Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Oncoplastic and Reconstructive Surgery

Plastic-reconstructive aspects after mastectomy

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- **Versions 2002–2019:**
  Audretsch / Bauerfeind / Blohmer / Brunnert / Dall / Ditsch / Fersis / Friedrich/ Gerber / Hanf / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Solbach / Thomssen

- **Version 2020:**
  Blohmer / Kühn

Definition of oncoplastic surgical procedures

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Use of plastic surgical techniques at the time of tumor removal to enable safe resection margins and to preserve aesthetic breast contour.

Focus on favorable scar placement, adequate soft tissue formation, choice of proper reconstruction procedure (including in the context of radiation) and reconstruction of the contralateral side to achieve symmetric results.

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Oncoplastic Breast Conserving Surgery

	Oxford		
	LoE	GR	AGO
▪ Tumor-adapted reduction mammaplasty	2a	B	+
▪ Local flap techniques	2a	B	+
▪ Partial mastectomy with tissue transfer	3b	B	+/-

Algorithm of Breast Reconstruction

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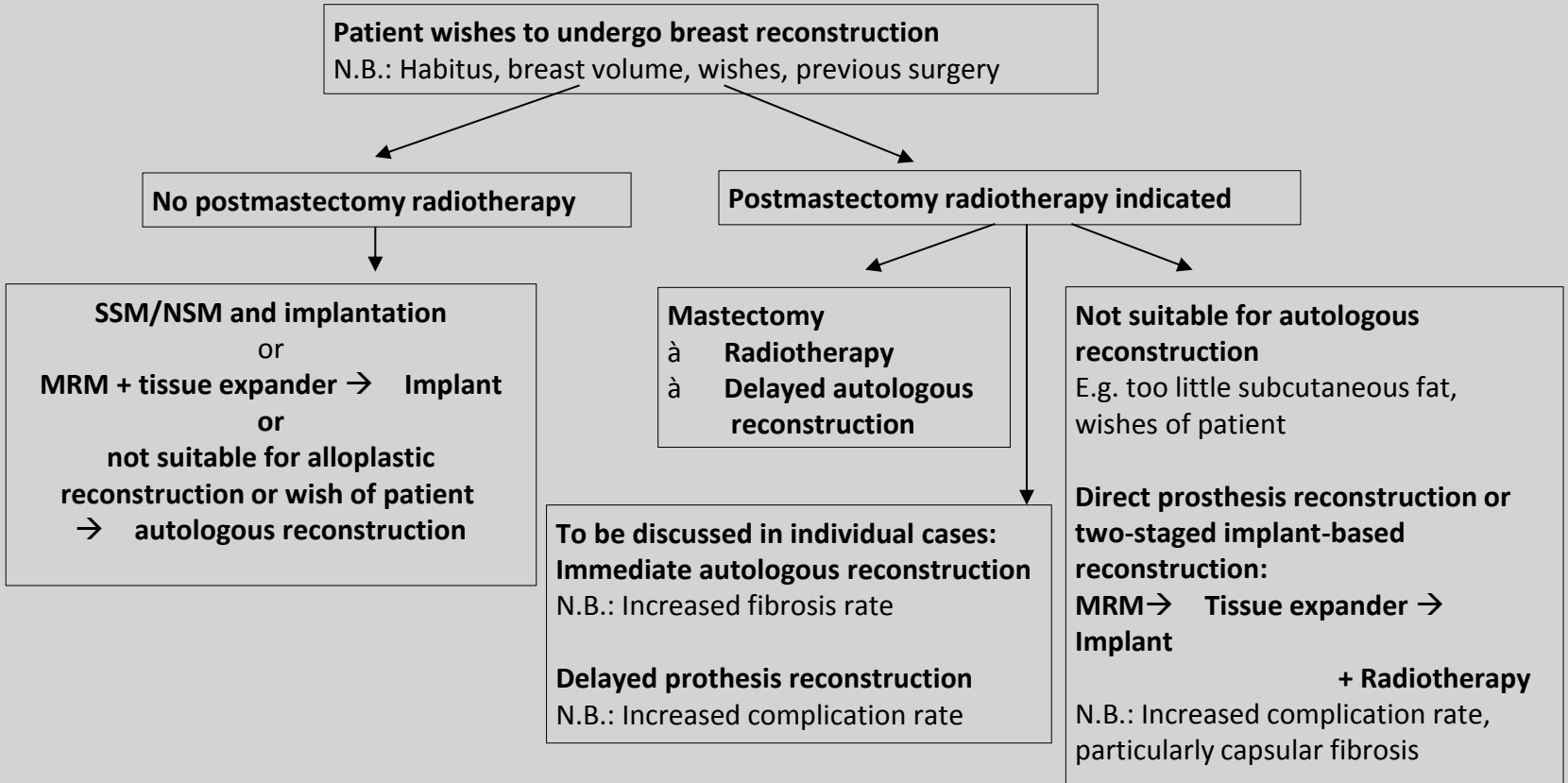

Breast Reconstruction Principles - AGO: ++

- Planning of reconstructive procedure by interdisciplinary tumor board before mastectomy
- Counseling regarding all surgical techniques, including advantages and disadvantages
- Offer second opinion
- Discussion of neoadjuvant treatment if unfavorable tumor-breast-relation
- Consideration of contralateral breast;
  - discuss possible alignment / sequencing surgical procedures to produce symmetry; usually after at least 3-6 months (Caveat: need for post-resections, consider effects of radiotherapy for affected side)
- Preference for less stressful surgical technique with stable long-term esthetic result (prefer BCS over mastectomy)
- Avoid delay of adjuvant therapy due to reconstruction
- Assessment of outcome (e.g. PROM)
- Oncologic safety is not impaired

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Postmastectomy Reconstruction

	Oxford		
	LoE	GR	AGO
▪ Use of silicone gel filled breast implants one step or two steps after expander	2a	B	+
▪ Safety comparable to saline implants	2b	B	
▪ Autologous tissue reconstruction	2a	B	+
▪ Pedicled tissue reconstruction	2a	B	+
▪ Free tissue reconstruction (including vascular anastomoses)	2a	B	+
▪ Autologous tissue procedure plus implants	3a	C	+

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

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Timing of Reconstruction

	Oxford LoE	Oxford GR	AGO
▪ **Immediate Breast Reconstruction**	3b	B	++
▪ Mandatory: SSM/NSM			
▪ Avoidance of a postmastectomy syndrome			
▪ **Delayed Breast Reconstruction**	3b	B	++
▪ No interference with adjuvant procedures (CHT, RT)			
▪ Disadvantage: loss of skin envelope			
▪ **„Delayed-immediate“ Breast Reconstruction**	3b	B	+/-

Timing of implant Based Reconstruction and Radiotherapy

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	Oxford		
	LoE	GR	AGO
▪ Implant Reconstruktion (IR)	2a	B	+
▪ IR without radiotherapy	2a	B	++
▪ IR prior to radiotherapy	2a	B	+
▪ IR following radiotherapy	2b	B	+/-
▪ IR following secondary mastectomy (after BCS* with radiotherapy)	2a	B	+/-
▪ Perioperative antibiotic prophylaxis (at least 24 hours)	2b	B	+

* BCS: Breast Conserving Surgery

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Radiotherapy and Implant-based Reconstruction

Caveat: High complication rate in combination with radiotherapy (capsular contracture, revision surgery, reconstruction failure, reduced cosmetic outcome and patient satisfaction)

Caveat: Lower patient satisfaction with implant-based reconstruction plus radiotherapy compared to autologous reconstruction plus radiotherapy

LoE 2b B

Possible Associations between Implants and rare Diseases

- **US FDA Breast Implant Postapproval Studies (LPAS)**
  Long-term Outcomes in 99,993 Patients
  (Primary Augmentation: N= 71.937 / Primary Reconstruction: N= 9942)
  - 56% of implants were silicone implants
- **Possible Associations:**
  - **Sjogren syndrome: (SIR*8.14)**
  - **scleroderma: (SIR 7.00)**
  - **rheumatoid arthritis: (SIR5.96)**
  - **stillbirth: (SIR4.50)**
  - **melanoma: (SIR3.71)**
- **At 7 years, reoperation rate is 11.7% for primary augmentation, and 25% for primary/revision reconstruction.**
- **One case of BI-ALCL**

Associations need to be further analyzed with patient-level data to provide conclusive evidence !

***Standardized incidence ratio**

Possible Associations between Implants and rare Diseases

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Rare Systemic Harms Compared With the General Population:

	Manufacturer [y]	Study Events	Study Event Rate (Per 10,000 Person Yr)	General Population Event Rate (Per 10,000 Person Yr)	SIR	SIR 95% CI	P Value
Fibromyalgia	Allergan	9	1.8	112.8	0.02	0.01–0.03	<0.001
	Mentor	307	28.4	112.8	0.25	0.22–0.28	<0.001
Rheumatoid arthritis	Allergan	4	0.8	5.4	0.15	0.04–0.38	<0.001
	Mentor	349	32.2	5.4	5.96	5.35–6.62	<0.001
Scleroderma	Mentor	46	4.2	0.6	7.00	5.12–9.34	<0.001
Sjogren syndrome	Mentor	62	5.7	0.7	8.14	6.24–10.44	<0.001
Systemic lupus erythematosus	Allergan	3	0.6	5.4	0.11	0.02–0.32	<0.001
	Mentor	66	6.0	5.4	1.11	0.86–1.41	0.398
Cancer	Allergan	80	16.0	41.3	0.39	0.31–0.48	<0.001
	Mentor	532	63.8	41.3	1.54	1.42–1.68	<0.001
Breast cancer	Mentor	116	13.9	12.5	1.11	0.92–1.33	0.26
Lung cancer	Mentor	5	0.6	5.2	0.12	0.04–0.27	<0.001
Brain cancer	Mentor	3	0.4	0.6	0.67	0.14–1.95	0.639
Melanoma	Mentor	65	7.8	2.1	3.71	2.87–4.73	<0.001
Neurological disorder	Allergan	18	3.6	22.5	0.16	0.09–0.25	<0.001
	Mentor	394	35.8	22.5	1.59	1.44–1.76	<0.001
Multiple sclerosis	Mentor	47	4.3	2.5	1.72	1.26–2.29	0.001
Myositis	Mentor	17	1.5	0.8	1.88	1.09–3.00	0.018

Allergan follow-up 2 years
Mentor follow-up 7 years

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

- **Rare disease, 3 % of Non-Hodgkin Lymphomas, 0.04-0.5 % of all malignant breast diseases**
- **Estimated incidence 0.6-1.2 / 100.000 women with implants (median age: 54 y)**
- **Mainly associated with textured implants**
- **Interval to diagnosis: 8 years (median)**
- **Clinical symptoms**
  - **Swelling and seroma. (60 %)**
  - **Solid tumor (17 %)**
  - **Seroma and solid tumor (20 %)**
- **Histology: CD30+ / ALK-T-Cell Lymphoma**
- **Compulsory registration as SAE (§3 MPSV to BfArM)**

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BIA-ALCL - Surfaces of Breast Implants

- The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface. **The risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces.**

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/ Nano
Surface Area	high	intermediate	intermediate	low	low	minimal
Roughness	high	intermediate	low	low	low	minimal
SURFACE TYPE	4	3	3	2	2	1

BIA-ALCL– Diagnosis

	Oxford LoE	Oxford GR	AGO
▪ **Breast US (assessment of new seromas > 1 year after implant insert, solid lesion)**	3a	D	++
▪ **Mamma-MRT in confirmed cases**	3a	D	++
▪ **Staging (Imaging, e.g. CT, PET-CT)**	3a	D	++
▪ **Cytology of late seromas** ▪ **- > 50 ml** ▪ **- Complete assessment** ▪ **- flow-cytology (T-cell clone)** ▪ **- BIA-ALCL specific cytologic diagnostic (CD 30+)**	3a	D	++
▪ **Core needle biopsy in solid lesions** ▪ **Lymphoma assessment of resected tissue and histologic staging**	3a	D	++
▪ **Documentation of the implant** (manufacturer, size, volume, surface, Batch-number) **and enter in registry**	5	D	++

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BIA-ALCL – Therapy

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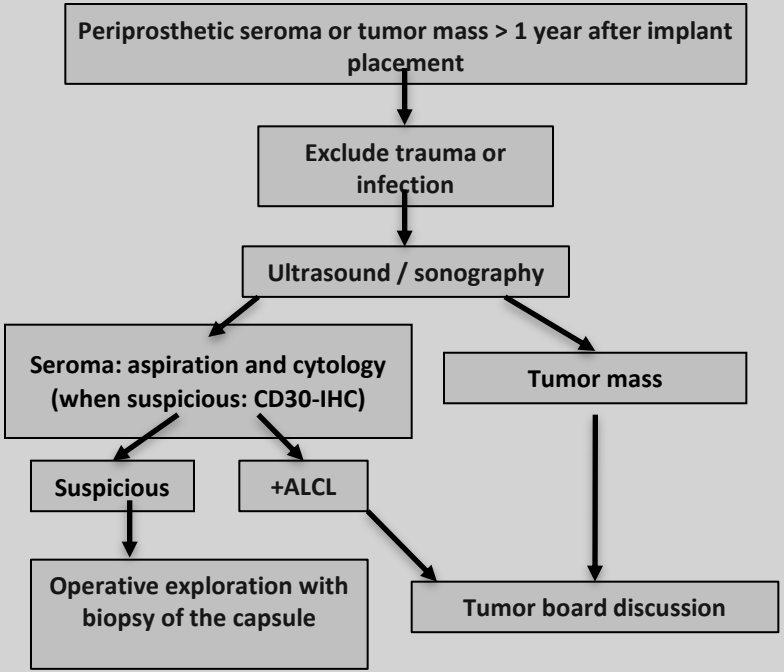
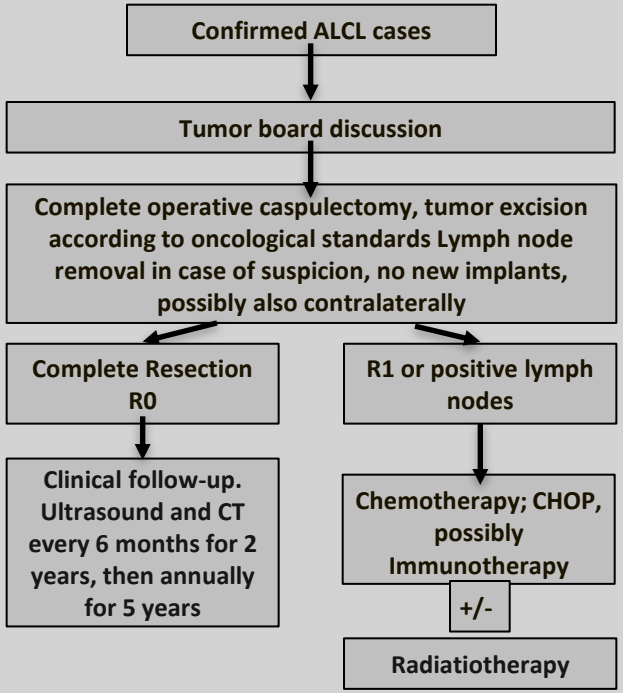
	Oxford		
	LoE	GR	AGO
▪ Implant resection and complete capsulectomy including tumorectomy	3a	C	++
▪ Resection of suspicious lymph nodes, no routine use of Sentinel-Node-Biopsy, no axillarx dissection	4	D	++
▪ Polychemotherapy (e.g. CHOP) in cases of extra capsular extension	4	D	+
▪ Radiotherapy in unresectable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

Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)
- Summary of the Management (acc. to Noah 2017) -





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Stage Adapted Therapy of BIA-ALCL

TNM	Description
T= tumor extent T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggreates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
N= lymph node N0	No lymph node involvement
N1	One regional lympho nodes positive
N2	Multiple regional lymph nodes positive
M= metastasis M0	No distant spread
M1	Spread to other organs /distant sides

IA-IC/(IIA): surgical **complete resection** of capsula, implant, suspected nodular lesions and, only if suspicious, regional lymph nodes
no indication for mastectomy, sentinel node exstirpation or axillary dissection

IIA/IIB-IV: 2-18%

- surgical complet resection (see above)
- **CHO(E)P** (Cyclophosphamide, Vincristin, Doxorubicin,Prednison) +/- Etoposid
- **Brentuximab Vedotin** (Adcetris®)

antibody-drug-conjugate (ADC) containing monoclonal antibody against human CD30 antigen and 3-5 molecules of cytostatic drug Monomethylauristatin E

- **CHT & stem cell transplantation**

and **radiotherapy** only in for patients with incomplete resection and advanced stages

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BIA-ALCL – EUSOMA-Recommendation

- **Despite an increase of BIA-ALCL in association with texture 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."

Tissue Replacement Techniques and Meshes (Details of Implant Reconstruction)

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	Oxford		
	LoE	GR	AGO
▪ Autologous tissue (e.g. autodermal graft, TDAP§,LDF *)	3b	C	+
▪ Acellular dermal matrix (ADM)	2a	B	+#
▪ Synthetic meshes	2b	B	+#
▪ Pre- or subpectoral implant position comparable (with or without meshes or ADM)	2b	B	+#

§ Thoracodorsal Arteries Perforator flap
* Latissimus dorsi flap
# Participation in registry studies recommended

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Lipotransfer

- **Lipotransfer following mastectomy and reconstruction**
- **Lipotransfer after BCS***
- **Autologous adipose derived stem cells (ASCs)-enriched fat grafting**

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

*BCS: Breast Conserving Surgery

Postmastectomy Pedicled Reconstruction

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	Oxford		
	LoE	GR	AGO
Breast reconstruction (BR) with autologous tissue			
▪ TRAM, Latissimus-dorsi-flap (both can be performed as a muscle-sparing technique)	3b	C	+
▪ Delayed TRAM in patients at high-risk	3a	B	+
▪ Ipsilateral pedicled TRAM	3b	A	+
▪ Radiotherapy:			
▪ BR following radiotherapy	2a	B	+
▪ BR prior to radiotherapy	2a	B	+/-
▪ (higher rates of fibrosis, wound healing problems, liponecrosis and reduced aesthetic outcome)			

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Free flaps for reconstruction

	Oxford		
	LoE	GR	AGO
Type of free flap			
▪ DIEP	2a	B	+
▪ Free TRAM	2a	B	+
▪ SIEA	3a	C	+/-
▪ Glutealis flaps (SGAP- / IGAP, FCI)	4	C	+/-
▪ Free gracilis flap (TMG)	4	C	+/-

Advantages

- DIEP and free TRAM are potentially muscle-sparing procedures. DIEP has a lower rate of abdominal hernias.

Disadvantages

- Time- and personnel consuming microsurgical procedures
- Intensified postoperative monitoring
- Higher reoperation rate
- Pre-reconstruction radiotherapy increases rate of vascular complications

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Pedicled versus free tissue transfer

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) in all patient groups**
- **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration with all flap techniques**

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Flap-implant combination

	Oxford		
	LoE	GR	AGO
LDF* + Implant	2b	C	+
▪ IR following RT	3b	C	+
▪ IR prior to RT	5	D	-
Additional flap techniques + implant	5	C	+/-

Advantages:

- TRAM: staged procedure preferable
- Improved implant coverage
- Suitable for irradiated tissue

Disadvantage:

- muscle contraction (LDF)

* LDF = Latissimus dorsi flap

Skin-/nipple-sparing Mastectomy (SSM/NSM) and Reconstruction

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	Oxford LoE	GR	AGO
Skin-/nipple-sparing Mastectomy (SSM/NSM)			
Safe (same recurrence rate as MX)	2b	B	++
Higher QoL for patients	2b	B	++
NAC can be preserved under special conditions	2b	B	++
Feasible after mastopexy / reduction mammoplasty	4	C	++
Use of ICG* to predict necrosis of the skin	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

Risk-reducing bilateral mastectomy for healthy women (RRBM)

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	Oxford LoE	GR	AGO
▪ RRBM reduces breast cancer incidence	1b	A	++
▪ RRBM in deleterious BRCA1/2 mutation	2a	B	+*
▪ RRBM in high-risk situation without BRCA 1/2 mutation (individual decision depending on personal- family history and mutational status – e.g. high and moderate-risk genes, Hodgkin lymphoma)	4	D	+/-*
▪ High risk and no BRCA counselling in specialized centre*	5	D	--
▪ Non-directive counselling prior to RR-BM	2b	B	++*
▪ RR-BM should be considered with other risk-reducing surgical options incl. bilateral salpingoophorectomy (BSO) and in the context of pre-existing diseases	2a	A	++*
▪ Further need for education of physicians regarding possibilities and advantages of RRBM	1b	A	++

* Counselling, risk prediction, and follow-up in specialized centers recommended

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

	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)	2a	B	+*
▪ Reduces BC incidence			
▪ Reduces BC mortality in *BRCA1* mutation carriers***	2b	B	+*

*study participation recommended

** The RRSO 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. RRM counselling should be individualised.

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Forms of risk-reducing (bilateral) mastectomy (RRBM)

	Oxford LoE	Oxford GR	AGO
RRBM reduces breast cancer incidence; bc-spec mortality also likely reduced**			
▪ Simple mastectomy	2b	B	+
▪ RRBM by SSM*	2b	C	+
▪ RRBM by NSM* (NAC# sparing)	2b	C	+
▪ Contralateral prophylactic mastectomy	4	C	+/-

* SSM / NSM: Skin-/Nipple-Sparing Mastectomy
\# NAC: nipple-areola complex
** depending on prior illnesses, e. g. pre-existing ovarian cancer 1-2% (stage III-IV)