brunello A et al., Adjuvant chemotherapy for elderly patients (> or =70 years) with early high-risk breast cancer: a retrospective analysis of 260 patients. *Ann Oncol.* 2005 16:1276-82.

Statement: Chemotherapy in pts. > 70 years

1. Qin A, Thompson CL, Silverman P. Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. *J Cancer Surviv.* 2015 Jun;9(2):252-9.
2. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol.* 2007 Sep 1;25(25):3808-15.
3. von Minckwitz G, Reimer T, Potenberg J, et al. The phase III ICE study: Adjuvant Ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. *SABCS 2014 (S3-04).*
4. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients *Breast Care* 2012;7:439-444
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.
10. Tamirisa N, Lin H, Shen Y, et al. Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor-Positive, Node-Positive Breast Cancer. *JAMA Oncol* 2020;6:1548-54.

Statement: Radiotherapy

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

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
7. Kunkler IH, Williams LJ, Jack WJ, et al: On behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.

Statement: Trastuzumab

1. Freedman RA, Vaz-Luis I, Barry WT, et al. Patterns of chemotherapy, toxicity, and short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. Breast Cancer Res Treat. 2014 Jun;145(2):491-501.
2. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol. 2013 Nov 20;31(33):4222-8
3. 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
5. Smith I, HERA study team: 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007 Jan 6;369(9555):29-36
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

Treatment for Frail Patients (Life Expectancy <5 yrs, Substantial Comorbidities)			
	Oxford		
	LoE	GR	AGO
	2b	C	++
• Reduced standard treatment			
• Options extrapolated from trials in elderly:			
• No breast surgery (consider endocrine options)	2b	C	+
• No axillary clearing (≥ 60 y, pN0, HR-pos)	2b	B	+
• No radiotherapy (Tumor size <3 cm, pN0, HR-pos)	2b	B	++
• Hypofractionated radiotherapy	2b	B	+
• No chemotherapy if >70y and negative risk-benefit analysis	2b	C	+

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

Statement: Reduced standard treatment

Statement: No breast surgery (consider endocrine options)

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

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

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

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

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

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

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

Statement: Hypofractionated radiotherapy

1. Vaidya JS, Joseph DJ, Tobias JS et al: Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010 Jul 10;376(9735):91-102.
2. Vaidya JS, Wenz F, Bulsara M, et al: TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2014 Feb 15;383(9917):603-13.
3. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013 Dec;14(13):1269-77.
4. Ortholan C, et al. Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. Int J Radiat Oncol Biol Phys. 2005 Jan 1;61(1):154-62.
5. Kirova YM, Campana F, Savignoni A, et al: for the Institut Curie Breast Cancer Study Group Breast-Conserving Treatment in the Elderly: Long-Term Results of Adjuvant Hypofractionated and Normofractionated Radiotherapy. Int J Radiat Oncol Biol Phys. 2009 Jan 2

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

1. Du XL, Jones DV, Zhang D. Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. J Gerontol A Biol Sci Med Sci. 2005 Sep;60(9):1137-44.
2. Kehl KL, Niu J, Chavez-MacGregor M et al. Hospitalization by cytotoxic chemotherapy regimen among older women with stage IV breast cancer. Cancer 2018;124(24):4685-91.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14-20;365(9472):1687-717
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. Lancet. 371;2008:1687-717

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

* Participative in-regional study recommended

International registry

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

General

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

Cancer 2018;18(5):e997-e1002

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

Statement: Diagnostic work up as in women

Statement: Mammography

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

Statement: Ultrasound

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

Statement: Standard-surgery: Mastectomy – men

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

4. Kuo SH et al. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence, *Int J Radiat Oncol Biol Phys*. 2008 Dec 1;72(5):1456-64. Epub 2008 Aug 7
5. Fogh S et al. Therapy for Male Breast Cancer: Functional Advantages With Comparable Outcomes Using Breast Conservation. *Clin Breast Cancer*. 2013;13(5):344-9.
6. Fields EC et al. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. *J Radiat Oncol Biol Phys* 2013;87(4):747-52
7. Cloyd et al. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983-2009. *Ann Surg Oncol*. 2013;20:1545–50
8. Zaenger D, Rabatic BM, Dasher B, Mourad WF. Is Breast Conserving Therapy a Safe Modality for Early-Stage Male Breast Cancer? *Clin Breast Cancer*. 2015 Nov 17. pii: S1526-8209(15)00278-5.

Statement: Surgery: BEO – men

1. Cloyd JM, Hernandez-Boussard T, Wapnir IL. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983–2009. *Ann Surg Oncol*. 2013;20(5):1545–50.
2. Bratman SV, Kapp DS, Horst KC. Evolving trends in the initial locoregional management of male breast cancer. *Breast*. 2012;21(3):296–302. <https://doi.org/10.1016/j.breast.2012.01.008>.
3. Cutuli B, Le-Nir CC, Serin D, Kirova Y, Gaci Z, Lemanski C, De Lafontan B, Zoubir M, Maingon P, Mignotte H, de Lara CT, Edeline J, Penault-Llorca F, Romestaing P, Delva C, Comet B, Belkacemi Y. Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. *Crit Rev Oncol Hematol*. 2010;73(3):246–54. <https://doi.org/10.1016/j.critrevonc.2009.04.002>.
4. Cutuli B, Lacroze M, Dilhuydy JM, Velten M, De Lafontan B, Marchal C, Resbeut M, Graic Y, Campana F, Moncho-Bernier V, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. *Eur J Cancer*. 1995;31A(12):1960–4.
5. Golshan M, Rusby J, Dominguez F, Smith BL. Breast conservation for male breast carcinoma. *Breast*. 2007;16(6):653–6.
6. Selcukbiricik F, Tural D, Aydog˘an F, Bes˘e N, Bu˘yu˘ku˘nal E, Serdengeç˘ti S. Male breast cancer: 37-year data study at a single experience center in Turkey. *J Breast Cancer*. 2013;16(1):60–5. <https://doi.org/10.4048/jbc.2013.16.1.60>.
7. Serarslan A, Gursel B, Okumus NO, Meydan D, Sullu Y, Gonullu G. Male breast cancer: 20 years experience of a tertiary hospital from the Middle Black Sea Region of Turkey. *Asian Pac J Cancer Prev*. 2015;16(15):6673–9.
8. Yildirim E, Berberog˘lu U. Male breast cancer: a 22-year experience. *Eur J Surg Oncol*. 1998;24(6):548–52.

Statement: Sentinel-node excision (SNE)

1. Port ER et al. Sentinel lymph node biopsy in patients with male breast carcinoma. Cancer 2001 91:319-323
2. Flynn LW et al. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg. 2008 Apr;206(4):616-21
3. Boughey JC: Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. J Am Coll Surg. 2006 Oct;203(4):475-80. Epub 2006 Aug 23
4. De Cicco C: Sentinel node biopsy in male breast cancer. Nucl Med Commun 2004; 25: 139-143
5. Albo D et al. Evaluation of lymph node status in male breast cancer patients: a role for sentinel lymph node biopsy. Breast Cancer Res Treat 2003 77:9-14

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

1. Ribeiro GG: A review of the management of the male breast carcinoma based on an analysis of 420 treated cases. Breast 1996; 5: 141-146
2. Schuchardt U et al. Adjuvant radiotherapy for breast carcinoma in men: a 20-year clinical experience. Am J Clin Oncol 1996 19:330
3. Eggemann H et al. Male breast cancer: 20-year survival data for post-mastectomy radiotherapy. Breast Care (Basel). 2013;8(4):270-5.

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

1. Ottini L et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Res Treat. 2008 Sep 26
2. Friedman LS, Gayther SA, Kurosaki T, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet 1997; 60: 313-319
3. Basham VM: BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. Breast Cancer Res 2002; 4: R2
4. Thorlacius S, Sigurdson S, Bjanadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet 1997; 60: 1079-1084

Statement: Screening for 2nd malignancies according guidelines

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

Statement: Systemic therapy

1. Doyen J et al., Ann Oncol. 2009 Oct 27. [Epub ahead of print], Aromatase inhibition in male breast cancer patients: biological and clinical implications.
2. Eggemann H et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat. 2013;137(2):465-70.
3. Patten DK et al. New Approaches in the Management of Male Breast. Cancer Clinical Breast Cancer 2013;13(5) 309–314
4. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer Breast Cancer Res Treat. 2013;141(1):119-23
5. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. Br J Cancer. 2013;108(11):2259-63

Review articles

1. Donegan WL: Carcinoma of the breast in males. Cancer 1998; 83: 498-509
2. Borgen PI et al. Current management of male breast cancer. A review of 104 cases. Ann Surg 1992 215:451
3. Erlichman C et al. Male breast cancer: a 13- year review of 89 patients. J Clin Oncol 1984 2: 903
4. Cutuli B, Lacroze M, Dilhuydy JM, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer 1995; 31A: 1960-1964
5. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet. 2006 Feb 18;367(9510):595-604. Review. Erratum in: Lancet. 2006 Jun 3;367(9525):1818
6. Agrawal A, Ayantunde AA, Rampaul R et al. Male breast cancer: a review of clinical management. Breast Cancer Res Treat. 2006 Oct 11;
7. Korde LA et al: Multidisciplinary meeting on male breast cancer; summary and research recommendations J Clin Oncol 28: 2114-2122, 2010
8. Patten DK et al. New Approaches in the Management of Male Breast. Cancer Clinical Breast Cancer 2013;13(5) 309–314
9. Sousa B et al. An update on male breast cancer and future directions for research and treatment. Eur J Pharmacol 2013;717(1-3)
10. Ruddy KJ et al. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol 2013; 24(6):1434-43.

Male breast cancer-prognostic factors			
	Oxford		
	LoE	GR	AGO
• Nodal status	2b	A	++
• Age	2b	B	+
• Tumor size	2b	A	++
• ER/PR Expression	2b	A	++
• Ki-67 Expression	2b	C	+/-
• Grade	2b	C	+/-
• Genomic signatures (e.g. OncotypeDx)	2b	B	+

Registries

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

Male Breast Cancer: Systemic Therapy			
	Oxford		
	LoE	GR	AGO
• Adjuvant chemotherapy as in women	2a	B	++
• HER2-targeted therapy (if HER2-positive)	5	D	++
• Endocrine therapy	4	D	++
• Tamoxifen	2b	B	++
• Aromatase inhibitors (adjuvant)	2b	B	+
• Aromatase inhibitors (metastatic BC)	4	C	++
• Exemestane and AI (metastatic BC)	4	C	++
• Fulvestrant (metastatic BC)	4	C	++
• CDK4/6 (in combination) *	2b	B	+
• Palliative chemotherapy as in women	4	C	++

* Study participation recommended

Statement: Adjuvant Chemotherapy

1. Patel HZ et al. Role of adjuvant chemotherapy in male breast cancer. Cancer 1989 64: 1583
2. Bagley CS et al. Adjuvant Chemotherapy in males with cancer of the breast. Am J Clin Oncol 1987; 2:903
3. Giordano SH, Perkins GH, Broglio K, et al. Adjuvant systemic therapy for male breast cancer. Cancer 2005; 104: 235-264
4. Walshe JM: A prospective study of adjuvant CMF in males with node positive breast cancer: 20-year follow-up. Breast Cancer Res Treat. 2007 Jun;103(2):177-83

Statement Trastuzumab

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

Statement CDK4/6i

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

Statement endocrine therapy

1. Ribeiro G et al. Adjuvant tamoxifen for male breast cancer (MBC). Br J Cancer 1992 65: 252
2. Anelli TF et al. Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. Cancer 1994 74: 74
3. Agrawal: Fulvestrant in advanced male breast cancer. Breast Cancer Res Treat. 2007 Jan;101(1):123. Epub 2006 Jun 29.
4. Zabolotny BP: Successful use of letrozole in male breast cancer: a case report and review of hormonal therapy for male breast cancer. J Surg Oncol. 2005 Apr 1; 90(1):26-30
5. Goss PE: Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955–1996. Cancer 1999; 85: 629-639
6. Giordano SH: Efficacy of anastrozole in male breast cancer. Am J Clin Oncol 2002 25: 235-237
7. Agrawal A: Fulvestrant in advanced male breast cancer. Breast Cancer Res Treat. 2007 Jan;101(1):123. Epub 2006 Jun 29. No abstract available
8. Giordano SH: Leuprolide acetate plus aromatase inhibition for male breast cancer. J Clin Oncol. 2006 Jul 20;24(21):e42-3. No abstract available.
9. Nahleh ZA: Hormonal therapy for male breast cancer: A different approach for a different disease. Cancer Treatment Reviews 2006 32:101-105
10. Arriola E: Aromatase inhibitors and male breast cancer. Clin Transl Oncol. 2007 Mar;9(3):192-4
11. Eggemann H, Ignatov A, Smith BJ, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat. 2013 Jan;137(2):465-70.
12. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer Breast Cancer Res Treat. 2013;141(1):119-23
13. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. Br J Cancer. 2013;108(11):2259-63
14. Eggemann H, Brucker C, Schrauder M, et al. Survival benefit of tamoxifen in male breast cancer: prospective cohort analysis. British journal of cancer 2020;123:33-7.

Statement palliative chemotherapy

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

Benefit from Trimodal Treatment in Inflammatory Breast Cancer			
 T-1000, p. 12 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000 Abstract 1000000000	Median survival probability		
	Trimodal therapy	27 months	post-RT
	Surgery alone	24 months	
	Overall survival probability (OS)		
		10 years OS	5 years OS
	Trimodal therapy	55.4%	37.3%
	Surgery & chemotherapy	41.3%	28.5%
	Surgery & radiotherapy	40.7%	23.5%
	Surgery alone		18.5%
	Multivariate analysis of OS		
		Hazard Ratio	95% CI
	Surgery & Chemotherapy & RT (trimodal therapy)	1.00	-
	Surgery & chemotherapy	1.34	1.46 to 1.84
	Surgery & radiotherapy	1.67	2.06 to 2.24
	Surgery alone	2.28	3.80 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.

Primary inflammatory breast cancer		
	5yr-OS	
pCR	17%	p=0.0002
Non-pCR	14%	
TN-IBC	17%	p=0.0002
other biologic subtypes (HR+/HER2-, HR+/HER2+, HR-/HER2+)	40%	

• N=8,550
 • On multivariable analysis, TNBC, positive margins, and not receiving either chemotherapy, hormonal therapy or radiotherapy were independently associated with poor 5-year survival ($p < 0.0001$).

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

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	+
• Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)	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.
5. Romanoff A, Zabor EC, Petruolo O et al. Does nonmetastatic inflammatory breast cancer have a worse prognosis than other nonmetastatic T4 cancers? Cancer 2018;124(22):4314-21.
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.

9. Costa R, Santa-Maria CA, Rossi G et al. Developmental therapeutics for inflammatory breast cancer: Biology and translational directions. *Oncotarget* 2017;8(7):12417-32.
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. 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
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Statement: in HER2 positive disease addition of trastuzumab and pertuzumab

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Statement: Sentinel lymph node

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Statement: Radiotherapy

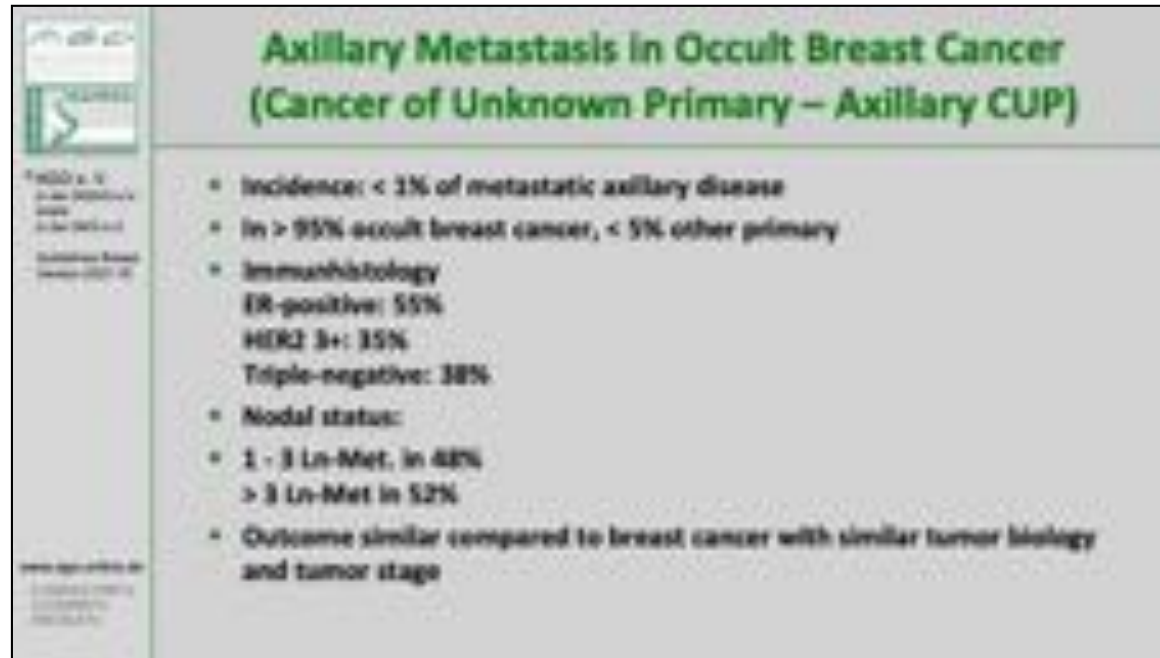
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2. Bristol IJ, Woodward WA, Strom EA, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. Int J Radiat Oncol Biol Phys. 2008;72:474–484

Statement: Postoperative systemic therapy as in non-inflammatory BC

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Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Imaging Diagnostics			
	Oxford		
	LoE	GR	AGO
• Breast imaging incl. 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	C	++
• Staging (CT thorax / abdomen, pelvis, in certain circumstances also thyroid sonography, 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

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>
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Axillary Metastasis in Occult Breast Cancer (ex. CUP)			
Pathology, molecular pathology			
	Oxford		
	1st	GR	AGO
• ER, PR, HER2, GATA3 [in some cases Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, and others]	1	0	++
• Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.	1	0	++
• Gene expression profiling for determination of primary site (e.g. CUPprint, Pathwork, TDT, Theras CTG)	2±	8	+/-
• NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPIcup)	2±	8	+/-
• Prognostic gene expression tests	1	0	—

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1. Ades, F., De Azambuja, E., Daugaard, G., et al. (2013). Comparison of a gene expression profiling strategy to standard clinical work-up for determination of tumour origin in cancer of unknown primary (CUP). *Journal of Chemotherapy (Florence, Italy)*, 25(4), 239–246. <http://doi.org/10.1179/1973947813Y.00000000085>
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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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<http://doi.org/10.1016/j.amjsurg.2005.06.026>
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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Statement: Axillary dissection

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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.
2. Barton, S. R., Smith, I. E., Kirby, et al. (2011). The role of ipsilateral breast radiotherapy in management of occult primary breast cancer presenting as axillary lymphadenopathy. *European Journal of Cancer* (Oxford, England : 1990), 47(14), 2099–2106. <http://doi.org/10.1016/j.ejca.2011.05.010>
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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)
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Paget's Disease of the Breast	
<p>FIGO 8.12 Paget's Disease of the Breast Invasive Breast Cancer (T1-T4, N0-N3, M0-M1)</p>	<ul style="list-style-type: none"> Definition: Paget's disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer. Clinical presentation: skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin
Feature	Frequency
Presentation	Paget's disease with invasive Ca. (87 - 18%) Paget's disease with DCIS (10 - 63%) Isolated Paget's disease (1 - 7%) Isolated Paget's disease with in-situ (rare)
HER2	HER2 positive (83 - 97%) ER positive (10 - 14%) AR positive (71 - 88%)
Prognosis and tumor biology	Better in isolated Paget's disease Worse if in combination with invasive breast cancer or DCIS, compared to isolated Paget's disease

Review

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Clinical Presentation

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200(2), 241–246. <http://doi.org/10.1016/j.amjsurg.2009.07.044>

Pathology and Immunohistochemistry

- 1.Chen, C.-Y., Sun, L.-M., & Anderson, B. O. (2006). Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer*, 107(7), 1448–1458. <http://doi.org/10.1002/cncr.22137>
- 2.Hanna, W., Alowami, S., & Malik, A. (2003). The role of HER-2/neu oncogene and vimentin filaments in the production of the Paget's phenotype. *The Breast Journal*, 9(6), 485–490.
- 3.Kothari, A. S., Beechey-Newman, N., Hamed, H., et al. (2002). Paget disease of the nipple: a multifocal manifestation of higher-risk disease. *Cancer*, 95(1), 1–7. <http://doi.org/10.1002/cncr.10638>
- 4.Lester, T., Wang, J., Bourne, P., et al. (2009). Different panels of markers should be used to predict mammary Paget's disease associated with in situ or invasive ductal carcinoma of the breast. *Annals of Clinical and Laboratory Science*, 39(1), 17–24.
- 5.Liegl, B., Horn, L.-C., & Moinfar, F. (2005). Androgen receptors are frequently expressed in mammary and extramammary Paget's disease. *Modern Pathology*, 18(10), 1283–1288. <http://doi.org/10.1038/modpathol.3800437>
- 6.Sanders, M. A., Dominici, L., Denison, C., et al. (2013). Paget disease of the breast with invasion from nipple skin into the dermis: an unusual type of skin invasion not associated with an adverse outcome. *Archives of Pathology & Laboratory Medicine*, 137(1), 72–76. <http://doi.org/10.5858/arpa.2011-0611-OA>
- 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.

Paget's Disease of the Breast Diagnosis			
	Oxford		
	LoE	GR	AGO
• Histological verification by skin biopsy			++
• Mammography, sonography	4	D	++
• MRI of the breast if other imaging negative	4	C	+
• Immunohistochemistry (ER, PR, HER2, Ck3)	5	D	++
to detect benign and HER2-negative cases			

Imaging

- 1.Morrogh, M., Morris, E. A., Liberman, L. et al. (2008). MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. *Journal of the American College of Surgeons*, 206(2), 316–321. <http://doi.org/10.1016/j.jamcollsurg.2007.07.046>
- 2.Günhan-Bilgen, I., & Oktay, A. (2006). Paget's disease of the breast: clinical, mammographic, sonographic and pathologic findings in 52 cases. *European Journal of Radiology*, 60(2), 256–263. <http://doi.org/10.1016/j.ejrad.2006.06.010>
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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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4. Raivoherivony TI, Feron J, Klijanienko J: MIAC1 he utility of nipple scraping in the diagnosis of Paget disease of the breast, Letter to the Editor; *Diagnostic Cytopathology*. 2019;47:249–250

Paget's Disease of the Breast - Therapy			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> • Paget's disease with underlying disease (invasive breast cancer, DCIS) <ul style="list-style-type: none"> • Therapy according to standard of underlying disease • Surgery must achieve R0 	5	0	++
	11	0	++
<ul style="list-style-type: none"> • Isolated Paget's disease of the NAC: <ul style="list-style-type: none"> • Surgery must achieve R0 • Surgical resection only, no adjuvant radiotherapy • Sentinel-node excision (SNE) 	11	0	++
	4	0	++
	20	0	—

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>
3. Dominici, L. S., Lester, S. C., Liao, G.-S., et al. (2012). Current surgical approach to Paget's disease. *American Journal of Surgery*, 204(1), 18–22. <http://doi.org/10.1016/j.amjsurg.2011.07.01>

Treatment of isolated Paget's disease

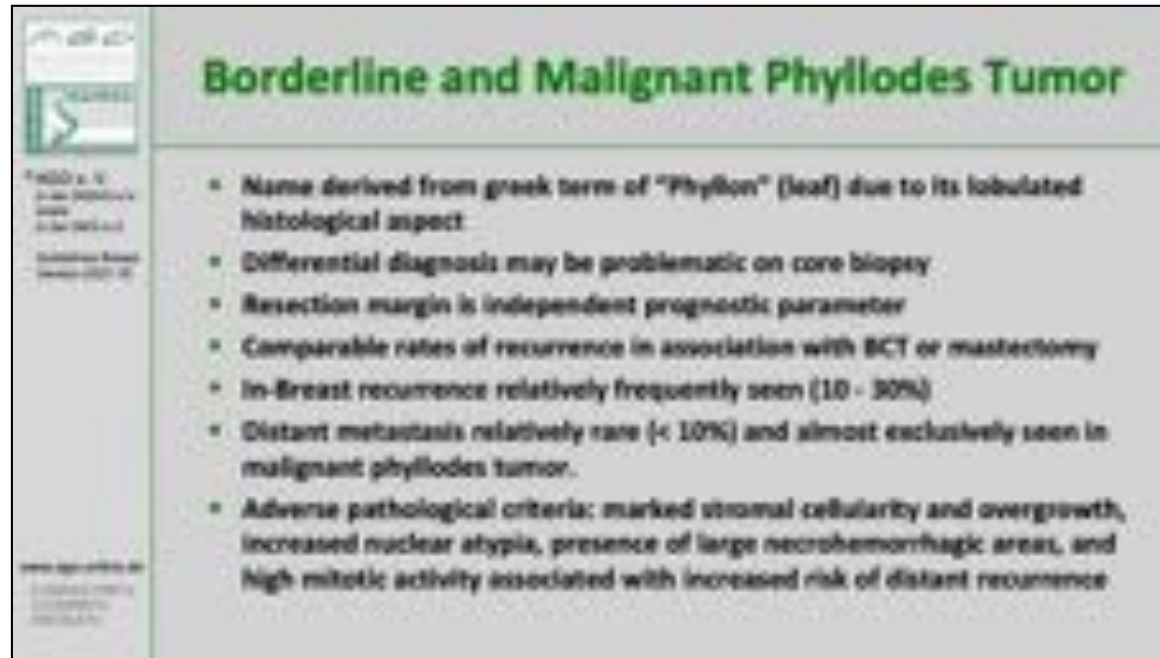
1. Durkan, B., Bresee, C., Bose, S. et al. (2013). Paget's disease of the nipple with parenchymal ductal carcinoma in situ is associated with worse prognosis than Paget's disease alone. *The American Surgeon*, 79(10), 1009–1012.

Statement: Sentinel-node excision (SNE)

1. Bijker, N., Rutgers, E. J., Duchateau, L. EORTC Breast Cancer Cooperative Group et al. (2001). Breast-conserving therapy for Paget

disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer*, 91(3), 472–477.

2. Laronga, C., Hasson, D., Hoover, S., et al. (2006). Paget's disease in the era of sentinel lymph node biopsy. *American Journal of Surgery*, 192(4), 481–483. <http://doi.org/10.1016/j.amjsurg.2006.06.023>



Review

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

Pathology and Outcome

1. Barrio, A., Clark, B., Goldberg, J. et al. (2007). Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. *Annals of Surgical Oncology*.
2. Chaney, A. W., Pollack, A., McNeese, M. D., et al. (2000). Primary treatment of cystosarcoma phyllodes of the breast. *Cancer*, 89(7), 1502–1511.
3. Esposito, N. N., Mohan, D., Brufsky, A., et al. (2006). Phyllodes tumor: a clinicopathologic and immunohistochemical study of 30 cases. *Archives of Pathology & Laboratory Medicine*, 130(10), 1516–1521. [http://doi.org/10.1043/1543-2165\(2006\)130\[1516:PTACAI\]2.0.CO;2](http://doi.org/10.1043/1543-2165(2006)130[1516:PTACAI]2.0.CO;2)
4. Roa, J. C., Tapia, O., Carrasco, P., et al. (2006). Prognostic factors of phyllodes tumor of the breast. *Pathology International*, 56(6), 309–314. <http://doi.org/10.1111/j.1440-1827.2006.01965.x>
5. Tan, P. H., Jayabaskar, T., Chuah, K.-L. et al. (2005). Phyllodes tumors of the breast: the role of pathologic parameters. *American Journal of Clinical Pathology*, 123(4), 529–540. <http://doi.org/10.1309/U6DV-BFM8-1MLJ-C1FN>

6. Tan, P. H., Thike, A. A., Tan, W. J., et al. (2012). Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *Journal of Clinical Pathology*, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>
7. Chao X, Chen K, Zeng J, et al.: Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer*. 2019 Apr 23;19(1):372. doi: 10.1186/s12885-019-5585-5
8. Choi N, Kim K, Shin KH, et al.: The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and Borderline Phyllodes Tumors of the Breast (KROG 16-08). *Clin Breast Cancer*. 2019 Oct;19(5):345-353.e2. doi: 10.1016/j.clbc.2019.04.003.
9. Lu Y, Chen Y, Zhu L, et al.: Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019 May;26(5):1263-1275. doi: 10.1245/s10434-018-07134-5
10. Spanheimer PM, Murray MP, Zabor EC, et al.: Long-Term Outcomes After Surgical Treatment of Malignant/ Borderline Phyllodes Tumors of the Breast. *Ann Surg Oncol* (2019) 26:2136–2143 <https://doi.org/10.1245/s10434-019-07210-4>

Phyllodes tumor	
* Fibroepithelial tumors of the breast: frequency 0.3 – 2% of all primary breast tumors	
parameter	frequency
Grading [1-5] (P histological grading system)	Benign (75%) Borderline (18%) Malignant (6%)
Median age at time of diagnosis	Benign PT: 39 y Borderline PT: 45 y Malignant PT: 47 y
Local recurrence	Benign PT: 4 – 17% Borderline PT: 14 – 25% Malignant PT: 23 – 30%
Metastasis	Benign PT: <1% Borderline PT: 1.8% Malignant PT: 16-23%
10y OS: 80-90% (range: 17-100%) depending on subtype and reference histological criteria	

Review

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

Pathology and Outcome

1. Barrio, A., Clark, B., Goldberg, J. et al. (2007). Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. *Annals of Surgical Oncology*.
2. Tan, P. H., Jayabaskar, T., Chuah, K.-L. 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>
3. Tan, P. H., Thike, A. A., Tan, W. J., et al. (2012). Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *Journal of Clinical Pathology*, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>
4. Chao X, Chen K, Zeng J, et al.: Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer*. 2019 Apr 23;19(1):372. doi: 10.1186/s12885-019-5585-5
5. Choi N, Kim K, Shin KH, et al.: The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and Borderline Phyllodes Tumors of the Breast (KROG 16-08). *Clin Breast Cancer*. 2019 Oct;19(5):345-353.e2. doi:

10.1016/j.clbc.2019.04.003.

6. Lu Y, Chen Y, Zhu L, et al.: Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019 May;26(5):1263-1275. doi: 10.1245/s10434-018-07134-5
7. Spanheimer PM, Murray MP, Zabor EC, et al.: Long-Term Outcomes After Surgical Treatment of Malignant/ Borderline Phyllodes Tumors of the Breast. *Ann Surg Oncol* (2019) 26:2136–2143 <https://doi.org/10.1245/s10434-019-07210-4>

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

Imaging

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

Core biopsy

1. Abdulcadir, D., Nori, J., Meattini, I., et al. (2014). Phyllodes tumours of the breast diagnosed as B3 category on image-guided 14-gauge core biopsy: analysis of 51 cases from a single institution and review of the literature. *European Journal of Surgical Oncology* 40(7), 859–864. <http://doi.org/10.1016/j.ejso.2014.02.222>
2. Jung, H. K., Moon, H. J., Kim, M. J., et al. (2014). Benign core biopsy of probably benign breast lesions 2 cm or larger: correlation with excisional biopsy and long-term follow-up. *Ultrasonography (Seoul, Korea)*, 33(3), 200–205. <http://doi.org/10.14366/usg.14011>

Borderline and Malignant Phyllodes Tumor Surgery			
<p>Thind A, Patel B, Thind K, et al. Surgical margins for borderline and malignant phyllodes tumours. <i>Ann R Coll Surg Engl</i>. 2020;102(3):165-173. doi:10.1308/rcsann.2019.0140.</p> <p>Lu Y, Chen Y, Zhu L, et al. Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. <i>Ann Surg Oncol</i>. 2019;90:342–13. doi:10.1245/s10434-018-07134-5.</p>	<ul style="list-style-type: none"> • Borderline /malignant phyllodes tumor: Complete resection with adequate margins, min. > 1 mm • SLNE / Axillary dissection • Treatment of local recurrence <ul style="list-style-type: none"> • B0 resection or simple mastectomy 	Oxford	
		LoE	GR
		2B	B
		4	C
		ASO	
		++	
		--	
		++	

Statement: Complete (wide) local excision or MRM

Surgical margins: Systematic review

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

Operative management and prognosis of Phyllodes Tumors

1. Macdonald, O. K., Lee, C. M., Tward, J. D., et al. (2006). Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. *Cancer*, 107(9), 2127–2133. <http://doi.org/10.1002/cncr.22228>
2. Mituś, J., Reinfuss, M., Mituś, J. W., et al. (2014). Malignant phyllodes tumor of the breast: treatment and prognosis. *Breast Journal*, 20(6), 639–644. <http://doi.org/10.1111/tbj.12333>
3. Mishra, S. P., Tiwary, S. K., Mishra, M., et al. (2013). Phyllodes tumor of breast: a review article. *ISRN Surgery*, 2013(3), 361469–10. <http://doi.org/10.1155/2013/361469>

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

Statement: SNE / Axillary dissection in cN0

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

Statement: Staging

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

Systematic Reviews (2016 – 2021)		
<p>Rosenberger TA, et al. J Clin Oncol 39: 179-188, 2021. PMID: 33401374</p> <p>FIGO 9, 10 in situ (borderline & stage) in situ (borderline & stage)</p> <p>Borderline Ovarian Tumors (2021-22)</p>	<p>Contemporary Multi-institutional Cohort of 1540 Cases of Ovarian Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines</p>	<p>Local recurrence (all PT graded) was not reduced with wider negative margins (width ≥ 2 mm vs < 2 mm) in final margin status (positive vs negative)</p>
<p>Thiel H, et al. Ann R Coll Surg Engl. 2020;102:185-176, 2020. PMID: 32304843</p>	<p>Surgical margins for borderline and malignant epithelial tumours: (20 studies, 456 cases, 1990 – 2018)</p>	<p>No statistically significant difference between <10mm and ≥ 10mm margins in terms of local recurrence rates or distant metastases.</p>
<p>Lu R, et al. Ann Surg Oncol. 30:343-51, 2023. PMID: 36617671</p>	<p>Local Recurrence of Benign, Borderline, and Malignant Epithelial Tumors of the Breast: A Systematic Review and Meta-analysis (34 studies, 6536 cases, 1995 – 2018)</p>	<p>A positive margin and DCIS/lobular carcinoma in situ were significantly correlated with a higher risk for malignant PTs but not for benign and borderline PTs.</p>
<p>Tan BL, et al. Histopathology. 2024;86(2):1-11. PMID: 38788024</p>	<p>Epithelial tumours of the breast: a consensus review</p>	<p>Tumour cut ink, at ≥ 1 mm, should be considered as a positive margin. Tumours with negative margins should be achieved for recurrent and malignant epithelial tumours.</p>

Borderline and Malignant Phyllodes Tumor Adjuvant Therapy			
	Oxford LoE GR AGO		
• Adjuvant radiotherapy (younger age, increased tumor volume > 5 cm, close resection margin)			
• Local control	B	B	+
• Effect on disease-free survival	2b	B	+
• Systemic adjuvant therapy (chemo, endocrine)	4	C	—
• Adjuvant treatment of local recurrence			
• Radiotherapy, chemotherapy after R1 resection	4	C	+/
• Distant metastasis (very rare)			
• Treatment like soft tissue sarcoma	4	C	+/

Statements: Systemic adjuvant therapy/ Chemotherapy and Endocrine therapy

1. Soumarová, R., Šeneklová, Z., Horová, H., et al. (2004). Retrospective analysis of 25 women with malignant cystosarcoma phyllodes--treatment results. Archives of Gynecology and Obstetrics, 269(4), 278–281. <http://doi.org/10.1007/s00404-003-0593-7>
2. Tan, E. Y., Tan, P. H., Hoon, T. P., et al. (2006). Recurrent phyllodes tumours of the breast: pathological features and clinical implications. ANZ J Surg, 76(6), 476–480. <http://doi.org/10.1111/j.1445-2197.2006.03754.x>
3. Morales-Vásquez, F., Gonzalez-Angulo, A. M., Broglio, K., et al. (2007). Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. The Breast Journal, 13(6), 551–556. <http://doi.org/10.1111/j.1524-4741.2007.00510.x>

Statement: Adjuvant radiotherapy

1. Barth, R. J., Wells, W. A., Mitchell, S. E., et al. (2009). A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Annals of Surgical Oncology, 16(8), 2288–2294. <http://doi.org/10.1245/s10434-009-0489-2>
2. Gnerlich, J. L., Williams, R. T., Yao, K., et al. (2014). Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer Data Base, 1998-2009. Annals of Surgical Oncology, 21(4), 1222–1230. <http://doi.org/10.1245/s10434-013-3395-6>

3. Mituś, J., Reinfuss, M., Mituś, J. W., (2014). Malignant phyllodes tumor of the breast: treatment and prognosis. *Breast Journal*, 20(6), 639–644. <http://doi.org/10.1111/tbj.12333>
4. Kim, Y.-J., & Kim, K. (2017). Radiation therapy for malignant phyllodes tumor of the breast: An analysis of SEER data. *Breast (Edinburgh, Scotland)*, 32, 26–32. <http://doi.org/10.1016/j.breast.2016.12.006>
5. Choi, N., Kim, K., Shin, K.H., et al. (2018). Malignant and borderline phyllodes tumors of the breast: a multicenter study of 362 patients (KROG 16-08). *Breast Cancer Res Treat.* 2018 Sep;171(2):335-344. doi: 10.1007/s10549-018-4838-3. Epub 2018 May 28.
6. Chao X, Chen K, Zeng J, et al.: Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer.* 2019 Apr 23;19(1):372. doi: 10.1186/s12885-019-5585-5.
7. Choi N, Kim K, Shin KH, et al.: The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and Borderline Phyllodes Tumors of the Breast (KROG 16-08). *Clin Breast Cancer.* 2019 Oct;19(5):345-353.e2. doi: 10.1016/j.clbc.2019.04.003.
8. Lu Y, Chen Y, Zhu L, et al.: Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol.* 2019 May;26(5):1263-1275. doi: 10.1245/s10434-018-07134-5.


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

1. Soumarová, R., Šeneklová, Z., Horová, H. et al. (2004). Retrospective analysis of 25 women with malignant cystosarcoma phyllodes--treatment results. *Archives of Gynecology and Obstetrics*, 269(4), 278–281. <http://doi.org/10.1007/s00404-003-0593-7>
2. Tan, E. Y., Tan, P. H., Hoon, T. P., et al. (2006). Recurrent phyllodes tumours of the breast: pathological features and clinical implications. *ANZ J Surg*, 76(6), 476–480. <http://doi.org/10.1111/j.1445-2197.2006.03754.x>
3. Mituś, J., Reinfuss, M., Mituś, J. W., et al. (2014). Malignant phyllodes tumor of the breast: treatment and prognosis. *Breast Journal*, 20(6), 639–644. <http://doi.org/10.1111/tbj.12333>

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>

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



ESCS
ESHG

ESCS
 European Society of Breast Cancer Specialists
 10000, 10000, 10000

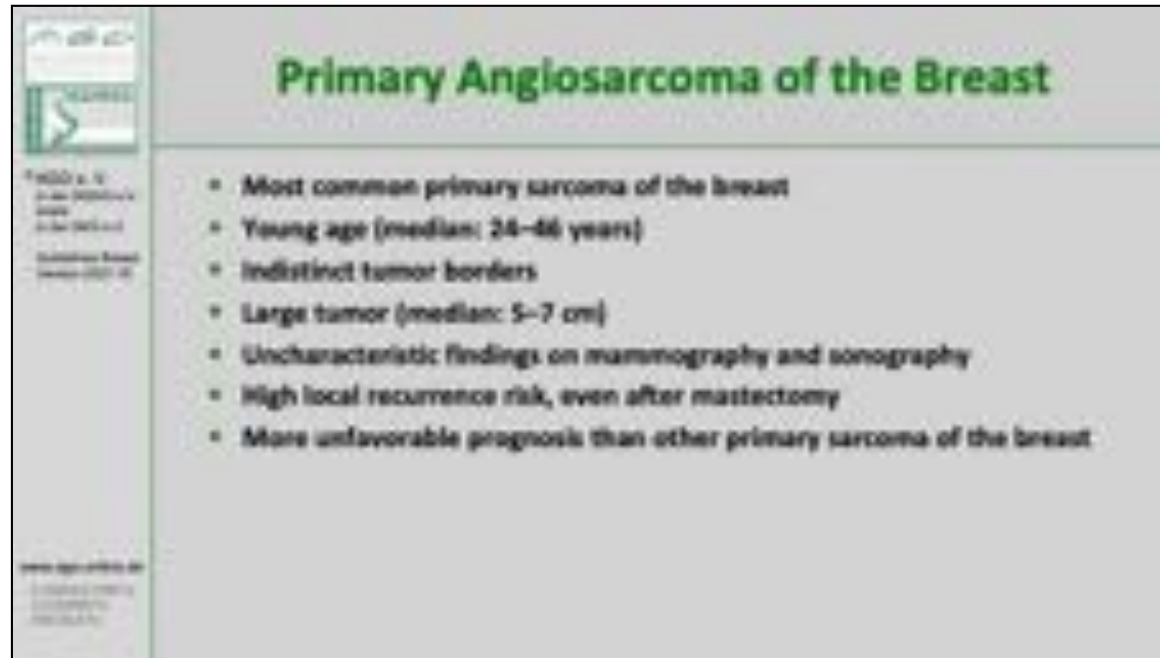
ESHG
 European Society of Human Genetics
 10000, 10000, 10000

Sarcomas of the Breast

ESCS
 European Society of Breast Cancer Specialists
 10000, 10000, 10000

ESHG
 European Society of Human Genetics
 10000, 10000, 10000

- 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



Reviews

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

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>
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Pathology

1. Nascimento, A. F., Raut, C. P., & Fletcher, C. D. M. (2008). Primary angiosarcoma of the breast: clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic. *The American Journal of Surgical Pathology*, 32(12), 1896–1904. <http://doi.org/10.1097/PAS.0b013e318176dbc7>
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of the literature. *British Journal of Cancer*, 91(2), 237–241. <http://doi.org/10.1038/sj.bjc.6601920>

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Prognostic Factors

1. Wang, L., Lao, I. W., Yu, L., et al. (2016). Primary Breast Angiosarcoma: A Retrospective Study of 36 Cases from a Single Chinese Medical Institute with Clinicopathologic and Radiologic Correlations. *Breast Journal*. <http://doi.org/10.1111/tbj.12731>
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>
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Primary Angiosarcoma of the Breast*			
Therapy			
	Oxford LoE	GR	AGO
• Surgery with wide clear margins, mostly as mastectomy	2b	C	++
+ Breast-conserving therapy	3a	C	-
• SLNE or axillary dissection if cN0	3a	C	-
• Adjuvant chemotherapy (anthracycline/taxane-based)	4	C	+/-
• Adjuvant radiotherapy if high risk (size > 5 cm, R1)	4	C	+/-

* Therapy in specialist centres recommended

Surgery

1. Hui, A., Henderson, M., Speakman, D., et al. (2012). Angiosarcoma of the breast: a difficult surgical challenge. *Breast (Edinburgh, Scotland)*, 21(4), 584–589. <http://doi.org/10.1016/j.breast.2012.01.001>
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Adjuvant Treatment (Chemotherapy, Radiotherapy)

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

Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

- Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years
- Clinical presentation
 - > 1 years after BCT or mastectomy with irradiation
 - usually intracutananeously or subcutaneously in the irradiation area with fold dysplasia
 - multiple foci
 - most often in advanced stages (II-III)
 - metastasis mostly pulmonary
 - lymph node metastasis possible
- Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma
- Survival: after 5 yrs up to 50.5%, after 10 yrs up to 25.2%

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>
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<http://doi.org/10.1016/j.jaad.2005.10.017>
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Secondary Angiosarcoma of the Breast Therapy			
	Oxford		
	LoE	GR	AGG
• 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>
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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3. Azzariti, A., Porcelli, L., Mangia, A., et al. (2014). Irradiation-induced angiosarcoma and anti-angiogenic therapy: a therapeutic hope? *Exp Cell Res*, 321(2), 240–247. <http://doi.org/10.1016/j.yexcr.2013.12.018>
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angiosarcoma. *Acta Oncologica*, 48(7), 1078–1079. <http://doi.org/10.1080/02841860902777115>

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Adjuvant Radiotherapy

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

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3. Linthorst, M., van Geel, A. N., Baartman, E. A., et al. (2013). Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. *Strahlenther Onkol*, 189(5), 387–393. <http://doi.org/10.1007/s00066-013-0316-3>
4. Mathis, S. (2010). Hyperthermie. Systematischer Review. Ludwig Boltzmann Institut (pp. 1–59). http://eprints.hta.lbg.ac.at/883/1/DSD_36.pdf

5. Sauer, R., Creeze, H., Hulshof, M., et al. Interdisciplinary Working Group for Clinical Hyperthermia (Atzelsberg Circle) of the German Cancer Society and the German Society of Radiooncology. (2012). Concerning the final report “Hyperthermia: a systematic review” of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010. *Strahlenther Onkol*, 188(3), 209–213. <http://doi.org/10.1007/s00066-012-0072-9>

Angiosarcoma of the Breast

Treatment of Local Recurrence and Metastases

Treatment of Local Recurrence:

- R0 resection
- Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)

Distant Metastases / Unresectable Tumors:

- Treatment like soft-tissue sarcoma
- Paclitaxel/weekly / liposomal doxorubicin (as in angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)

Oxford
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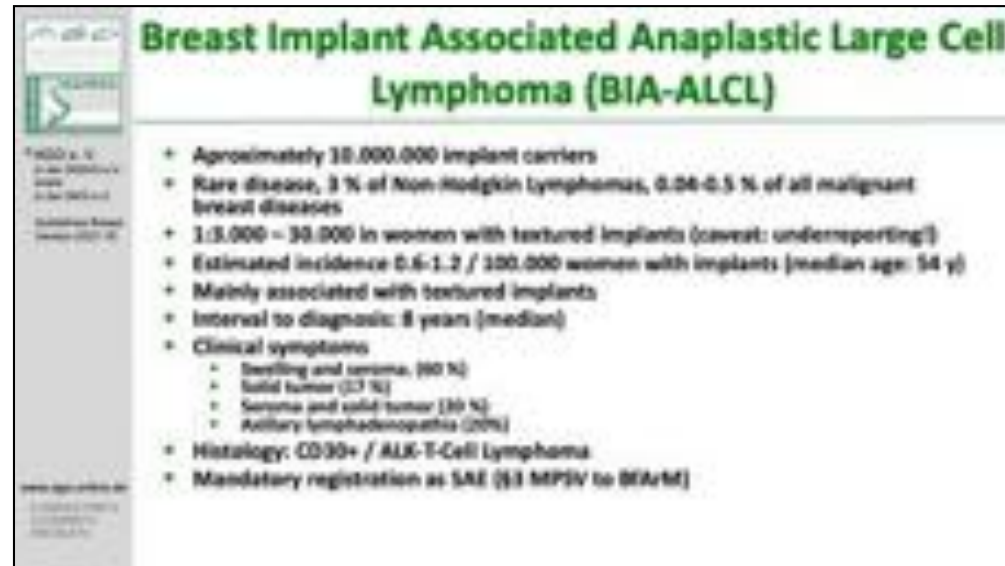
Treatment of local recurrences

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. <http://doi.org/10.1245/s10434-009-0569-3>
2. 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>

Treatment of metastatic and non-resectable tumors

1. Lindner, L. H., Angele, M., Dürr, H. R., et al. (2014). Systemische Therapie und Hyperthermie beim lokal fortgeschrittenen Weichteilsarkom. *Chirurg*, 85(5), 398–403. <http://doi.org/10.1007/s00104-013-2687-5>
2. 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>
3. Gambini, D., Visintin, R., Locatelli, E., et al. (2009). Paclitaxel-dependent prolonged and persistent complete remission four years from first recurrence of secondary breast angiosarcoma. *Tumori*, 95(6), 828–831.
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



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

- Approximately 10,000,000 implant carriers
- Rare disease, 3% of Non-Hodgkin Lymphomas, 0.04-0.5% of all malignant breast diseases
- 1:3,000 – 30,000 in women with textured implants (caveat: underreporting!)
- Estimated incidence 0.6-1.2 / 100,000 women with implants (median age: 54 y)
- Mainly associated with textured implants
- Interval to diagnosis: 8 years (median)
- Clinical symptoms
 - Swelling and seroma (90%)
 - Solid tumor (27%)
 - Seroma and solid tumor (30%)
 - Axillary lymphadenopathy (20%)
- Histology: CD30+ / ALK-T-Cell Lymphoma
- Mandatory registration as SAE (S3 MPN to BIA-ALCL)

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. *Plast Reconstr Surg Glob Open*. 2015 Feb 6;3(1):e296. doi: 10.1097/GOX.0000000000000268. eCollection 2015 Jan. PMID: 25674377
2. Eaves F, Nahai F. Anaplastic large cell lymphoma and breast implants: FDA report. *Aesthetic Surgery Journal* 2011; 31(4), 467–468. <http://doi.org/10.1177/1090820X11407872>
3. Rupani A et al. Lymphomas Associated with Breast Implants: A Review of the Literature. *Aesthetic Surgery Journal* 2015;35(5), 533–544. <http://doi.org/10.1093/asj/sjv016>
4. Clemens MW and Miranda RN. Commentary on: Lymphomas Associated With Breast Implants: A Review of the Literature. *Aesthetic Surgery Journal* 2015;35(5), 545–547. <http://doi.org/10.1093/asj/sjv056>
5. Gidengil CA et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *Plast Reconstr Surg* 2015;135(3), 713–720. <http://doi.org/10.1097/PRS.0000000000001037>
6. Brody GS et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg* 2015; 135(3), 695–705. <http://doi.org/10.1097/PRS.0000000000001033>

7. Miranda RN et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. *Journal of Clinical Oncology* 2014;32(2), 114–120. <http://doi.org/10.1200/JCO.2013.52.7911>
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10. Kricheldorf J, Fallenberg EM, Solbach C et al. Breast Implant-Associated Lymphoma. *Dtsch Arztebl Int.* 2018;115(38):628-635. doi: 10.3238/arztebl.2018.0628.
11. Quesada AE, Medeiros LJ, Clemens MW, et al. Breast implant-associated anaplastic large cell lymphoma: a review. *Mod Pathol.* 2019 Feb;32(2):166-188. doi: 10.1038/s41379-018-0134-3. Epub 2018 Sep 11. PMID: 30206414
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13. Clemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). *Aesthet Surg J.* 2019 Jan 31;39(Suppl_1):S3-S13. doi: 10.1093/asj/sjy331. PMID: 30715173
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https://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/Brustimplantate_ALCL_FDA.html (access 30.01.2021)

BIA-ALCL - Surfaces of Breast Implants						
<p>▶ The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface. The risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces.</p>						
Process	Polyurethane foam	Salt Less (BioCell/ EuroCell)	Gas Diffusion	Salt Less (Rugorex)	Imprinting	Smooth/ Nano
Surface Area	high	intermediate	intermediate	low	low	minimal
Roughness	high	intermediate	low	low	low	minimal
SURFACE TYPE	4	3	3	2	2	1

1. Jones P, Mempin M, Hu H et al. The functional influence of breast implant outer shell morphology on bacterial attachment and growth. *Plast Reconstr Surg.* 2018;142:837–849
2. Collett DJ, Rakhorst H, Lennox P et al.: Current Risk Estimate of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants. *Plast Reconstr Surg.* 2019 Mar;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):30S-40S. doi: 10.1097/PRS.0000000000005567.
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BIA-ALCL– Diagnosis			
	Oxford		
	Loil	GB	AGO
+ Breast US (assessment of new seroma > 1 year after implant insert, solid lesion (sensitivity: 88%, specificity: 79%))	3a	D	++
+ Breast-MRI in confirmed cases	3a	D	++
+ Staging (imaging, e.g. CT, PET-CT)	3a	D	++
+ Cytology of late seromas	3a	D	++
+ - > 50 ml			
+ - Complete assessment			
+ - Flow cytology (T cell clone)			
+ - BIA-ALCL specific cytologic diagnosis (CD 30+)			
+ Core needle biopsy in solid lesions	3a	D	++
+ Lymphoma assessment of resected tissue and histologic staging			
+ Documentation of the implant (manufacturer, size, volume, surface, batch number) and entry in registry	5	D	++

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BIA-ALCL – Therapy			
	Oxford		
	LoE	QR	AGO
• Implant resection and complete capsulectomy including tumorectomy	3a	C	++
• Resection of suspicious lymph nodes, no routine use of Sentinel Node Biopsy, no axillary dissection	4	D	++
• Polychemotherapy (e.g. CHOP) in cases of extra capsular extension	4	D	+
• Radiotherapy in unresectable tumors	5	D	+/-
• Case discussion in an interdisciplinary tumor board in the presence of a lymphoma specialist	5	D	++

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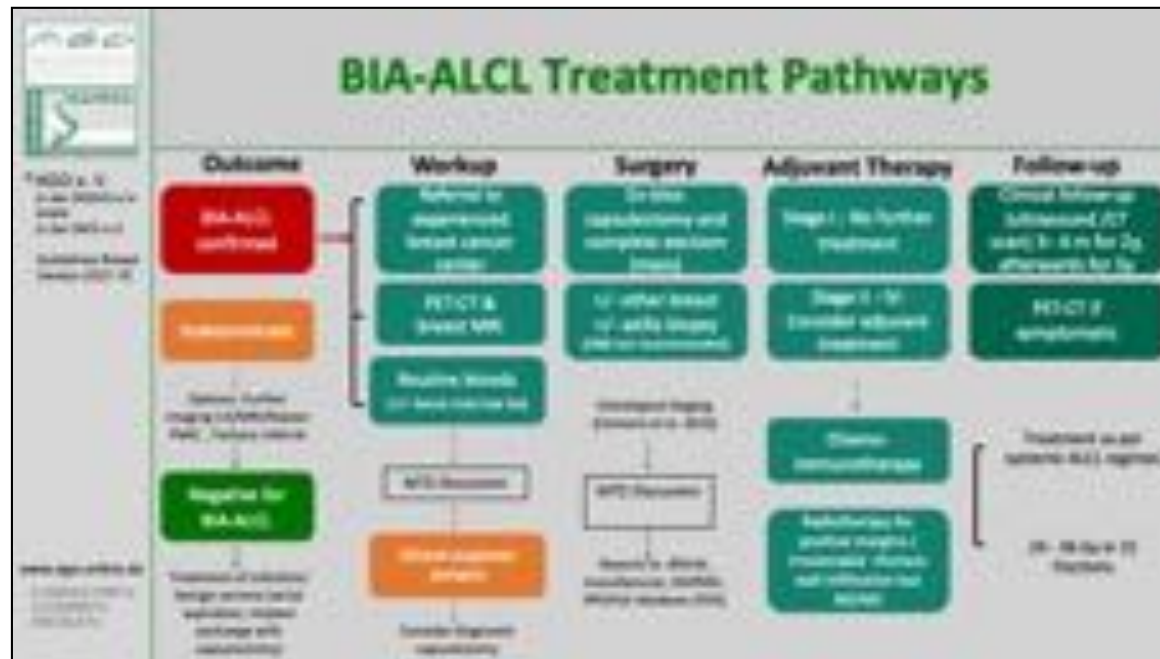
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TNM Staging of BIA-ALCL (proposed)			
TNM Category		Definition	
Tumor extent (pT)	T1	Confined to contents of a lumen on luminal side of capsule	
	T2	Early capsule infiltration	
	T3	Lymph node infiltration on directly infiltrating the capsule	
	T4	Lymph node infiltration beyond the capsule	
Regional lymph nodes (pN)	N0	No lymph node involvement	
	N1	One regional lymph node positive	
	N2	Multiple regional lymph nodes positive	
Metastasis (pM)	M0	No distant spread	
	M1	Spread to other organ or distant sites	

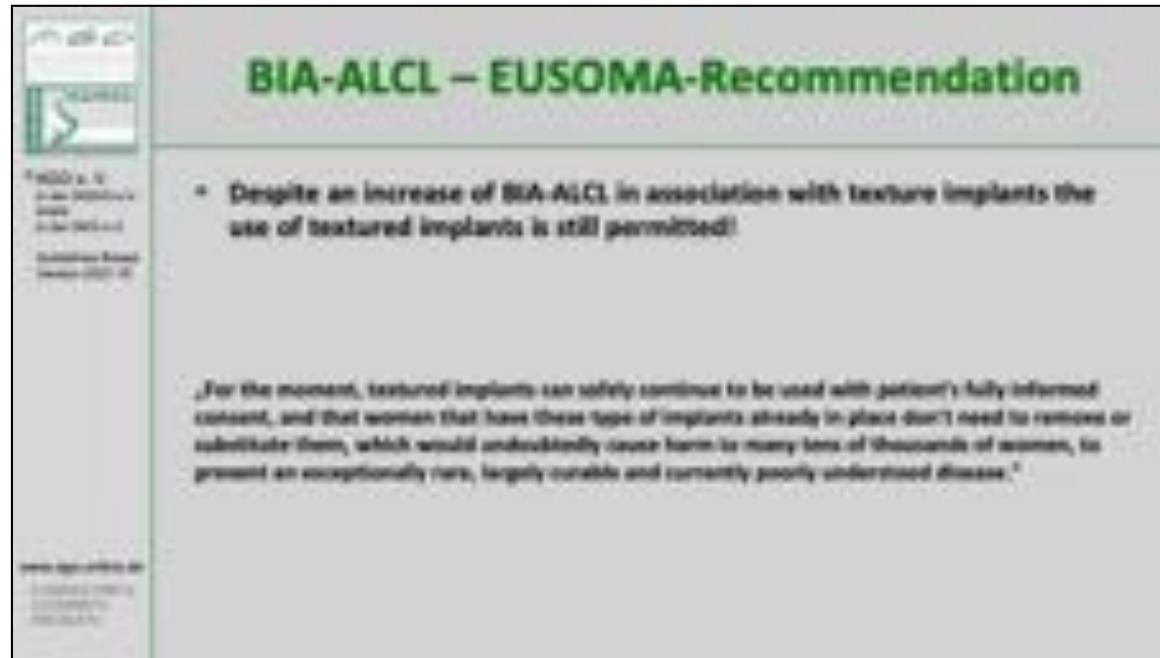
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 <p>FIGO v. 2 In situ, Metastatic & Solid In situ, Metastatic & Solid In situ, Metastatic & Solid In situ, Metastatic & Solid</p> <p>www.who.int/classifications/tumours</p>	<h2 style="text-align: center;">Metaplastic breast carcinoma</h2> <p>Definition: Metaplastic transformation of glandular tumor cells.</p> <ul style="list-style-type: none"> • Epithelial differentiation: squamous cell carcinoma, spindle cell carcinoma • Heterologous (mesenchymal) differentiation: chondroid, osseous, or rhabdoid metaplastic breast carcinoma <p>Clinicopathologic characteristics:</p> <ul style="list-style-type: none"> • < 1% of malignancies of the breast • Same age group as NST carcinomas • Circumscribed, palpable • Rapidly growing, poor response to chemotherapy • > 90% triple-negative <p>Aggressive:</p> <ul style="list-style-type: none"> • Highly malignant with heterologous (mesenchymal), squamous or high-grade spindle cell differentiation • Uncertain malignant potential (low-grade) in adenosquamous or fibromatous-like differentiation
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Outcome

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Metaplastic breast carcinoma - high-grade -			
	Cellular		
	1st	CR	ASO
• Surgical therapy and axillary staging according to standard	4	C	++
• Adjuvant chemotherapy (rather chemoresistant)	4	C	++
• Neoadjuvant chemotherapy (rather chemoresistant)	4	C	+/
• Adjuvant endocrine therapy if receptor-positive	4	C	+
• Adjuvant radiotherapy according to standard	4	C	++

Therapy review:

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Axilla

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Adjuvant radiotherapy

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Metaplastic breast carcinoma with uncertain malignant potential (fibromatous and adenosquamous Ca.)*			
	Cellular		
	LC	CR	ASO
• Surgical therapy and axillary staging according to standard	4	4	4+
• Adjuvant chemotherapy	4	4	+
• Neoadjuvant chemotherapy	4	4	++
• Adjuvant endocrine therapy (not applicable, since triple-negative tumors)	4	4	+
• Adjuvant radiotherapy according to standard	4	4	4

* Reference pathology recommended

Fibromatose-ähnliches Mammakarzinom (low-grade)

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Adenosquamöses metaplastisches Karzinom (low grade)

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