Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

In collaboration with:

Oncoplastic and Reconstructive Breast Surgery

Oncoplastic and Reconstructive Breast Surgery

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In collaboration with:

- **Versions 2002–2023:**
  Audretsch / Bauerfeind / Blohmer / Brunnert / Dall / Ditsch / Fersis / Friedrich / Gerber / Hanf/ Heil / Kühn / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Solbach / Thill / Thomssen / Wöckel

- **Version 2024:**
  Banys-Paluchowski / Solbach

Definition of oncoplastic surgery

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Use of plastic surgical techniques at the time of tumor removal to improve aesthetic and quality of life outcomes without compromising oncological safety.

Focus on favorable scar placement, adequate soft tissue formation, choice of a suitable reconstructive technique (taking radiation therapy into consideration) and contralateral symmetrization.

Classifications

1. Hoffmann / Wallwiener (2009):
Classification by reconstructive surgery complexity with respect to breast conservation and mastectomy

2. Clough et al. (2010):
Oncoplastic classification for breast conservation according to relative resection volume: Level 1: < 20 % of breast volume resection („simple oncoplastic surgery“) and Level 2 > 20 % of breast volume resection with quadrant per quadrant techniques of mastopexy

3. American Society of Society of Breast Surgeons (2019):
Level 1: < 20% breast tissue removed; Level 2: 20–50% of breast tissue removed; Volume replacement: > 50% of breast tissue removed

Hoffmann D et al., BMC 2009; Clough KB et al., Ann Surg Oncol 2010; Chatterjee A et al. Ann Surg Oncol 2019

Oncoplastic Breast-Conserving Surgery (OPS)

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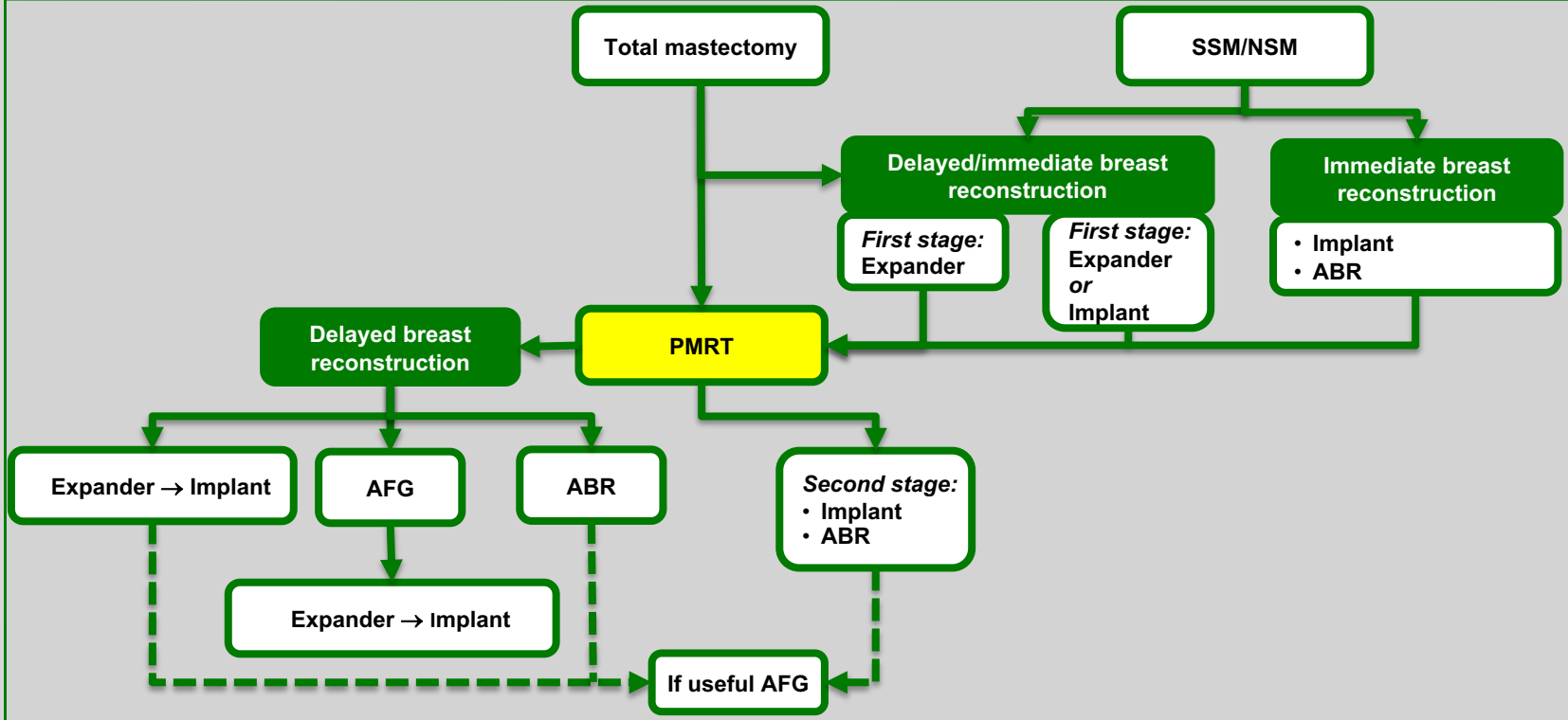
In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ OPS may replace mastectomy in selected patients	2b	B	+
▪ also in case of multicentric / multifocal tumors	2b	B	+
▪ OPS and BCS have equivalent oncological safety	2a	B	++
▪ Complication rates of OPS and BCS are similar	2a	B	+/-

Options for Breast Reconstruction When Radiotherapy is Planned

For patients who ask for breast reconstruction and are scheduled to undergo radiotherapy*



*Influencing factors: tumor related factors, breast size/shape, skin flap, previous surgery/RT, BMI, comorbidities, patient wishes, physical activities, oncological situation; ABR, autologous breast reconstruction; AFG, autologous fat grafting; PMRT, post mastectomy radiotherapy; SSM/NSM, skin sparing/nipple sparing mastectomy

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Breast Reconstruction Principles
Good Clinical Practice

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AGO: ++

- **Planning of breast reconstruction by interdisciplinary tumor board before mastectomy**
- **Counseling regarding all surgical techniques, including advantages and disadvantages**
- **Preference for autologous reconstruction after radiotherapy or if radiotherapy is planned**
- **Offer second opinion**
- **Discussion of neoadjuvant treatment (if indicated based on tumor biology) in case of unfavorable breast-tumor relation**
- **Consideration of contralateral breast:**
  - **Discuss symmetrization procedures**
- **Preference for less radical surgical technique with stable long-term aesthetic result (prefer BCS / OPS over mastectomy)**
- **Avoid delay of adjuvant therapy due to reconstruction**
- **Assessment of outcome, e.g. Patient Reported Outcome (PRO)**
- **Oncologic safety is not impaired**

Mastectomy and Reconstruction Options

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	Oxford		
	LoE	GR	AGO
▪ Heterologous reconstruction *	2a	B	+
▪ Autologous reconstruction	2a	B	+
▪ Pedicled flap reconstruction	2a	B	+
▪ Free flap reconstruction (including vascular anastomoses)	2a	B	+
▪ Autologous reconstruction combined with implant placement	3a	C	+/-

Caveat: BMI > 30, smoking, diabetes, radiotherapy, age, bilateral mastectomy

*** Documentation in implant registry**

Germany: https://www.bundesgesundheitsministerium.de/implantateregister-deutschland,
Mandatory documentation of breast implants in the Medical Implants Registry begins on 1st July 2024

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Timing of Reconstruction

	Oxford		
	LoE	GR	AGO
▪ Immediate breast reconstruction	3b	B	++
▪ Prevention of postmastectomy syndrome			
▪ Delayed breast reconstruction (2-step)	3b	B	++
▪ No interference with adjuvant (CHT, RT)			
▪ Disadvantage: loss of skin envelope			
▪ „Delayed-immediate“ breast reconstruction (placeholder before definitive reconstruction)	3b	B	+

Timing of Implant-Based Reconstruction and Radiotherapy

	Oxford		
	LoE	GR	AGO
▪ **Implant reconstruction**	2a	B	+
▪ **without radiotherapy**	2a	B	++
▪ **prior to radiotherapy**	2a	B	+
▪ **following radiotherapy**	2b	B	+/-
▪ **following secondary mastectomy after breast-conserving therapy**	2a	B	+/-

Antibiotics and Breast Reconstruction

	Oxford		
	LoE	GR	AGO
Heterologous reconstruction:			
▪ Perioperative antibiotic prophylaxis (max. 24 h)	1a	A	+
▪ Extended antibiotic prophylaxis > 24 h	2a	B	+/-
Autologous reconstruction:			
▪ Perioperative antibiotic prophylaxis (max. 24 h)	2b	B	+
▪ Extended antibiotic prophylaxis > 24 h	2a	B	+/-

Tranexamic Acid in Complex Breast Surgery

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In collaboration with:

	Oxford		
	LoE	GR	AGO
Prevention of:			
▪ **Hematoma**	2a	B	+/-
▪ **Seroma**	2a	B	+/-
No increased risk for thromboembolic complications in patients without history of thromboembolic events	2a	B	+

CAVE: Dosage and application routes (local, i.v., oral) differ between studies, consider history of thromboembolic events

Breast Implant-associated Diseases

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In collaboration with:

BIA-ALCL = Breast implant-associated anaplastic large cell lymphoma

BIA-SCC = Breast implant-associated squamous cell carcinoma

SSBI = Systemic Symptoms Associated with Breast Implants

Synonyms:

Breast Implant Illness (BII); Autoimmune syndrome induced by adjuvants (ASIA); Shoenfeld's syndrome; Silicone implant incompatibility syndrome (SIIS)

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)

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- Peripheral non-Hodgkin's T-cell lymphoma arising around a textured breast implant or in a patient with a history of a textured surface device
- Number of global cases reported as MDR (medical device regulation) to the FDA by 30.06.2023: 1264 with 63 deaths
- Approximately 35,000,000 implant carriers worldwide
  (According to a survey by the International Society of Aesthetic Plastic Surgeons (ISAPS) 2023: 2,174,616 augmentations worldwide were performed)
- Prevalence and incidence vary greatly, as the number of women with implants can only be estimated
- The current lifetime risk ranges between 1:355 and 1:86,029 patients with textured implants
- Time interval between last implantation and lymphoma diagnosis: 8 years (median)
- 5-year-OS 89-92 %
- Clinical presentation
  - Frequently periprosthetic seroma, breast asymmetry
  - in rarer cases tumor, regional lymphadenopathy, skin rash and/or capsular contracture
- Tumor cells are CD30-positive / ALK-negative
- Obligation to notify the BfArM as SAE according to §3 MPSV*

* Germany: BfArM https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html

BIA-ALCL – Diagnosis

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound (assessment of new seromas > 1 year after implant placement, solid lesions, axillary lymph nodes)	3a	D	++
▪ Cytology of late seromas ▪ Assessment of min. 50 ml ▪ Complete assessment incl. BIA-ALCL specific cytologic diagnostic (CD 30+) ▪ Flow cytometry (T-cell clone)	3a	D	++
▪ Core needle biopsy of solid lesions	3a	D	++
▪ Breast-MRI in confirmed cases	3a	D	++
▪ Staging (PET-CT, alternatively: CT [neck, chest, abdomen, pelvis])	3a	D	++
▪ Lymphoma assessment in resected tissue and histologic staging	3a	D	++
▪ Documentation of the implant in the Implant Registry *	5	D	++

* Germany: https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html

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BIA-ALCL – Therapy

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	Oxford		
	LoE	GR	AGO
▪ Case discussion in a multidisciplinary tumor board in the presence of a lymphoma specialist	5	D	++
▪ Implant resection and complete capsulectomy including tumorectomy	3a	C	++
▪ Contralateral implant removal and capsulectomy in case of bilateral implants (4-6% bilateral BIA-ALCL)	4	D	+/-
▪ Resection of suspicious lymph nodes, no routine use of sentinel node biopsy or axillary lymph node dissection	4	D	++
▪ Systemic therapy depending on disease stage	4	D	+
▪ Radiotherapy in unresectable tumors	5	D	+/-

BIA-ALCL Treatment Pathways

Outcome

- BIA-ALCL confirmed
- Indeterminate
  - Options: Further imaging US / MRI / Repeat biopsy, Tertiary referral
- Negative for BIA-ALCL
  - Treatment of infection / benign seroma (serial aspiration, implant exchange with capsulectomy)

Workup

- Referral to experienced breast cancer center
- PET-CT & breast MRI
- Routine bloods (+/- bone marrow bx)
- MTD Discussion
- Clinical suspicion remains
  - Consider diagnostic capsulectomy

Surgery

- En-bloc capsulectomy and complete excision (mass)
- +/- other breast +/- axilla biopsy (SNB not recommended)
- Histological Staging (Clemens et al. 2016)
- MTD Discussion
- Reports to BfArM (Germany), manufacturers, PROFILE registry (USA); MedWatch (FDA)

Adjuvant Therapy

- Stage I : No further treatment
- Stage II - IV: Consider adjuvant treatment
- Chemo-immunotherapy
- Radiotherapy for positive margins / irresectable thoracic wall infiltration but N0/M0

Follow-up

- Clinical follow-up (ultrasound / CT scan) 3–6 m for 2 y, afterwards for 5 y
- PET-CT if symptomatic

Treatment as per systemic ALCL regimes

24-36 Gy in 15 fractions

TNM Staging of BIA-ALCL

	TNM-Kategorie	Definition
Tumor extent (cT/pT)	T1	Confined to seroma or a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
Regional lymph nodes (cN/pN)	N0	No lymph node involvement
	N1	One regional lymph node positive
	N2	Multiple regional lymph nodes positive
Metastasis (cM/pM)	M0	No distant spread
	M1	Spread to other organs or distant sites

Stage	Definition
IA	T1 N0 M0
IB	T2 N0 M0
IC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	T any N any M1

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Breast Implant Capsule-Associated Squamous Cell Carcinoma

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In Zusammenarbeit mit:

- By March 22, 2023, the FDA had reported 19 cases of BIA-SCC; 21 cases were described up to 5/2023 (J Surg Oncol. 2023;128(4):495-501)
- BIA-SCC occurred approximately 7 to 42 years after initial implant placement (median time 18 years) in aesthetic and reconstructive cases
- BIA-SCC was located in the capsule around the breast implant, often in the posterior aspect
- There is not a consistent type of implant (textured vs. smooth), content (silicone vs. saline), or location (subglandular vs. retropectoral) that is associated with BIA-SCC
- Periprosthetic fluid should be sent for CK5/6 and p63, should be rich in keratin and cytology should display abnormal squamous cells
- Initial presentation with breast pain, erythema and swelling
- Overall poorer prognosis
  - 7/21 cases had recurrent cancer within 12 months after definitive resection
  - in a review of 18 cases the estimated 12-month mortality rate was 23.8% (calculated from 10 cases with survival data reported)
- In this limited cohort it is difficult to ascribe prognostic factors, but extracapsular extension does appear to be a concerning finding.

Systemic Symptoms Associated with Breast Implants = SSBI

Breast Implant Illness (BII); Autoimmune syndrome induced by adjuvants (ASIA); Shoenfeld's syndrome; Silicone implant incompatibility syndrome (SIIS);

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In Zusammenarbeit mit:

- Summarize a variety of systemic symptoms that have been reported by some women following reconstruction or augmentation with breast implants, independent of the type of implant, filling, shape or surface characteristics, with an onset anywhere from immediately after implantation to years later

- The most frequent systemic symptoms reported in the FDA MDR database (sorted by frequency more to less common):

>40%	Fatigue
>30%	Joint pain
>20%	Brain fog, Autoimmune diseases, Hair loss
10-20%	Depression, Rash, Headache, Weight changes

- Currently SSBI are not recognized as a formal medical diagnosis
- SSBI remain a diagnosis of exclusion, there are no specific tests or defined criteria to characterize it
- Any persistent symptoms reported by patients with breast implants should be evaluated for other medical diseases prior to consider implant removal surgery
- Breast implant explantation can show significant improvement of systemic complaints as well as improvement of overall quality of life

BIA-ALCL – EUSOMA-Recommendation

- **Despite an increase of BIA-ALCL in association with textured implants the use of textured implants is still permitted!**

„For the moment, textured implants can safely continue to be used with patient's fully informed consent, and that women that have these type of implants already in place don't need to remove or substitute them, which would undoubtedly cause harm to many tens of thousands of women, to prevent an exceptionally rare, largely curable and currently poorly understood disease."

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Implant Position, Meshes and ADMs in Implant-Based Reconstruction: Outcome QoL / Complication Rate

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ **Insufficient evidence to conclude superiority of the prepectoral or subpectoral approach**	3a	C	+/-
▪ **Acellular dermal matrix (ADM)**			
▪ **subpectoral**	1b	A	+/-
▪ **prepectoral**	2b	B	+/-
▪ **Synthetic meshes**			
▪ **subpectoral**	2b	B	+/-
▪ **prepectoral**	2b	B	+/-

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In collaboration with:

Lipotransfer

	Oxford		
	LoE	GR	AGO
▪ Lipotransfer following mastectomy and reconstruction	2a	B	+
▪ Lipotransfer after breast-conserving therapy	2a	B	+
▪ Autologous adipose derived stem cells (ASCs)-enriched fat grafting vs. without stem cells	2a	B	+/-

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In collaboration with:

Pedicled Flap Reconstruction

	Oxford		
	LoE	GR	AGO
▪ TRAM, latissimus dorsi flap (both can be performed as muscle-sparing techniques)	2a	C	+
▪ Delayed TRAM in high-risk patients	3a	B	+
▪ Ipsilateral pedicled TRAM	2a	B	+
▪ Omentum Flap	4	C	+/-
▪ Radiotherapy:			
▪ Breast reconstruction following radiotherapy	2a	B	+
▪ Breast reconstruction prior to radiotherapy	2a	B	+/-

(higher rates of fibrosis, wound healing disorders, liponecrosis and reduced aesthetic outcome)

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In collaboration with:

Free Flaps for Reconstruction

	Oxford		
	LoE	GR	AGO
▪ **DIEP** (deep inferior epigastric artery perforator)	2a	B	+
▪ **Free TRAM** (transverse rectus abdominis myocutaneus)	2a	B	+
▪ **SIEA** (superficial inferior epigastric artery)	3a	C	+/-
▪ **Glutealis flaps (SGAP** [superior gluteal artery perforator] / **IGAP** [inferior gluteal artery perforator]**, FCI** [fasciocutaneous infragluteal])	4	C	+/-
▪ **Free gracilis flap (TMG,** transverse myocutaneous gracilis**)**	4	C	+/-
▪ **PAP** (profunda artery perforator)	2b	B	+/-
▪ **Omentum Flap**	4	C	+/-
Use of ICG* to assess flap perfusion	2a	B	+

Advantages

- **DIEP and free TRAM are potentially muscle-sparing procedures. DIEP has a lower rate of abdominal hernias, especially in obese patients**

Disadvantages

- **Time- and personnel consuming microsurgical procedures, intensified postoperative monitoring**

* **ICG: indocyanin green**

Pedicled versus Free Tissue Transfer

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In collaboration with:

Oxford		
LoE	GR	AGO
3a	A	++

- **Muscle-sparing techniques and accuracy of abdominal wall closure lead to low rates of late donor site complications independent of method used**
- **Autologous abdominal-based reconstructions have highest satisfaction rates (PROM)**
- **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration with all flap techniques**

Skin-/ Nipple-Sparing Mastectomy (SSM / NSM) and Reconstruction

	Oxford LoE	Oxford GR	AGO
Skin-/nipple-sparing Mastectomy (SSM / NSM)			
Oncologically safe (equivalent recurrence rate as in total mastectomy in suitable patients)	2b	B	++
Higher QoL	2b	B	++
NAC can be preserved under special conditions	2b	B	++
Feasible after mastopexy / reduction mammoplasty	4	C	++
Use of ICG* to predict skin necrosis	1b	B	+
Skin incisions → different possibilities:			
Periareolar			
Hemi-periareolar with / without medial / lateral extension			
Reduction pattern: „inverted-T“ or vertical			
Inferior lateral approach, inframammary fold			
Lowest incidence of complications	2b	B	+

* ICG = Indocyanine Green

Mastectomy + Reconstruction

Risk of complications with the addition of radiotherapy

Autologous reconstruction		Implant-based reconstruction	
Endpoint	**Risk Ratio with addition of radiotherapy (95%-CI)**	**Endpoint**	**Risk Ratio with addition of radiotherapy (95%-CI)**
Wound infection	1.14 (NA)	Wound infection	2.49 (1.43,4.35)
Secondary surgery	1.62 (1.06, 2.48)	Secondary surgery	1.64 (1.17-2.31)
Reconstructive failure	0.80 (NA)	Reconstructive failure	2.89 (1.30,6.39)
Volume loss	8.16 (4.26,15.63)		
Fat necrosis	1.91 (1.45, 2.52)		
		Capsular contracture	5.17 (1.93,13.80)
		ME skin flap nekrosis	1.62 (1.27, 2.08)
		Implant extrusion	3.44 (2.18, 5.43)

Further risks of autologous reconstruction:
Distorsion of breast shape, fibrosis, vascular complications
Autologous reconstruction is favored in terms of patient satisfaction and and assessment of the aesthetic outcome.

NA: not available

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Prevention and Therapy of Capsular Contracture

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In collaboration with:

	Oxford LoE	Oxford GR	AGO
Prevention			
Textured implantats (Caveat: BIA-ALCL)	1a	A	+
Acellular Dermal Matrix (ADM) vs. nil	2a	B	+
Synthetic mesh vs. nil	3a	C	+
Topical antibiotics / antiseptics	2a	B	+
PVP (Povidone-Iodine)	2a	B	+/-
Leukotriene-antagonists	2a	B	+/-
Breast massage	3a	C	-
Surgical interventions			
Capsulectomy	3b	C	+
Capsulotomy (Caveat: exclusion of BIA-ALCL)	3b	C	+

Seroma after Implant-Based Reconstruction I

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	Oxford	
	LoE	GR
▪ Incidence: approx. 5-10 % (2-50 %)	2a	B
Influencing factors:		
▪ History of radiation increases risk (RR approx. 3)	2a	B
▪ Obesity increases risk (e.g. BMI > 30 vs. < 30; RR approx. 3)	2a	B
▪ Use of ADM increases risk (RR approx. 3)	2a	B
▪ Use of expander with smooth surface increases risk (RR approx. 5)	3b	C
▪ History of neoadj. chemotherapy does not appear to increase risk	2a	B
▪ Prepectoral approach does not appear to increase risk	2b	B

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Seroma after Implant-Based Reconstruction II

	Oxford		
	LoE	GR	AGO
Prevention			
▪ Drain	3b	C	+
▪ Drain removal at < 30ml per 24 hours	2b	B	+
Therapy			
▪ Evacuation of serma by FNA or re-insertion of drain	4	C	+
▪ Pressure dressing	5	D	+/-
▪ Revision surgery with capsulectomy (ultima ratio)	5	D	+
▪ Revision surgery with implant removal (ultima ratio)	5	D	+

Skin necrosis after mastectomy

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In collaboration with:

	Oxford		
	LoE	GR	AGO
Prevention			
▪ Local nitroglycerin *	1a	A	+
▪ Closed-incision negative pressure therapy (ciNPT)	2a	B	+/-
▪ Local dimethylsulfoxid	2b	B	+/-
▪ Oral cilostazol	2b	B	+/-
▪ Preoperative local heat preconditioning	2b	B	+/-

* Dose and regimen vary between studies, off-label

Efficacy and safety of topical nitroglycerin in the prevention of mastectomy flap necrosis – a systematic review and meta-analysis

Wang P et al. Sci Rep 2020

- 7074 patients (3 randomized clinical trials, 2 retrospective cohort studies)
- Intervention: transdermal nitroglycerin treatment (ointment; 4.5-45 mg nitroglycerin, applied immediately after end of surgery and in some studies in the first postoperative period until day 6)
- Nitroglycerin significantly reduced the mastectomy flap necrosis rate (immediate breast reconstruction [IBR]: OR, 0.48, 95% CI, 0.33–0.70, P < 0.01)
- Full-thickness flap necrosis rate in patients receiving IBR was significantly lower in the nitroglycerin group than in the control group (OR, 0.42; 95% CI, 0.25–0.70; P < 0.01)

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Siliconomas

- In breast parenchyma or regional lymph nodes, rarely in distant organs (pleura, ribs, muscles)
- Incidence unclear
- May occur with or without implant rupture (“silicone bleeding”)
- Migration of silicone to the lymph nodes takes 6-10 years
- Risk of malignancy is not increased

	Oxford		
	LoE	GR	AGO
▪ Asymptomatic siliconomas do not require removal	2b	B	+
▪ Complete removal of implant and silicone gel (in capsule, if possible) in case of implant rupture	2b	B	+

Surgical Prevention

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing unilateral or bilateral mastectomy (RRME) without the presence of clearly defined genetic risk factors	2a	B	-*
▪ Axillary dissection or Sentinel lymph node excision during RRME	2a	B	--

* study participation recommended

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

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In collaboration with:

	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ Reduces OvCa incidence and mortality			++*
▪ Reduces overall mortality			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ Reduces BC incidence	2b	B	+*
▪ Reduces BC mortality in *BRCA1* mutation carriers***	2b	B	+*

* Study participation recommended

** The RR-BSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.

*** No reduction in mortality could be shown for BRCA2 mutation carriers. RRBM counselling should be individualised.

Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM)*	2b	B	+*
▪ Reduces BC incidence and mortality			
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended
** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age