



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer: Specific Situations

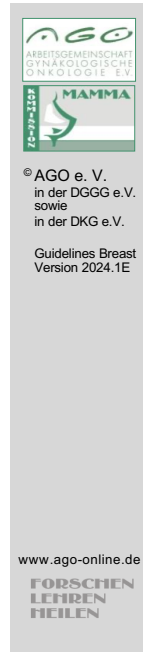
Screened data bases:

Pubmed 2007 - 2023, ASCO 2010 – 2023, SABCS 2010 – 2023, Cochrane Data Base (2023)

Screened Guidelines:

1. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol 2022;33:1097–1118.
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
3. <https://www.esmo.org/guidelines/breast-cancer>
4. ASCO (American Association of Clinical Oncology, Practice Guidelines) <http://www.asco.org>
5. CMA (Canadian Medical Association): <http://www.cmaj.ca>
6. NCCN (National Comprehensive Cancer Network) vs. 5/2023: <http://www.nccn.org>
7. https://www.awmf.org/uploads/tx_szleitlinien/032-045Olk_S3_Mammakarzinom_2021-07_1.pdf

Breast Cancer: Specific Situations



▪ Versions 2005–2023:

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

▪ Version 2024

Harbeck / Sinn / Thomssen

Screened data bases:

Pubmed 2007 - 2023, ASCO 2010 – 2023, SABCS 2010 – 2023, Cochrane Data Base (2023)

Screened Guidelines:

1. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol 2022;33:1097–1118.
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
3. <https://www.esmo.org/guidelines/breast-cancer>
4. ASCO (American Association of Clinical Oncology, Practice Guidelines) <http://www.asco.org>
5. CMA (Canadian Medical Association): <http://www.cmaj.ca>
6. NCCN (National Comprehensive Cancer Network) vs. 5/2023: <http://www.nccn.org>
7. https://www.awmf.org/uploads/tx_szleitlinien/032-045Olk_S3_Mammakarzinom_2021-07_1.pdf



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Content – Specific Situations


- Young patients ≤ 40 years
- Pregnancy and breast feeding-associated BC
- Elderly patients
 - Geriatric assessment
- Male patients
- Inflammatory breast cancer (IBC, cT4d)
- Occult breast cancer - axillary CUP („Cancer of Unknown Primary“)
- Paget's disease
- Malignant and Boderline Phylloides-Tumor
- Sarcoma, Angiosarcoma
- Metaplastisc breast cancer

Breast Cancer in Young Women ≤ 40 Years



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	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	++
▪ ET interruption (max. 2 years after at least 18 months of previous therapy) in case of desire to have children without short-term survival disadvantage	2b	B	+
▪ GnRHa as ovarian protection (see chapter gynecological problems)	1a	B	+
▪ Genetic and fertility counseling	2b	B	++
▪ Contraception counseling	2b	B	++

1. Ribnikar D, Ribeiro JM, Pinto D et al.: Breast cancer under age 40: a different approach. *Curr Treat Options Oncol.* 2015 Apr;16(4):16.
2. Pursche T, Hedderich M, Heinrichs A et al. Guideline conformity treatment in young women with early-onset breast cancer in Germany. *Breast Care (Basel).* 2014 Oct;9(5):349-54
3. Paluch-Shimon S, Cardoso F, Partridge AH, et al.: ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). *Ann Oncol* 2022;33:1097–1118.

Prognosis in young women

1. Shoemaker ML, White MC, Wu M et al. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013. *Breast Cancer Res Treat* 2018;169(3):595-606.
2. Ann H. Partridge et al. Model Program to Improve Care for a Unique Cancer Population: Young Women With Breast Cancer *J Oncol Pract.* 2012; 8(5): e105–e110.
3. Hironaka-Mitsuhashi A, Tsuda H, Yoshida M et al. Invasive breast cancers in adolescent and young adult women show more aggressive immunohistochemical and clinical features than those in women aged 40-44 years. *Breast Cancer* 2018.
4. Johansson ALV, Trewin CB, Hjerkind KV et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. *Int J Cancer* 2018.
5. Liu Z, Sahli Z, Wang Y, Wolff AC et al. Young age at diagnosis is associated with worse prognosis in the Luminal A breast cancer

- subtype: a retrospective institutional cohort study. *Breast Cancer Res Treat* 2018;172(3):689-702.
6. Kroman N. et al, Factors influencing the effect of age on prognosis in breast cancer: population based study. *BMJ*. 2000 Feb 19;320(7233):474-8.
 7. Gonzalez-Angulo AM et al., Women age < or = 35 years with primary breast carcinoma: Disease features at presentation. *Cancer* 2005;103: 2466-2472
 8. Rapiti E, et al. Survival of young and older breast cancer patients in Geneva from 1990 to 2001. *Eur J Cancer* 2005;41(10):1446-52.
 9. Oh JL, Bonnen M, Outlaw ED, et al . The impact of young age on locooregional recurrence after doxorubicin-based breast conservation therapy in patients 40 years old or younger: How young is "young"? *Int J Radiat Oncol Biol Phys* 2006;65:1345-52.
 10. Anders CK, Hsu DS, Broadwater G, et al . Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol* 2008;26:3324-30.
 11. Freedman RA et al. Management of breast cancer in very young women. *Breast*. 2013;22 Suppl 2:S176-9. *J Natl Compr Canc Netw*. 2013;11(9):1060-9.
 12. Tichy JR et al. Breast cancer in adolescents and young adults: a review with a focus on biology. *J Natl Compr Canc Netw*. 2013;11(9):1060-9.
 13. Kim HJ, Kim S, Freedman RA, Partridge AH: The impact of young age at diagnosis (age <40 years) on prognosis varies by breast cancer subtype: A U.S. SEER database analysis. *Breast* 2022;61:77–83.

Chemotherapy in young women

1. Passildas J, Collard O, Savoye AM et al. Impact of Chemotherapy-induced Menopause in Women of Childbearing Age With Non-metastatic Breast Cancer - Preliminary Results From the MENOCOR Study. *Clin Breast Cancer* 2018.
2. Oktay K, Harvey BE, Partridge AH et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2018;36(19):1994-2001.
3. Aebi S. Special issues related to the adjuvant therapy in very young women. *Breast* 2005, 14: 594-599 (Review)
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365: 1687–1717
5. M. De Laurentiis et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2008;26 (1),44–53.
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Endocrine therapy in young women

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

1. Partridge AH, Pagani O, Niman SM, et al. Pregnancy outcomes and safety of interrupting therapy for women with endocrine responsive breast cancer: Primary results from the POSITIVE trial (IBCSG 48-14/BIG 8-13). Presented at SABCS 2022. December 6-10, 2022. Abstract GS4-09.

Benefit from trastuzumab

1. Smith I, HERA study team: 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet.* 2007;369(9555):29-36
2. A.H. Partridge et al. The effect of age on breast cancer outcomes in women with her-2 positive breast cancer: results from the HERA trial *J Clin Oncol* 2013;44,2692–2698

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

1. M. Gnant et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360 (7) 679–691
2. Gerber B et al. Effect of Luteinizing Hormone-Releasing Hormone Agonist on ovarian function after adjuvant breast cancer chemotherapy: by the GBG 37 ZORO study. *J. Clin Oncol* 2011;29 (17) 2334-2341

3. Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial *J Natl Cancer Inst* 2007 ;99:516–525
4. S.M. Swain, J.H. Jeong, C.E. Geyer Jr., et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med* 2010 ; (362);2053–2065
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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].
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4. Cao JQ et al. Comparison of recurrence and survival rates after breast-conserving therapy and mastectomy in young women with breast cancer. *Curr Oncol.* 2013;20(6):e593-e601. Review.

5. Recio-Saucedo A, Gerty S, Foster C, et al. Information requirements of young women with breast cancer treated with mastectomy or breast conserving surgery: A systematic review. *Breast*. 2016 Feb;25:1-13.
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; (3):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.



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Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery

	Oxford		
	LoE	GR	AGO
▪ Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)	4	C	++
▪ Staging if indicated (bone scan after delivery)	5	D	+
▪ Full body MRI (without contrast agent)	4	C	+/-
▪ Surgery like in non-pregnant patients	4	C	++
▪ Sentinel node excision (technetium only)	2a	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. Loibl S, Azim HA Jr, Bachelot T et al. ESMO Expert Consensus Statements on the management of breast cancer during pregnancy (PrBC). Ann Oncol. 2023 Oct;34(10):849-866.
2. 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
3. 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. Bothou A, Margioulou-Siarkou C, Petousis S, et al. Sentinel lymph node biopsy for breast cancer during pregnancy: A comprehensive update. *Eur J Clin Invest* 2023; Dec 14:e14134
2. Han SN, Amant F, Cardonick EH, et al. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. *Breast Cancer Res Treat* 2018;168(2):551-57.
3. 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.
4. Khera SY, Kiluk JV, Hasson DM et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J*. 2008 May-Jun;14(3):250-4

Reviews

1. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. *Cancer*. 2006 Jan 15;106(2):237-46.
2. Shachar SS, Gallagher K, McGuire K, et al. Multidisciplinary Management of Breast Cancer During Pregnancy. *Oncologist* 2017;22(3):324-34.
3. Lee GE, Mayer EL, Partridge A. Prognosis of pregnancy-associated breast cancer. *Breast Cancer Res Treat* 2017;163(3):417-21.
4. Ruiz R, Herrero C, Strasser-Weippl K, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review. *Breast* 2017;35:136-41.
5. Talele AC, Slanetz PJ, Edmister WB, et al. The lactating breast: MRI findings and literature review. *Breast J* 2003, 9: 237-240
6. hachar SS, Gallagher K, McGuire K et al. Multidisciplinary Management of Breast Cancer During Pregnancy. *Oncologist* 2017;22(3):324-34.
7. Framarino-Dei-Malatesta M, Sammartino P, Napoli A. Does anthracycline-based chemotherapy in pregnant women with cancer offer safe cardiac and neurodevelopmental outcomes for the developing fetus? *BMC Cancer* 2017;17(1):777.
8. Scharl A, Ahr A, Göhring U-J: Malignome in der Schwangerschaft. In: Kaufmann M, Costa SD, Scharl A (eds) *Die Gynäkologie*. Springer, Heidelberg, 2002 pp 509
9. Gadducci A, Cosio S, Fanuchi A, et al; Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and a review of the literature. *Anticancer Res* 2003; 23: 5225-5229
10. Ben Brahim E, Mrad K, Driss M, et al. Placental metastasis of breast cancer. *Gynecol Obstet Fertil* 2001, 29: 545-548
11. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5
12. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi160-70

Breast Cancer During Pregnancy or Breast Feeding - (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	2b	B	++
▪ Dose-dense regimens with short-acting G-CSF	4	C	+/-
▪ Taxanes	2a	B	++
▪ Platinum salts (carboplatin, cisplatinum)	4	C	+/-
▪ MTX (e.g. CMF)	4	D	--
▪ Endocrine treatment	4	D	--
▪ HER2-targeted treatment	3a	C	--
▪ Checkpoint inhibitors	4	D	--
▪ Bisphosphonates, denosumab	4	D	--

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

General principles

1. Amant F, Nekljudova V, Maggen C, et al: Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer 2022;170:54–63.
2. Loibl S, Azim HA Jr., Bachelot T, et al. ESMO Expert Consensus on the management of breast cancer during pregnancy (PrBC). Ann Oncol 2023; 34(10): 849-866.

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. Auger N, Maniraho A, Ayoub A, Arbour L. Association of maternal cancer with congenital anomalies in offspring. Paediatr Perinat Epidemiol. 2023 Dec 19.
2. 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)
3. 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

4. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol*. 2008 Apr;19(4):607-13.
5. Del Gobbo A, et al. Chemotherapy for breast cancer during pregnancy induces vascular alterations and impaired development of placental villi: A preliminary histopathological study. *Eur J Obstet Gynecol Reprod Biol*. 2020;250:155–161 (11).
6. Vandembroucke T, et al. Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. *International Network on Cancer, Infertility and Pregnancy (INCIP)*. *Eur J Cancer* 2020;138:57–67

Statement: Anthracyclines: AC, EC

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

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

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

Statement: Taxanes

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

4. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer* 2013;13:16-23.
5. Cardonick E et al. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012;23:3016-3023.
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Statement: Platinum salts

1. Köhler C, Oppelt P, Favero G, et al. How much platinum passes through the placental barriers? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. *Am J Obstet Gynecol*. 2015 Aug;213(2):206.
2. Zheng X, Zhu Y, Zhao Y, et al. Taxanes in combination with platinum derivatives for the treatment of ovarian cancer during pregnancy: A literature review. *International journal of clinical pharmacology and therapeutics* 2017;55(9):753-60.
3. Calsteren KV, Verbesselt R, Devlieger R, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. *Int J Gynecol Cancer* 2010 Dec;20(9):1456-64.
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. Andrikopoulou A, Apostolidou K, Chatzinikolaou S, et al.: an update. *BMC Cancer* 2021;21:463.
2. Paluch-Shimon S, Cardoso F, Partridge AH, et al.: ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). *Ann Oncol* 2022;33:1097–1118.
3. 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.
4. Yildirim N, Bahceci A. Use of pertuzumab and trastuzumab during pregnancy. *Anticancer Drugs* 2018;29(8):810-13.
5. Fanale MA et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clin Breast Cancer* 2005, 6: 354-356 (Case Report)
6. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. *Obstetrics and Gynecology* 2005, 105: 642-643 (Case Report)
7. Loibl S. New Therapeutic Options for Breast Cancer during Pregnancy. *Breast Care* 2008; 3:171-176. (table overview of trastuzumab cases)
8. Aebi S, Loibl S. Breast cancer during pregnancy: medical therapy and prognosis. *Recent Results Cancer Res.* 2008;178:45-55.
9. Clemons M, Goss P: Estrogen and the risk of breast cancer. *New Engl J Med* 2001, 344: 276-285
10. 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.
11. Zagouri F et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013 Jan;137(2):349-57.
12. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* 2013; 5(7):733-41.
13. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Lambertini M, et al. *Cancer.* 2019

Statement Immunotherapy during pregnancy

1. Garutti M, Lambertini M, Puglisi F: Checkpoint inhibitors, fertility, pregnancy, and sexual life: a systematic review. *ESMO Open* 2021;6:100276.
2. Borgers JSW, et al. Immunotherapy for cancer treatment during pregnancy. *Lancet Oncol.* 2021 Dec;22(12):e550-e561. doi: 10.1016/S1470-2045(21)00525-8..

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

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

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

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

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

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

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

Breast Cancer and Pregnancy* or Breast Feeding – Family Planning

	Oxford		
	LoE	GR	AGO
▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
▪ Assisted reproductive treatment after breast cancer	4	D	+/-
▪ Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients	3b	D	
▪ Breast cancer patients should not be advised against getting pregnant independent of their tumor's hormone receptor status and gBRCA status	2a	B	

* Participation in register study recommended

1. Lambertini M, Blondeaux E et al., Partridge AH; BRCA BCY Collaboration. Pregnancy After Breast Cancer in Young BRCA Carriers: An International Hospital-Based Cohort Study. JAMA. 2024 Jan 2;331(1):49-59.
2. Arecco L, Blondeaux E, Bruzzone M, et al. Safety of pregnancy after breast cancer in young women with hormone-receptor-positive disease: A systematic review and metaanalysis. ESMO Open 2023, Dec; 8(6): 102031
3. Partridge AH, Niman SM, Ruggeri M et al., POSITIVE Trial Collaborators. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. N Engl J Med. 2023 May 4;388(18):1645-1656.
4. Condorelli M, Bruzzone M, Ceppi M, et al.: Safety of assisted reproductive techniques in young women harboring germline pathogenic variants in BRCA1/2 with a pregnancy after prior history of breast cancer. ESMO Open 2021;6:100300.
5. Rosenberg E, et al. No increased risk of relapse of breast cancer for women who give birth after assisted conception. Hum Reprod Open. 2019 Dec 18;2019(4):hoz039. doi: 10.1093/hropen/hoz039
6. Lambertini M, et al., Pregnancy After Breast Cancer in Patients With Germline BRCA Mutations. J Clin Oncol. 2020;38:3012–3023
7. Oktay K et al. Increased chemotherapy-induced ovarian reserve loss in women with germline BRCA mutations due to oocyte deoxyribonucleic acid double strand break repair deficiency. Fertil Steril 2020;113:1251–1260
8. Turan V, et al. The impact of malignancy on response to ovarian stimulation for fertility preservation: a meta-analysis. Fertil Steril 2018 Dec;110(7):1347–1355. doi: 10.1016/j.fertnstert.2018.08.013
9. Grynberg M et al. BRCA1/2 gene mutations do not affect the capacity of oocytes from breast cancer candidates for fertility

preservation to mature in vitro. Hum Reprod 2019 ;34(2):374–379

10. Gunnala V et al. BRCA carriers have similar reproductive potential at baseline to non-carriers: comparisons in cancer and cancer-free cohorts undergoing fertility preservation. Fertil Steril. 2019;111(2):363–371
11. Turan V, et al. Association of Germline BRCA Pathogenic Variants With Diminished Ovarian Reserve: A Meta-Analysis of Individual Patient-Level Data. J Clin Oncol. 2021 Jun 20;39(18):2016-2024.

Breast Cancer During Pregnancy* and Breast Feeding - Outcome -

	Oxford LoE
<ul style="list-style-type: none"> ▪ BC during pregnancy <ul style="list-style-type: none"> ▪ Prognosis is not worse if adequately treated 	3a
<ul style="list-style-type: none"> ▪ BC during lactation and within the first year after pregnancy <ul style="list-style-type: none"> ▪ Prognosis worse than in BCP and if unrelated to pregnancy 	3a
<ul style="list-style-type: none"> ▪ Pregnancy / lactation after BC <ul style="list-style-type: none"> ▪ Outcome not compromised 	3a

* Participation in register study recommended

General principles

1. Amant F, Lefrère H, Borges VF, et al.: The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Lancet Oncol 2021;22:753–754.
2. Amant F, Nekljudova V, Maggen C, et al: Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer 2022;170:54–63.
3. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9.
4. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.
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. 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.
7. Loibl S, Azim HA Jr, Bachelot T, et al. ESMO Expert Consensus on the management of breast cancer during pregnancy (PrBC). Ann Oncol 2023: 34(10): 849-866.

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, Ameys 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.
15. Iqbal J, Amir E, Rochon PA, et al. Association of the Timing of Pregnancy With Survival in Women With Breast Cancer *JAMA Oncol* 2017;3(5):659–665
16. O'sullivan et al. Clinico-pathologic features, treatment and outcomes of breast cancer during pregnancy or the post-partum period. *Breast Cancer Res Treat* 2020;180(3):695–706
17. Lefrère H, et al. Breast cancer diagnosed in the post-weaning period. *Lancet Oncol*. 2021: 22:1139-50

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

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

Review articles

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

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 (HR+)	1a	A	++
▪ Chemotherapy (standard regimens)			
▪ ≤ 70 years	1a	A	+
▪ > 70 years (especially N+, ER / PR-)	2a	C	+*
▪ Radiotherapy	1a	A	+
▪ Omit radiotherapy after BCS if low-risk, and if endocrine treatment is administered	1b	B	+
▪ Anti-HER2-therapy	2b	C	+

* Study participation recommended

1. Lorentsen MK, Vohra S, Muss HB, et al.: Age and competing concerns in treatment selection for women with non-metastatic HR+ and HER2- breast cancer: Current clinical practice. J Geriatr Oncol 2022;13:839–843.
2. 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. Battisti NML, Glas N de, Soto-Perez-de-Celis E, et al.: Chemotherapy and gene expression profiling in older early luminal breast cancer patients: An International Society of Geriatric Oncology systematic review. *Eur J Cancer* 2022;172:158–170
2. Brain E, Viansone AA, Bourbouloux E, et al. Final results from a phase III randomized clinical trial of adjuvant endocrine therapy ± chemotherapy in women ≥ 70 years old with ER+ HER2- breast cancer and a high genomic grade index: The Unicancer ASTER 70s trial. *JCO.* 2022;40(16_suppl):500. doi:10.1200/JCO.2022.40.16_suppl.500.
3. Schmidt M, Nitz U, Reimer T et al. Adjuvant capecitabine versus nihil in elderly patients with moderate or high-risk early breast cancer receiving ibandronate – The ICE Randomized Clinical Trial. Submitted
4. Lemij AA, Baltussen JC, Glas NA de, et al.: Gene expression signatures in older patients with breast cancer: A systematic review. *Crit Rev Oncol Hematol* 2023;181:103884.
5. 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.
6. 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.
7. 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).*
8. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients *Breast Care* 2012;7:439-444
9. Muss HB, Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med.* 2009 May 14;360(20):2055-65.
10. Muss HB: CLGB: Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol.* 2007 Aug 20;25(24):3699-704

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12. 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.
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Statement: Radiotherapy

1. Kunkler I Radiotherapy issues in elderly breast cancer patients *Breast Cancer Patients Breast Care* 2012;7:453-459
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Statement: Trastuzumab

1. Freedman RA, Vaz-Luis I, Barry WT, et al. Patterns of chemotherapy, toxicity, and short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. *Breast Cancer Res Treat*. 2014 Jun;145(2):491-501.
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paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol.* 2005 Nov 1;23(31):7811-9

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Treatment for Frail Patients (Life Expectancy < 5 yrs., Substantial Comorbidities)

	Oxford		
	LoE	GR	AGO
▪ Reduced standard treatment	2b	C	++
▪ Options extrapolated from trials in elderly:			
▪ No breast surgery (consider endocrine therapy)	2b	C	+
▪ No axillary clearing (≥ 60 y, cN0, HR-pos)	2b	B	+
▪ No radiotherapy (Tumor size < 3 cm, pN0, HR-pos)	1b	B	++
▪ Hypofractionated radiotherapy	2b	B	+
▪ No chemotherapy if > 70 yrs. and negative risk-benefit analysis	2b	C	+

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3. Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
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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)

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2. Fentiman IS, et al. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. Eur J Cancer (2003) 39(3):309-16
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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.
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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.
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Statement: No chemotherapy > 70 years and negative risk benefit analysis

1. Du XL, Jones DV, Zhang D. Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. J 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
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HEILEN

Geriatric Assessment

Links to current frailty scales:

- **Ability to tolerate treatment varies greatly („functional reserve“)**
- **Comprehensive geriatric assessment describes a multidisciplinary evaluation of independent predictors of morbidity & mortality for older individuals (CGA)**
 - 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
- **General assessment tools:**
 - Charlson Comorbidity Index (CCI, widely used; good predictor over a 10-year period)
 - 12 prognostic indicators to estimate 4-year mortality risk
 - Short screening tests (more qualitative evaluation)
 - IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured)
 - G8 (Age plus Malnutrition Assessment, MNA)
 - Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (food intake in the last 3 months, >3 prescribed drugs, mobility and autonomy)
 - Timed-up-and-go-test
 - Frailty Index (FI), Carolina Frailty Index (CFI)

1. Jung C, Bruno RR, Wernly B et al. Frailty as a Prognostic Indicator in Intensive Care. Dtsch Arztebl Int. 2020 Oct 2;117(40):668-673.
2. van Walree IC, Scheepers E, van Huis-Tanja L et al. A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. J Geriatr Oncol. 2019 Nov;10(6):847-858.
3. Williams GR, Deal AM, Sanoff HK et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer. 2019 Jul;27(7):2693-2698.
4. 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.
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Breast 2013;22(5):753-60.

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14. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006 295:801-08.
15. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev.* 1996 Jan;54(1 Pt 2):S59-65.
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Male Breast Cancer*: Diagnostic Work-Up and Loco-Regional Therapy

	Oxford		
	LoE	GR	AGO
▪ Diagnostic work-up as in women	4	C	+
▪ Ultrasound	2b	B	++
▪ Mammography	3b	C	+
▪ Standard-surgery: Mastectomy	4	C	++**
▪ BCT is an option (tumor / breast relation)	4	C	++
▪ Sentinel-node excision (SLNE)	2b	B	+
▪ In occult breast cancer	2b	B	+
▪ Radiotherapy as in women (consider tumor / breast relation!)	4	C	+
▪ Genetic counseling (see genetics chapter)	2b	B	++
▪ Screening for 2nd malignancies according to guidelines	GCP		++

* Treatment in certified breast cancer centers recommended; ** Participation in register 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

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2. Fentiman IS. Unmet needs of men with breast cancer. Eur J Surg Oncol 2018;44(8):1123-26.
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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.
 9. Wong WG, Perez Holguin RA, Kanwar R, et al. Management of Male Patients With Occult Breast Cancer: Analysis of the National Cancer Database. J Surg Res 2024; 293: 685-692

Statement: Surgery: BEO – men

1. Cloyd JM, Hernandez-Boussard T, Wapnir IL. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983–2009. Ann Surg Oncol. 2013;20(5):1545–50.
2. Bratman SV, Kapp DS, Horst KC. Evolving trends in the initial locoregional management of male breast cancer. Breast. 2012;21(3):296–302. <https://doi.org/10.1016/j.breast.2012.01.008>.
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5. Golshan M, Rusby J, Dominguez F, et al. Breast conservation for male breast carcinoma. Breast. 2007;16(6):653–6.
6. Selcukbiricik F, Tural D, Aydog˘an F, et al. 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, et al. 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
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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
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8. Patten DK et al. New Approaches in the Management of Male Breast. Cancer Clinical Breast Cancer 2013;13(5) 309–314
9. Sousa B et al. An update on male breast cancer and future directions for research and treatment. Eur J Pharmacol 2013;717(1-3)
10. Ruddy KJ et al. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol 2013; 24(6):1434-43.

Male Breast Cancer: Prognostic Factors

- Nodal status
- Age
- Tumor size
- ER / PR Expression
- Ki-67 Expression
- Grade
- Genomic signatures

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

Statement: Adjuvant Chemotherapy

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

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

Statement CDK4/6i

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Statement endocrine therapy

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Inflammatory Breast Cancer (IBC, cT4d)

	Oxford		
	LoE	GR	AGO
▪ Invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d			++
▪ Staging (including adequate breast imaging)	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	+/-
▪ Delayed breast reconstruction	3b	C	+
▪ Sentinel excision only	3b	C	-
▪ Radiotherapy of the chest wall including regional lymph nodes independent of therapy response	2c	B	++

General

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5. Wu SG, Zhang WW, Wang J et al. Inflammatory breast cancer outcomes by breast cancer subtype: a population-based study. Future Oncol 2018.
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In case of invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d

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

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Statement: Staging

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Statement: Regimens as in non-inflammatory BC

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

Statement: Mastectomy after chemotherapy

1. Chen H, Wu K, Wang M, et al: A standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: A large population-based study in the Surveillance, Epidemiology, and End results database 18. *Breast*. 2017 Oct;35:48-54.
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Statement: Sentinel lymph node

1. Hidar S et al Sentinel lymph node biopsy after neoadjuvant chemotherapy in inflammatory breast cancer. Int J Surg. 2009 Jun;7(3):272-5. doi: 10.1016/j.ijsu.2009.04.012. Epub 2009 May 3.
2. Adesoye T, Lucci A. Current Surgical Management of Inflammatory Breast Cancer. Ann Surg Oncol. 2021 Oct;28(10):5461-5467. doi: 10.1245/s10434-021-10522-z..

Statement: Radiotherapy

1. Chargari C, Kirova YM, Cottu P, et al: Progressive inflammatory breast cancer in patient receiving chemotherapy: The importance of radiotherapy as a part of locoregional treatment. Radiother Oncol. 2009 Jan;90(1):160-1. Epub 2008 Sep 2
2. Bristol IJ, Woodward WA, Strom EA, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. Int J Radiat Oncol Biol Phys. 2008;72:474–484
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 2.2022. NCCN.org (Inflammatory Breast Cancer. IBC-1)

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

	Oxford		
	LoE	GR	AGO
▪ Breast imaging incl. Breast-MRI	3	B	++
▪ Exclude contralateral cancer	3	B	++
▪ Staging (CT thorax / abdomen, pelvis, bone scan)	3	B	++
If histological diagnosis is not certain			
▪ Exclude non-breast malignancy, especially in case of TNBC (e.g. NEC, female genital tract, lung, thyroid gland, stomach, skin, ENT)	5	D	++
▪ PET / PET-CT	3b	B	+

Statement: Mammography / Breast ultrasound/ Breast MRI

- Schneeweiss, A. & Buschhorn, L. „Breast-like cancer of unknown primary“. Implikationen für die radiologische Diagnostik. Die Radiol. 63, 366–370 (2023)
- Fehm, T., & Souchon, R. (2013). Axillary lymph node metastasis in CUP. Der Onkologe, 19(1), 40–43. <http://doi.org/10.1007/s00761-012-2314-y>
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Statement: Staging

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Statement: PET

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

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

Guidelines

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- cancer. *Breast (Edinburgh, Scotland)*, 18(4), 225–227. <http://doi.org/10.1016/j.breast.2009.07.002>
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Pathology

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Outcome

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- McCartan DP, Zabor EC, Morrow M et al. Oncologic Outcomes After Treatment for MRI Occult Breast Cancer (pT0N+). *Ann Surg Oncol* 2017;24(11):3141-47
- Ge LP, Liu XY, Xiao Y et al. Clinicopathological characteristics and treatment outcomes of occult breast cancer: a SEER population-based study. *Cancer Manag Res* 2018;10:4381-91.
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- Huang KY, Zhang J, Fu WF, et al. Different Clinicopathological Characteristics and Prognostic Factors for Occult and Non-occult Breast Cancer: Analysis of the SEER Database. *Front Oncol*. 2020 Aug 19;10:1420. doi: 10.3389/fonc.2020.01420.

Axillary Metastasis in Occult Breast Cancer (ex. CUP)

Pathology, Molecular Pathology

	Oxford		
	LoE	GR	AGO
▪ Immunohistochemistry (ER, PR, HER2, Ki-67, GATA)	5	D	++
▪ Immunohistochemistry (e.g. Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, Synaptophysin etc.) to exclude other primary malignancies in case of TNBC phenotype or unusual histology, e.g. NEC, female genital tract, lung, ENT tumors, thyroid, stomach, skin	5	D	++
▪ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)	2c	B	+/-
▪ NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)	2c	B	+/-
▪ Prognostic gene expression tests	5	D	--

Immunohistochemistry

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3. Montagna, E., Bagnardi, V., Rotmensz, N. et al. (2011). Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation. *Breast Cancer Research and Treatment*, 129(3), 867–875. <http://doi.org/10.1007/s10549-011-1697-6>
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primary: clinical presentation, immunohistochemistry, and molecular analysis. *Case Reports in Oncology*, 5(1), 9–16.
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Gene expression profiling and other molecular approaches in CUP disease

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

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

Guidelines

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2. Fizazi K, Greco FA, Pavlidis N et al. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v133-8.

Reviews

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Statement: Axillary dissection

1. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast Cancer Research and Treatment, 119(1), 1–11. <http://doi.org/10.1007/s10549-009-0554-3>
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<http://doi.org/10.1007/s00117-013-2549-7>

3. Botty Van den Bruele A, Lavery J, Plitas G, Pilewskie ML. Axillary Downstaging in Occult Primary Breast Cancer After Neoadjuvant Chemotherapy. *Ann Surg Oncol*. 2021 Feb;28(2):968-974. doi: 10.1245/s10434-020-08863-2. Epub 2020 Aug 19.

Statement TALD + RT nach NACT

1. Cohen BL, Collier AL, Kelly KN et al. Surgical Management of the Axilla in Patients with Occult Breast Cancer (cT0 N+) After Neoadjuvant Chemotherapy. *Ann Surg Oncol*. 2020 Jun;27(6):1830-1841.

Statement: Mastectomy without (in-)breast tumor

1. Li J, Liu G, Jia Z, Ren F, Dong D, Zhang M, Wang X, Wang Y. Occult breast cancer patients with mastectomy have better prognosis than those with breast-conserving therapy. *Future Oncol*. 2023 Nov;19(36):2405-2416. (Kommentar: Ergebnis: Mastektomie besser (DFS, OS) als BCT. Retrospektiv. Widersprüchliche Daten, z.B. mit Radiotherapie schlechter (Faktor 2-5) als ohne (!))
2. Ofri A, Moore K. Occult breast cancer: Where are we at? *Breast*. 2020 Dec;54:211-215. doi: 10.1016/j.breast.2020.10.012. Epub 2020 Oct 27. PMID: 33130487; PMCID: PMC7599122.
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7. Pavlidis, N., Briasoulis, E., Hainsworth et al. (2003). Diagnostic and therapeutic management of cancer of an unknown primary. *European Journal of Cancer (Oxford, England : 1990)*, 39(14), 1990–2005.



Statement: Breast irradiation if breast MRI is negative

1. Tsai C, Zhao B, Chan T, Blair SL. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. *Am J Surg*. 2020 Jul;220(1):153-160.
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Statement: Systemic treatment according N+ tumor

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2. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. *Breast Cancer Research and Treatment*, 119(1), 1–11. <http://doi.org/10.1007/s10549-009-0554-3>
3. Ofri A, Moore K. Occult breast cancer: Where are we at? *Breast.* 2020 Dec;54:211-215. doi: 10.1016/j.breast.2020.10.012. Epub 2020 Oct 27.

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„BCT“ in patients with axillary met's and occult primary (AxCUP, OBC)

Kim H, Park W, Kim SS et al. Prognosis of patients with axillary lymph node metastases from occult breast cancer analysis of multicenter data. Radiat Oncol J. 2021 Jun;39(2):107-112.
 Retrospective analysis, n = 53 with AxCUP and OBC (adenocarcinoma); exclusion of a primary by extensive imaging. Eleven pts received blind upper quadrantectomy, 42 no breast surgery; 46 pts received whole breast irradiation (WBI), 7 did not; median F/U 85 months .
 Result: 2 in-breast recurrences, 1 RLN rec., 1 combined in-breast and RLN, no distant metastases.
5 year DFS with WBI: 97.8% without WBI 83,3% (p = 0.01 univariate; in multivariate analysis nor biology nor extent of the disease nor therapy had a significant impact).
 Discussion: ..in patients confirmed to have no lesion in the breast by contemporary imaging studies, it is necessary to include the ipsilateral breast in the radiation field in females with OBC presenting as AxCUP.

Tsai C, Zhao B, Chan T, Blair SL. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am J Surg. 2020 Jul;220(1):153-160.
 Given the equipoise in overall survival among the treatment options, we conclude that after axillary clearance, **breast preservation and radiation therapy alone may be sufficient** in the treatment of patients with occult breast cancer.

1. Kim H, Park W, Kim SS et al. Prognosis of patients with axillary lymph node metastases from occult breast cancer: analysis of multicenter data. Radiat Oncol J. 2021 Jun;39(2):107-112.
2. Tsai, C., Zhao, B., Chan, T. & Blair, S. L. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am. J. Surg. 220, 153–160 (2020).

Paget's Disease of the Breast Diagnosis

„Mammary Paget Disease is a Sentinel Sign“

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

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

* including all skin strata (e.g. by punch biopsy or wedge excision)

General recommendations / Guidelines:


1. Mariano L, Nicosia L, Pupo D et al. A Pictorial Exploration of Mammary Paget Disease: Insights and Perspectives. *Cancers (Basel)*. 2023 Nov 3;15(21):5276.
2. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (5.2023). Paget Disease (PAGET-1)

Imaging

1. Mariano L, Nicosia L, Pupo D et al. A Pictorial Exploration of Mammary Paget Disease: Insights and Perspectives. *Cancers (Basel)*. 2023 Nov 3;15(21):5276.
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Pathology

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3. Sek, P., Zawrocki, A., Biernat, W., et al(2010). HER2 molecular subtype is a dominant subtype of mammary Paget's cells. An immunohistochemical study. *Histopathology*, 57(4), 564–571. <http://doi.org/10.1111/j.1365-2559.2010.03665.x>



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Paget's Disease of the Breast

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

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

Review

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

Clinical Presentation

1. Dalberg, K., Hellborg, H., & Wärnberg, F. (2008). Paget's disease of the nipple in a population based cohort. *Breast Cancer Research and Treatment*, 111(2), 313–319. <http://doi.org/10.1007/s10549-007-9783-5>
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Pathology and Immunohistochemistry

1. Chen, C.-Y., Sun, L.-M., & Anderson, B. O. (2006). Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer*, 107(7), 1448–1458. <http://doi.org/10.1002/cncr.22137>
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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	D	++
	1c	B	++
<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 (SLNE) 	1c	B	++
	4	D	++
	2b	B	--

General recommendations / Guidelines:

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

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

1. Lin C-W, Chiang M-H, Tam K-W: Treatment of Mammary Paget Disease: A systematic review and meta-analysis of real-world data. Int J Surg 2022;107:106964.
2. Markarian S, Holmes DR: Mammary Paget's Disease: An Update. Cancers (Basel) 2022;14
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4. Caliskan, M., Gatti, G., Sosnovskikh, I., et al. (2008). Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. Breast Cancer Research and Treatment, 112(3), 513–521. <http://doi.org/10.1007/s10549-007-9880-5>
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Treatment of isolated Pagets's disease

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

Statement: Sentinel-node excision (SNE)

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

	Oxford		
	LoE	GR	AGO
▪ Mammography, sonography	3	C	++
▪ Diagnosis on core biopsy, grade determination on resection specimen	3	C	++
▪ Breast MRI	3	C	+/-
▪ Staging only malignant PT (CT thorax / abdomen, bone scan)	5	D	++

Review

1. Ofri, A. et al. Diagnosis and management of phyllodes tumours for the surgeon: An algorithm. *Surg.* 20, e355–e365 (2022).

Imaging

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

Core biopsy

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



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Borderline and Malignant Phyllodes Tumor

- Name derived from greek term of “Phyllon” (leaf) due to its lobulated histological aspect
- Differential diagnosis may be problematic on core biopsy
- Resection margin is independent prognostic parameter
- Comparable rates of recurrence in association with BCT or mastectomy
- In-Breast recurrence relatively frequently seen (10 - 30%)
- Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.
- Adverse pathological criteria: marked stromal cellularity and overgrowth, increased nuclear atypia, presence of large necrohemorrhagic areas, and high mitotic activity associated with increased risk of distant recurrence


Review

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

Pathology and Outcome


1. Barrio, A., Clark, B., Goldberg, J. et al. (2007). Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. *Annals of Surgical Oncology*.
2. Tan, P. H., Thike, A. A., Tan, W. J., et al. (2012). Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *Journal of Clinical Pathology*, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>
3. Chao X, Chen K, Zeng J, et al.: Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer*. 2019 Apr 23;19(1):372. doi: 10.1186/s12885-019-5585-5
4. Choi N, Kim K, Shin KH, et al.: The Characteristics of Local Recurrence After Breast-Conserving Surgery Alone for Malignant and Borderline Phyllodes Tumors of the Breast (KROG 16-08). *Clin Breast Cancer*. 2019 Oct;19(5):345-353.e2. doi: 10.1016/j.clbc.2019.04.003.
5. Lu Y, Chen Y, Zhu L, et al.: Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019 May;26(5):1263-1275. doi: 10.1245/s10434-018-07134-5

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



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Phyllodes Tumor

■ **Frequency 0.3 – 1% of all primary breast tumors**

parameter	frequencies
Grading system (3-STEP histological grading)	Benign (75%) Borderline (16%) Malignant (9%)
Median age at time of diagnosis	Benign PT: 39 y Borderline PT: 45 y Malignant PT: 47 y
Local recurrence	Benign PT: 4 – 17% Borderline PT: 14 – 25% Malignant PT: 23 – 30%
Metastasis	Benign PT: < 1% Borderline PT: 1.6% Malignant PT: 16-22%

10 y OS: 86–90% (range: 57–100%) depending on subtype and unfavorable 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., Thike, A. A., Tan, W. J., et al. (2012). Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *Journal of Clinical Pathology*, 65(1), 69–76. <http://doi.org/10.1136/jclinpath-2011-200368>
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Borderline and Malignant Phyllodes Tumor Surgery

	Oxford		
	LoE	GR	AGO
▪ Fibroepithelial lesions with rapid growth or size > 3 cm should be excised (independently from the any CNB result)	5	D	++
▪ If the result of the CNB is unclear or suspicious for PT, excision with clear margins should be performed	5	D	++
▪ SLNE / Axillary dissection (if clinically unsuspecting)	4	C	--
▪ Treatment of local recurrence			
▪ R0 resection or simple mastectomy	4	C	++

General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (5.2023). Phyllodes Tumor (Phyll-1)
2. Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
3. Louie AD, Rosenberger LH. Phyllodes Tumors of the Breast: Addressing the Gaps in Consensus Recommendations for Clinical Management. Ann Surg Oncol. 2023 Oct;30(11):6296-6298.
4. Goodwin B, Oyinlola AF, Palhang M et al.. Metastatic and Malignant Phyllodes Tumors of the Breast: An Update for Current Management. Am Surg. 2023 Aug 23;31348231198114.
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6. Sars C, Sackey H, Frisell J et al. Current clinical practice in the management of phyllodes tumors of the breast: an international cross-sectional study among surgeons and oncologists. Breast Cancer Res Treat. 2023 Jun;199(2):293-304.
7. Papas Y, Asmar AE, Ghandour F, Hajj I. Malignant phyllodes tumors of the breast: A comprehensive literature review. Breast J. 2020 Feb;26(2):240-244.
8. Lerwill, M. F., Lee, A. H. S. & Tan, P. H. Fibroepithelial tumours of the breast—a review. Virchows Arch. 480, 45–63 (2022).

Surgical margins: Observational study:

1. Ranjbar A, Zangouri V, Shokripour M. Margin status impact on recurrence of phyllodes tumors in high-risk groups: a retrospective observational study. *BMC Cancer*. 2024 Jan 9;24(1):48.

Surgical margins: Systematic review

1. Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. *Ann Surg Oncol*. 2023 Oct;30(11):6386-6397.
2. Yu C-Y, Huang T-W, Tam K-W: Management of phyllodes tumor: A systematic review and meta-analysis of real-world evidence. *Int J Surg* 2022;107:106969.
3. 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.
4. Lu Y, Chen Y, Zhu L, et al. Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019;90:342–13. doi:10.1245/s10434-018-07134-5.
3. Rosenberger LH, Thomas SM, Nimbkar SN, et al.. Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines. *J Clin Oncol*. 21 Jan 20;39(3):178-189.

Operative management and prognosis of Phyllodes Tumors


1. Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. *Ann Surg Oncol*. 2023 Oct;30(11):6386-6397.
2. 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>
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4. 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>
5. 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>



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Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology

Canadian Phyllodes Tumor Consensus Panel (23 panelists): Example of one out of 109 statements on diagnosis and therapy of phyllodes tumors that were discussed (73 with consensus).

The following statements are referring to MALIGNANT phyllodes (diagnosed on biopsy)

If the diagnosis of malignant PT is known preoperatively, malignant PT should under-go wide excision (clinical 1 cm), with the goal of negative microscopic margins 87%

- In patients with negative margins who undergo wide excision (clinical 1cm) – if the microscopic margin is:
 - < 2 mm: reexcision of margin can be offered 82%
 - 2–10 mm: no re-excision should be offered 65%
 - > 10 mm: no reexcision should be offered 100%
- Patients with tumor on ink after breast conservation, should be offered reexcision (this includes “shelled out” and positive margins) 96%

Bogach J et al. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.

1. Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.

Borderline and Malignant Phyllodes Tumor - Margins -

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Intended lesion-free surgical margins are* <ul style="list-style-type: none"> - in borderline PT: ≥ 2 mm - in malignant PT: ≥ 10 mm 	2b	B	++
<ul style="list-style-type: none"> Intended pathologically lesion-free margins are* <ul style="list-style-type: none"> - in borderline PT: negative („no ink on the tumor“) - in malignant PT: ≥ 2 mm 	2b	B	++
<ul style="list-style-type: none"> Re-resection recommended <ul style="list-style-type: none"> - in borderline PT: if margin* positive („tumor on ink“) - in malignant PT: if margin < 2 mm 	2b	B	++

* Margins related to breast tissue only (but not to skin or to the thoracic wall)

General recommendations / Guidelines:

- Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (5.2023). Phyllodes Tumor (Phyll-1)
- Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
- Louie AD, Rosenberger LH. Phyllodes Tumors of the Breast: Addressing the Gaps in Consensus Recommendations for Clinical Management. Ann Surg Oncol. 2023 Oct;30(11):6296-6298.
- Goodwin B, Oyinlola AF, Palhang M et al.. Metastatic and Malignant Phyllodes Tumors of the Breast: An Update for Current Management. Am Surg. 2023 Aug 23:31348231198114.
- Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. Cancers (Basel). 2023 Aug 2;15(15):3933.
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Surgical margins: Observational study:

1. Ranjbar A, Zangouri V, Shokripour M. Margin status impact on recurrence of phyllodes tumors in high-risk groups: a retrospective observational study. *BMC Cancer*. 2024 Jan 9;24(1):48.

Surgical margins: Systematic review

1. Yu C-Y, Huang T-W, Tam K-W: Management of phyllodes tumor: A systematic review and meta-analysis of real-world evidence. *Int J Surg* 2022;107:106969.
2. Thind A, Patel B, Thind K, et al. Surgical margins for borderline and malignant phyllodes tumours. *Ann R Coll Surg Engl*. 2020;102(3):165-173. doi:10.1308/rcsann.2019.0140.
3. Lu Y, Chen Y, Zhu L, et al. Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019;90:342–13. doi:10.1245/s10434-018-07134-5.
3. Rosenberger LH, Thomas SM, Nimbkar SN, et al.. Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines. *J Clin Oncol*. 21 Jan 20;39(3):178-189.

Operative management and prognosis of Phyllodes Tumors

1. Macdonald, O. K., Lee, C. M., Tward, J. D., et al. (2006). Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. *Cancer*, 107(9), 2127–2133. <http://doi.org/10.1002/cncr.22228>
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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>

Borderline and Malignant Phyllodes Tumor - Adjuvant Radiotherapy -

Adjuvant radiotherapy of the breast and the thoracic wall is aimed at local control.

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ BCS, R0-resection - Borderline PT: no - Malignant PT: yes (independently from the size of the lesion) 	2b	B	+
<ul style="list-style-type: none"> ▪ Mastectomy, R0-resection - Borderline PT: no - Malignant PT: < 5 cm: no - Malignant PT: ≥ 5 cm: with aggressive pathology or growth 	2b	B	+
<ul style="list-style-type: none"> ▪ Mastectomy, R1-resection - Borderline PT: no - Malignant PT: ja (independently from the size of the lesion) 	2b	B	+

General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (5.2023). Phyllodes Tumor (Phyll-1)
2. Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
3. Louie AD, Rosenberger LH. Phyllodes Tumors of the Breast: Addressing the Gaps in Consensus Recommendations for Clinical Management. Ann Surg Oncol. 2023 Oct;30(11):6296-6298.
4. Goodwin B, Oyinlola AF, Palhang M et al.. Metastatic and Malignant Phyllodes Tumors of the Breast: An Update for Current Management. Am Surg. 2023 Aug 23:31348231198114.
5. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. Cancers (Basel). 2023 Aug 2;15(15):3933.
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8. Chen, C., Huang, X., Xu, Y. & Sun, Q. Rethinking on the management strategy of malignant phyllodes tumor of the breast: An analysis based on the SEER database. Medicine 102, e33326 (2023).

Surgical margins: Systematic review

1. Yu C-Y, Huang T-W, Tam K-W: Management of phyllodes tumor: A systematic review and meta-analysis of real-world evidence. *Int J Surg* 2022;107:106969.
2. Thind A, Patel B, Thind K, et al. Surgical margins for borderline and malignant phyllodes tumours. *Ann R Coll Surg Engl*. 2020;102(3):165-173. doi:10.1308/rcsann.2019.0140.
3. Lu Y, Chen Y, Zhu L, et al. Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2019;90:342–13. doi:10.1245/s10434-018-07134-5.
3. Rosenberger LH, Thomas SM, Nimbkar SN, et al.. Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines. *J Clin Oncol*. 21 Jan 20;39(3):178-189.

Operative management and prognosis of Phyllodes Tumors

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

Borderline and Malignant Phyllodes Tumor Systemic Adjuvant Therapy

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Systemic adjuvant therapy (chemo, endocrine) <ul style="list-style-type: none"> ▪ Adjuvant endocrine therapy (irrespect. of ER/PR) ▪ Adjuvant chemotherapy ▪ Primary systemic therapy, if complete resection (R0) presumably cannot be achieved (Adriamycin/Ifosfamid) ▪ Adjuvant Treatment of local recurrence <ul style="list-style-type: none"> ▪ Radiotherapy, chemotherapy after R1 resection ▪ Distant metastasis (very rare) <ul style="list-style-type: none"> ▪ Multidisciplinary case discussion („Sarcoma board“) ▪ Treatment like soft tissue sarcomas ▪ Surgical resection of metastatic lesions 	5	D	-
	4	C	-
	4	C	+
	4	C	+/-
	5	D	++
	4	C	++
	4	C	+

General recommendations / Guidelines:

1. Breast Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). (5.2023). Phyllodes Tumor (Phyll-1)
2. Bogach J, Sriskandarajah A, Wright FC, Look Hong N; Canadian Phyllodes Tumor Consensus Panel. Phyllodes Tumors of the Breast: Canadian National Consensus Document Using Modified Delphi Methodology. Ann Surg Oncol. 2023 Oct;30(11):6386-6397.
3. Louie AD, Rosenberger LH. Phyllodes Tumors of the Breast: Addressing the Gaps in Consensus Recommendations for Clinical Management. Ann Surg Oncol. 2023 Oct;30(11):6296-6298.
4. Goodwin B, Oyinlola AF, Palhang M et al.. Metastatic and Malignant Phyllodes Tumors of the Breast: An Update for Current Management. Am Surg. 2023 Aug 23;31348231198114.
5. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. Cancers (Basel). 2023 Aug 2;15(15):3933.
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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>
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4. Chao X, Chen K, Zeng J, et al. Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer*. 2019;19(1):372. Published 2019 Apr 23. doi:10.1186/s12885-019-5585-5
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Statement: Adjuvant radiotherapy

1. Kim, Y.-J., & Kim, K. (2017). Radiation therapy for malignant phyllodes tumor of the breast: An analysis of SEER data. *Breast (Edinburgh, Scotland)*, 32, 26–32. <http://doi.org/10.1016/j.breast.2016.12.006>
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Statement: Treatment of local recurrence => R0 Resection: References (retrospective analysis , case reports)

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

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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>
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4. Samii E, Hurni Y, Huber D. Management and Outcomes of Metastatic and Recurrent Malignant Phyllodes Tumors of the Breast: A Systematic Literature Review. *Eur J Breast Health*. 2023 Jul 3;19(3):191-200.

Primary Angiosarcoma of the Breast*

Diagnosis

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

* Therapy in specialized centers recommended

Review

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

Imaging


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

1. Wang, L., Lao, I. W., Yu, L., et al. (2016). Primary Breast Angiosarcoma: A Retrospective Study of 36 Cases from a Single Chinese Medical Institute with Clinicopathologic and Radiologic Correlations. *Breast Journal*. <http://doi.org/10.1111/tbj.12731>
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Sarcomas of the Breast

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

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.
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10. Kunkiel, M., Maczkiewicz



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Primary Angiosarcoma of the Breast

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

Reviews

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.
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Sep;28(9):5112-5118.

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 specialized centres recommended

Reviews

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

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Secondary Angiosarcoma of the Breast Therapy

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Tumor resection (BCT / mastectomy) Radical surgery ist not associated with better outcome 	3a	C	+
<ul style="list-style-type: none"> (Neo-)adjuvant chemotherapy <ul style="list-style-type: none"> Consider „trimodality treatment“ in case of locally advanced angiosarcoma (neoadjuvant taxanes => neoadjuvant radiochemotherapy => surgical resektion) 	3a	C	+/-
<ul style="list-style-type: none"> Adjuvant radiotherapy if high risk (size > 5 cm, R1) 	2b	B	+/-
<ul style="list-style-type: none"> Regional hyperthermia (to improve local control) plus chemotherapy and / or radiotherapy 	2b	B	+/-

Review

- Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

Surgery (BEO/mastectomy)

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

1. Degnim AC, Siontis BL, Ahmed SK et al.. Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast. *Clin Cancer Res*. 2023 Aug 1;29(15):2885-2893.

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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Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast (RAASB)

38 patients (median age 69 years) with RAASB; median F/U 5,6 y

- **Trimodality therapy** consisted of
 - (i) taxane induction therapy, followed by
 - (ii) concurrent taxane and irradiation therapy, followed by
 - (iii) surgical resection with wide margins.


Results:

- n = 16 trimodal therapy: pCR 12/16.
Loc.rec.: 0/16; dist.met.: 1/16; death 1/16
Wound break / sec. wound-healing: 100%
- n = 22 monotherapy/dual therapy:
Loc.rec.: 10/22; dist.met.: 8/22; death 7/22
Wound break / sec. wound-healing: 48% (p < 0.001)
- **RFS; 93.8% vs. 42.9%; P = 0.004; HR, 7.6 (95% CI: 1.3-44.2)**

Degnim AC, Siontis BL, Ahmed SK et al. Clin Cancer Res. 2023 Aug 1;29(15):2885-2893.


Trimodality Therapy (Mayo)

1. Degnim AC, Siontis BL, Ahmed SK et al.. Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast. Clin Cancer Res. 2023 Aug 1;29(15):2885-2893.



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Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

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

Review

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

Radiotherapy

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Angiosarcoma of the Breast

Treatment of Local Recurrence and Metastases

	Oxford		
	LoE	GR	AGO
<u>Treatment of Local Recurrence:</u>			
▪ R0 resection	4	C	++
▪ Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)	4	C	+/-
<u>Distant Metastases / Unresectable Tumors:</u>			
▪ Treatment like as for soft tissue sarcomas (according to S3 guideline)	4	C	++
▪ Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)	2b	B	+
▪ Antiangiogenic treatment (e.g. in angiosarcoma)	4	C	+/-
<u>If clinically resistant to therapy</u>			
▪ Molecular diagnostics (Multidisciplinary molecular board)	5	D	+

Review

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

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>
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Molecular Diagnostics if clinically resistant to therapy

1. Esperança-Martins M, Melo-Alvim C, Dâmaso S et al. Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Turning the Magnifying Glass on Rare and Aggressive Entities. *Cancers (Basel)*. 2023 Aug 2;15(15):3933.

Metaplastic Breast Carcinoma - High-Grade -

Consider reference pathology and subtyping.

	Oxford		
	LoE	GR	AGO
▪ Surgical therapy and axillary staging as in case of NST	4	C	++
▪ Neoadjuvant chemotherapy (frequently chemoresistant)*			
▪ ER pos.	4	C	--
▪ ICPI (Pembrolizumab)-basierte PST (TNBC)	4	C	+/-
▪ HER2 pos. (inkl. Anti-HER2-Therapie)	4	C	+
▪ Adjuvant chemotherapy (frequently chemoresistant)	4	C	-
▪ Consider platin/taxane combination in case of mesenchymal differentiation (e.g. spindle cell)	4	C	+
▪ Adjuvant endocrine therapy if HR-positive	4	C	+
▪ Adjuvant radiotherapy according therapy of NST	4	C	++

* Note: control of local response in short intervals

Therapy review:

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2. Thomas, A., Douglas, E., Reis-Filho, J. S., Gurcan, M. N. & Wen, H. Y. Metaplastic Breast Cancer: Current Understanding and Future Directions. Clin. Breast Cancer (2023)
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Metaplastic Breast Cancer Treatment and Outcomes in 2500 Patients: A Retrospective Analysis of a National Oncology Database. *Ann Surg Oncol*. 2018 Aug;25(8):2249–2260. PMID: PMC6039971

Surgery

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Axilla

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Adjuvant chemotherapy

1. Tzanninis I-G, Kotteas EA, Ntanasis-Stathopoulos I, et al. Management and Outcomes in Metaplastic Breast Cancer. *Clinical breast cancer*. 2016 Dec;16(6):437–443. PMID: 27431460
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evaluated)

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Neoadjuvant chemotherapy

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Metaplastic Breast Carcinoma – Low Grade With Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)*

	Oxford		
	LoE	GR	AGO
▪ Surgical therapy and axillary staging as in case of NST	4	C	++
▪ Adjuvant chemotherapy (frequently chemoresistant)	4	C	-
▪ Neoadjuvant chemotherapy (frequently chemoresistant)	4	C	--
▪ Adjuvant endocrine therapy (not applicable, since triple-negative tumors)	4	C	-
▪ Adjuvant radiotherapy according therapy of NST	4	C	+

* Reference pathology recommended

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Metaplastic Breast Cancer

Definition: Metaplastic transformation of epithelial tumor cells

- Epithelial differentiation: squamous cell carcinoma, spindle-cell carcinoma
- Heterologous (mesenchymal) differentiation: chondroid, osseous or otherwise metaplastic breast cancer

Clinical and pathological characteristics:

- < 1 % of malignant breast neoplasms
- Similar age group as NST breast cancer
- Localized, mostly palpable
- Rapidly growing, poor response to chemotherapy
- > 90 % triple-negative

Subtypes:

- Highly aggressive with squamous cell or high-grade spindle-cell differentiation
- Less aggressive (low-grade) with mesenchymal, low grade adenosquamous or fibromatosis-like differentiation

Frequent mutations:

- *TP53, EGFR, PIK3CA, PTEN*
- Possible association to *gBRCA1*-mutation/HRD-positivity

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