

Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Breast Cancer Surgery Oncological Aspects

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Breast Cancer Surgery

Oncological Aspects

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- **Versions 2002–2023:**

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AGO: ++

Surgery is one sub-step out of multiple steps in breast cancer treatment. Thus, both diagnostic and oncological expertise are an essential requirement for every breast surgeon.

AGO: +

Avoidance of a significant delay in cancer treatment

AGO: ++

Surgical therapy decisions should be made in the context of a multimodal therapy concept; in particular, the waiver of diagnostic measures (e.g. SLNE) should be decided as part of a preoperative, interdisciplinary tumor conference.

Pre-therapeutic Assessment of Breast

Oxford

	LoE	GR	AGO
■ Clinical examination	5	D	++
■ Mammography (completion of the imaging)	2b	B	++
■ + Tomosynthesis (DBT)***	2b	B	+
■ Contrast-enhanced mammography (alone) adjusted with regards of radiation sensitivity of patient and availability*	2a	B	+
■ Sonography (breast[#])	2b [#]	B	++
■ MRI*	1b	A	+
■ Minimally invasive biopsy**	1b	A	++
■ Breast-CT	4	D	-
■ Axillary PET (PET-CT, PET-MR)	2b	B	-

- * MRI- or CEM guided vacuum biopsy is mandatory in case of MRI- or CEM detected additional lesions (in house or with cooperations). Individual decision for patients at high familiar risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocal disease.
- ** Histopathology of additional lesions if relevant for treatment
- *** Replacement of additional FFDM with SM

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Pre-therapeutic Assessment Axilla

Oxford		
LoE	GR	AGO
5	D	++
2b	B	-
2b	B	-
2a	B	-
2a [#]	B	++
1b	A	+
2b	B	++
4	D	-
2b	B	-

- **Clinical examination**
- **Mammography**
 - + Tomosynthesis***
 - CEM (alone) after unclear resection (Rx) if available
- **Ultrasound (Axilla[#])**
- **MRI**
- **CNB Axilla, if suspicious LN and marking of the node if TAD planned ≤ 3 susp. LK**
- **Breast-CT**
- **PET CT / MRI for axillary LN**

*** Replacement additional DM through SM

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Pre-therapeutic Staging

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	Oxford		
	LoE	GR	AGO
History and clinical examination	5	D	++
Only in case of high metastatic potential and/or symptoms and/or indication for (neo-) adjuvant chemotherapy and/or antibody-therapy:			
▪ CT scan of thorax / abdomen / pelvis	2a	B	+
▪ Bone scan	2b	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ Further investigation in case of additional suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
▪ FDG-PET or FDG-PET-CT** FDG-PET-MRT**	2b	B	+/-
▪ Whole body MRI	4	C	+/-

* Contrast enhanced ultrasound

** especially in patients with high tumor stage (III) if available

Evidence of Surgical Procedure

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	Oxford	
	LoE	GR
<ul style="list-style-type: none"> Survival rates after lumpectomy + RT are at least equivalent to those after (modified) radical mastectomy 	1a	A
<ul style="list-style-type: none"> Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy 	2b	B
<ul style="list-style-type: none"> Conservation of the NAC (nipple areola complex) is an adequate surgical procedure, if R0 resection is achieved 	2b	C

Breast-Conserving Surgery (BCS): Options to Localize Non-Palpable Lesions

	Oxford		
	LoE	GR	AGO
■ Wire-guided localization	1a	A	++
■ Wireless intraoperative ultrasound-guided localization*	1a	A	++
■ Other procedures:**			
Radar reflectors	2b	B	+/-
Magnetic marker***	2b	B	+/-
Paramagnetic markers***			
MagSeed™ (compared with wire localization)***	1b	A	+
Radiofrequency-based markers (RFID)***	2b	B	+/-
Radionuclide-guided localization (ROLL)	1a	A	+/-
Radioactive seeds****	1a	A	+/-

* The lesion must be sonographically visualized by the same examiner pre- and intraoperatively in its whole extension. Adequate equipment and training of the surgeon are mandatory.

** according to approval

*** not suitable for MRI-based response assessment under NACT

**** not approved in Germany

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Localization Methods for non-Palpable Breast Cancer: a Meta-Analysis



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Athanasiou et al. Eur J Surg Onc 2021:

- Meta-analysis of RCTs
- 18 studies with 3112 patients
- Pairwise and network meta-analysis

Ultrasound-guided surgery vs. wire-guided surgery:

- decreased positive margin both in the pairwise [OR = 0.19 (0.11, 0.35); P < 0.01] and network meta-analysis [OR = 0.19 (0.11, 0.60)]
- a statistically significant reduction in re-operation rate [OR = 0.19 (0.11, 0.36); P < 0.01] and operative time [MD = -4.24 (-7.85, -0.63); P = 0.02]

Ultrasound-guided surgery vs. ROLL / RSL:

- a statistically significant reduction in positive margin compared to ROLL [OR = 0.19 (0.11,0.6)] and RSL [OR = 0.26 (0.13, 0.52)]

„Ultrasound-guided surgery has potential benefits in reduction of positive surgical margin, the rest of the techniques seem to have equivalent efficacy.“

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Breast-Conserving Surgery (BCS): Resection Margins

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Invasive breast cancer without extensive intraductal component (EIC)* <ul style="list-style-type: none"> Aim: tumor-free margins (“no ink on tumor“ is sufficient even in case of unfavorable tumor biology) Re-excision for invasive or non-invasive tumor cells reaching margin (final histology) Invasive breast cancer with EIC* <ul style="list-style-type: none"> Re-excision for invasive or non-invasive tumor cells reaching margin (final histology) Re-excision in case of a close margin of the intraductal component (< 2 mm on final histology)** 	2a	A	++
	2a	B	++
	2a	B	++
	2a	B	-

* No clear definition of EIC in the literature. Increased risk of local recurrence in case of EIC with at least twice the greatest dimension of the invasive tumor component (definition according to the German S3 guideline).

** Individual approach with consideration of patient’s age and tumor extent

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Breast-Conserving Surgery (BCS): Surgical and Technical Aspects

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	Oxford		
	LoE	GR	AGO
▪ Specimen radiography and / or -sonography in non-palpable lesions and / or tumor-associated microcalcifications*	2b	B	++
▪ Intraoperative ultrasound to increase negative margin rates in non-palpable lesions	1a	A	+
▪ Intraoperative ultrasound to increase negative margins rates in palpable lesions (with smaller resection volumes)	1b	B	+
▪ Surgical clip marking of the tumor bed if boost or partial breast irradiation is indicated	2b	B	+
▪ Intraoperative margin evaluation (with Margin Probe®)	1b	A	+/-
▪ Therapeutic stereotactic excision alone	4	D	--

* Mandatory also for probe-guided detection systems (magnetic seeds, radar reflectors, RFID, radioactive seeds, ROLL)

Breast-Conserving Surgery (BCS) without Neoadjuvant Therapy

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- **Multifocality / Multicentricity
(R0 resection of all lesions required)**
- **Positive microscopic margins after repeated
excision**
- **Inflammatory breast cancer**

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

**For surgery after neoadjuvant chemotherapy see chapter
„Neoadjuvant chemotherapy“**

Axillary Lymph Node Dissection (ALND) without Neoadjuvant Chemotherapy

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	Oxford		
	LoE	GR	AGO
▪ Endpoint: Survival (if patient receives adequate multimodal therapy)	3	D	-
▪ Endpoint: Staging	3	A	-
▪ Endpoint: Locoregional control	2a	A	+/-
▪ pN+ (histologically confirmed pre-surgery)	2a	B	+
▪ cN0 pN0 (i+) (sn)	1b	A	--
▪ cN0 pN1mi (sn)	2b	B	--
▪ cN0 pN1 (sn) (T1/2, < 3 SN+*, BCS + RT + adequate systemic therapy)	1b	A	-
▪ cN0 pN1 (sn) and mastectomy (no chestwall radiotherapy)	1b	B	+**
▪ cN0 pN1 (sn) and mastectomy (T1/2, < 3 SN+, chestwall radiotherapy)	5	D	+/-**
▪ ALND indicated, but not feasible			
▪ Radiotherapy according to AMAROS trial (validated for cN0 pN1sn)	1b	B	+

* ACOSOG Z0011 trial protocol without clear definition of gross extra nodal disease

** Study participation recommended

Axillary Surgery and NACT

Oxford

LoE

GR

AGO

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology			
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

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Axillary Surgery and NACT (cN+)

Oxford

LoE

GR

AGO

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	LoE	GR	AGO
cN+*	pN+ ^{CNB}	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in AXSANA recommended, ** Cave: In 30.3% false-positive findings, consider CNB if necessary

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Targeted Axillary Dissection (TAD) = TLNE + SLNE

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	Oxford		
	LoE	GR	AGO
▪ Core needle biopsy and marking of suspicious lymph nodes (LN)	2b	B	++
▪ Marking of multiple LN if more than one LN is suspicious	2b	B	+/-
▪ Evidence for comparison of different markers (clip / coil, carbon, magnetic seed, radar reflector, radiofrequency-based marker etc.) is insufficient *	2b	B	
▪ TAD in case of 1-3 suspicious LN before NACT	2b	B	+
▪ TAD in case of ≥ 4 suspicious LN before NACT	5	D	+/-
▪ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
▪ Immunohistochemistry for ITC detection	5	D	+/-
▪ ALND in case of pre- or intraoperatively undetectable marker	5	D	+
▪ Further intervention to retrieve lost marker (incl. after ALND)	5	D	-
▪ TLNE only without SLNE	2B	B	+/-

* Study participation in AXSANA recommended

Sentinel Lymph Node Excision (SLNE)

Indications I



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- Clinically / sonographically negative axilla (cN0)
- cT 1–2
omission of SLNE according to SOUND trial
- cT 3–4c
- Multifocal / multicentric breast cancer
- DCIS
 - Mastectomy
 - BCT
 - DCIS in male
- Male breast cancer
- Omission of axillary intervention in elderly patients (≥ 70 yrs., co-morbidities, pT1, HR+)

	Oxford		
	LoE	GR	AGO
	1b	A	++
	2b	A	++
	1b	B	+
	3b	B	+
	2b	B	+
	3b	B	+
	3b	B	-
	5	D	+/-
	2b	B	+
	3b	B	+/-

Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes

The SOUND Randomized Clinical Trial

Gentilini et al. JAMA Oncology, 2023



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- Prospective noninferiority phase 3 randomized clinical trial
- cT1a-c, preoperative negative axillary ultrasound = cN0 (ultrasound)
- 1463 patients included, 1405 intention-to-treat analysis, 708 SLNB, 697 no-SLNB
- Median age 60 years (52-68 years), median tumor size 1.1 cm (0,8-1.5 cm)
- Tumor biology: 87,8% HR+/HER2 neg.
- Results
 - Follow up 5.7 years (5.0-6.8 years), positive LN SLNB-group 13.7% (≥ 4 LN 0.6%)
 - No statistical difference according to BCT, mastectomy, hormone therapy (97.9% vs. 98.9%) chemotherapy (20.1 vs. 17.5%), radiotherapy (98.0 vs. 97.6%)
 - **5 years DDFS 97.7% SLNB group vs. 98.0% in no-SLNB group ($p = 0.67$, HR 0.84, 90CI 0.45-1.54, noninferiority $p = 0.02$)**
 - Locoregional relapse 1.7% SLNB group vs. 1.6% in no-SLNB group
 - Axilla recurrence 1.7% SLNB group vs. 1.6% in no-SLNB group
 - Distant metastases 1.8% SLNB group vs. 2.0% in no-SLNB group
 - Deaths 3.0% SLNB group vs. 2.6% in no-SLNB group
- **CAVE: ultrasonography of axilla might be difficult, no details of radiotherapy presented, impact on systemic treatment decisions possible (e.g. CDK4/6 inhibitors), longer follow up needed**

Sentinel Lymph Node Excision (SLNE)

Indications II



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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> During pregnancy and / or breast feeding (only ^{99m}Tc-colloid, no patent or methylene blue dye, no data to SPIO or ICG) 	3	C	++
<ul style="list-style-type: none"> After prior tumor excision 	2b	B	+
<ul style="list-style-type: none"> After prior major breast surgery (e.g. reduction mammoplasty) 	3b	C	+/-
<ul style="list-style-type: none"> Ipsilateral breast recurrence after prior BCS and prior SLNE 	4	D	-
<ul style="list-style-type: none"> SLNE in the mammary internal chain 	2b	B	-
<ul style="list-style-type: none"> After axillary surgery 	3b	B	+/-
<ul style="list-style-type: none"> Prophylactic bilateral / contralateral mastectomy 	3b	B	--
<ul style="list-style-type: none"> Inflammatory breast cancer 	3b	C	-

Sentinel Lymph Node Excision (SLNE) Marking



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- **^{99m}Tc Kolloid**
- **Preoperative lymphoscintigraphy (added information limited, but mandatory by legal regulations)***
- **Patent blue dye**
- **Indocyanin green (ICG)[°]**
- **SPIO[#]**
- **Methylene blue**

Oxford

LoE	GR	AGO
1a	A	++
1b	A	+
1a	A	+/-
2a	B	+
2a	B	+
2a	B	+/-

* In Germany required for quality assurance of nuclear medicine

SPIO: Superparamagnetic Iron Oxide (Caveat: impaired MRI-sensitivity during follow-up)

° no approval for LN marking in the axilla, off-label

Surgical Approach in the Neoadjuvant Setting

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- **Early marking of tumor (incl. detailed topographic documentation)**
- **Surgical removal of tumor / representative excision of post-therapeutic, marked tumor area**
- **Tumor resection in new margins**
- **Microscopically clear margins**

Oxford		
LoE	GR	AGO
5	D	++
2b	C	++
2b	C	++
2a	B	++

For „Surgery after neoadjuvant chemotherapy“ see chapter „Neoadjuvant chemotherapy“

Begin of Adjuvant Therapy after Primary Surgery



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- **Start adjuvant systemic therapy and radiotherapy (RT) as soon as possible (asap) after surgery**
- **Start of adjuvant chemotherapy +/- HER2 therapy asap after surgery, prior to RT**
- **Without cytotoxic therapy +/- anti-HER2 therapy:**
 - **Start adjuvant RT within 6–8 weeks after surgery**
 - **Start endocrine therapy after surgery asap**
 - **Endocrine therapy concurrent with RT**

Oxford		
LoE	GR	AGO
1b	A	++
1b	A	++
2b	B	++
5	D	++
2b	B	+