NEOADJUVANT THERAPIES AND LOCO-REGIONAL TREATMENT Challenges for the (oncoplastic) breast surgeon

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Disclosures

None

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FACTS CHALLENGES CHALLENGES FOR THE SURGEON

- ❑ Around 20% of Breast Cancers occur in premenopausal women
- ❑ **The available data in clinical trials weakens evidence levels**
- ❑ Tend to have poorer prognosis
- ❑ **Chemotherapy / biological treatments are more frequent, prolonged HT therapy**
- ❑ Tend to be higher stage at diagnosis
- ❑ **More neo-adjuvant treatments /need to have optimal locoregional control**
- ❑ Tend to be higher-grade tumours, higher Ki67, oestrogen-receptor -, Her2+
- ❑ **More neo-adjuvant /adjuvant treatments, Chemotherapy / biological treatments, prolonged HT therapy**
- ❑ Have a higher lifetime relapse risk despite improvement in systemic treatments
- ❑ **Choice between more conservative or more radical approaches**
- ❑ Higher likelihood of genetic predisposition
- ❑ **Gene testing and integration of results with treatment on time**
- ❑ Improvement in OS leads to more survivorship issues – prolonged lifespan
- ❑ **Impact of locoregional and systemic treatments on QOL**

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CHALLENGES FOR THE SURGEON

- The available data in clinical trials weakens evidence levels
- More neo-adjuvant treatments /need to have optimal locoregional control
- Choice between more conservative or more radical approaches
- Gene testing and integration of results with treatment on time
- Impact of locoregional and systemic treatments on QOL

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ADDITIONAL CHALLENGES

- Younger women are more systematic in their approach to information often
- Younger women often need and seek a second opinion
- Younger women wish to learn more about the disease
- Younger women wish to learn more about treatment options especially if opting for BCS

Main factors influencing young womens choices:

- Disruptions to personal life caused by treatment
- Genetic predisposition
- Surgical preferences
- Distress levels
- Surgical recommendation
- Objective result of genetic test

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Information requirements of young women with breast cancer treated with mastectomy or breast conserving surgery: A systematic review.
Recio-Saucedo A et Al, Breast 2016 Feb

- **The available data in clinical trials weakens evidence levels**

- Although randomized controlled trials (RCTs) suggest equivalent survival for mastectomy and BCS, **very few young patients were included** in these analyses.

- **Young women are not routinely analysed or reported separately** in individual RCTs of BCS versus mastectomy

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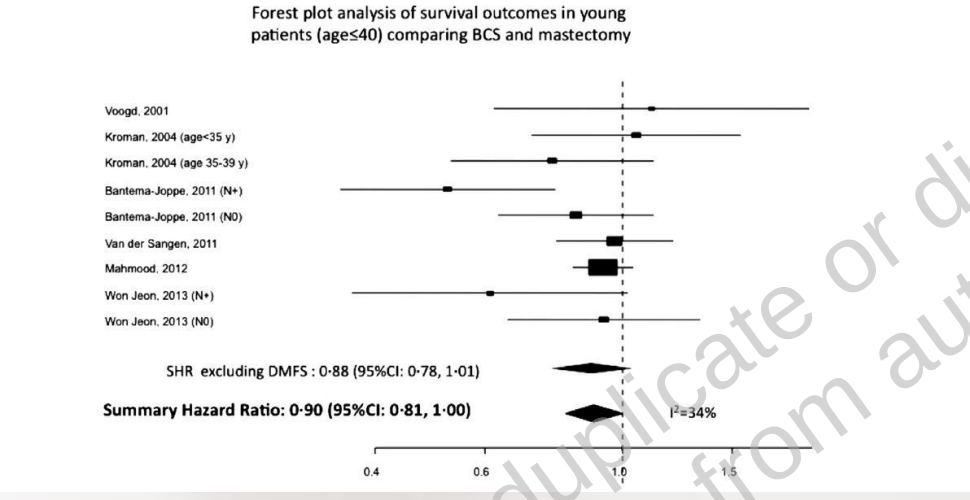
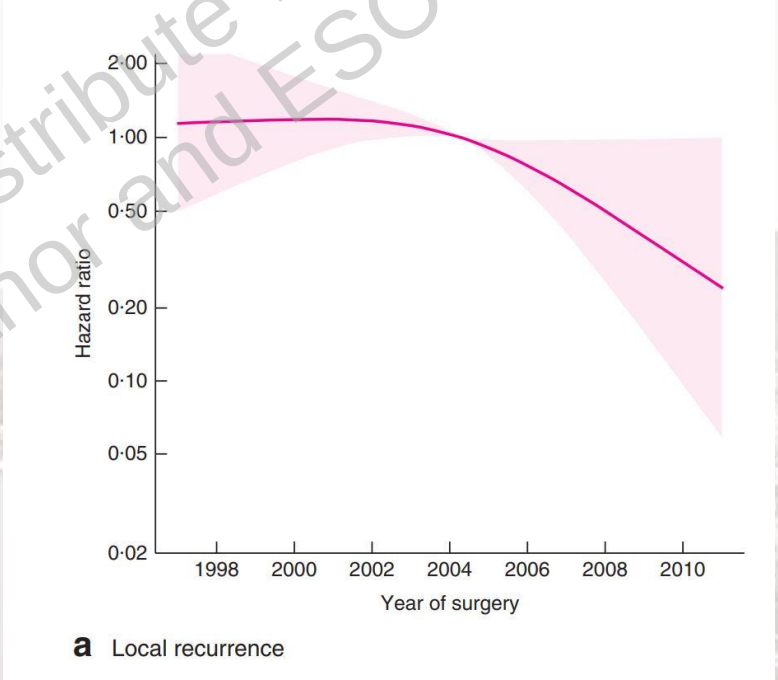
- **The available data in clinical trials weakens evidence levels (retrospective)**





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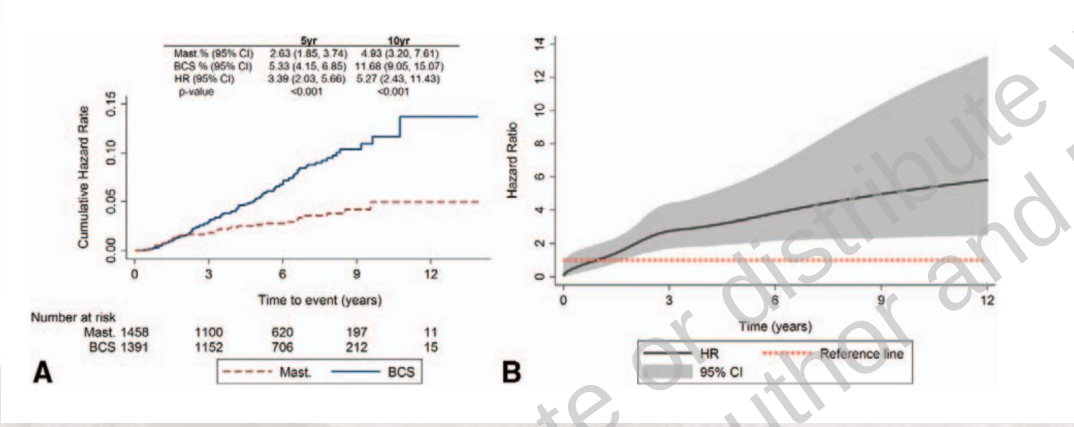
Overall survival according to type of surgery in young (≤40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy.
Vila J, Gandini S, Gentilini O. Breast. 2015

mproved prognosis of young patients with breast cancer undergoing breast-conserving surgery.
Botteri E, Veronesi P, Vila J, Rotmensz N, Galimberti V, Thomazini MV, Viale G, Orecchia R, Goldhirsch A, Gentilini O. Br J Surg. 2017

- **The available data in clinical trials weakens evidence levels prospective cohort non -randomized**



- ✓ No survival advantages for surgical type after adjusting for known prognostic factors.
- ✓ No difference in LRI between BCS and mastectomy in the short-term
- ✓ Beyond 18 months, LRR are higher after BCS.
- ✓ Local recurrence is associated with increased risk of distant relapse
- ✓ For Patients undergoing BCS, a positive surgical margin increases the likelihood of a distant relapse.
- ✓ For those undergoing mastectomy, RT reduces the likelihood of distant relapse.
- ✓ Surgical extent therefore appears less important for DDFI than completeness of excision or, where appropriate

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Ann Surg. 2017
Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study.
Maishman T et Al.

More neo-adjuvant treatments/need to have optimal locoregional control

TABLE 1. (*Continued*)

Characteristic	Mastectomy (n = 1464)	Breast Conserving Surgery (n = 1395)	Total* (n = 2882)	P†
Chemotherapy treatment period				<0.001
Adjuvant	1088 (74.3%)	1055 (75.6%)	2149 (74.6%)	
Neoadjuvant	275 (18.8%)	155 (11.1%)	447 (15.5%)	
Palliative	1 (0.1%)	0	1 (0.0%)	
Not applicable	100 (6.8%)	185 (13.3%)	285 (9.9%)	
Missing	0	0	0	

Ann Surg. 2017
Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study.
Maishman T et Al.

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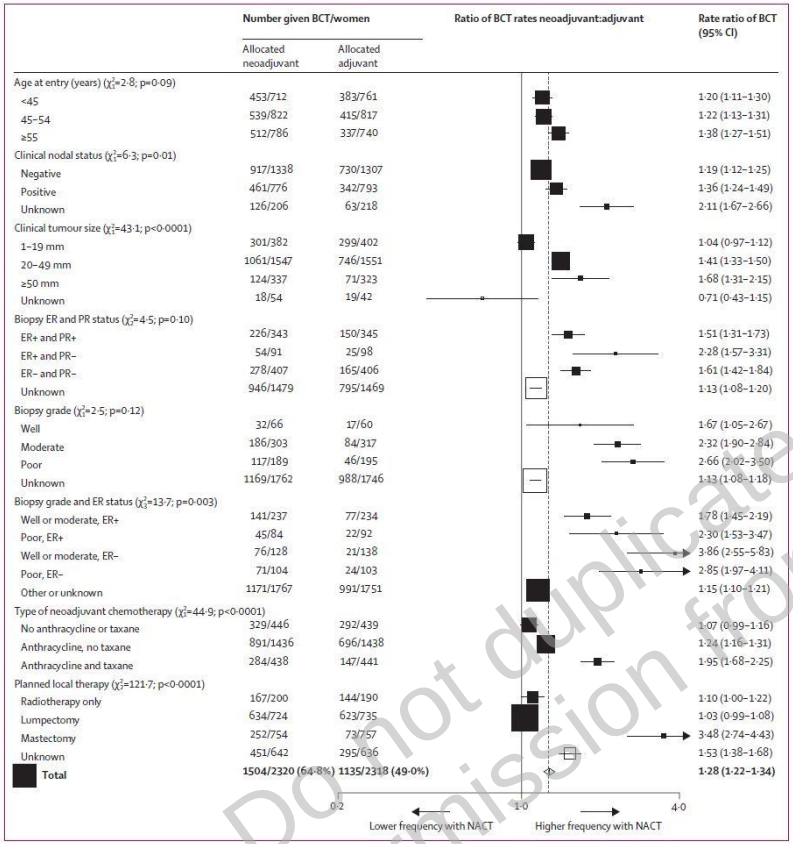
More neo-adjuvant treatments/need to have optimal locoregional control



	Number given BCT/women		Ratio of BCT rates neoadjuvant:adjuvant	Rate ratio of BCT (95% CI)
	Allocated neoadjuvant	Allocated adjuvant		
Age at entry (years) (χ^2_2=2·8; p=0·09)				
<45	453/712	383/761		1·20 (1·11–1·30)
45–54	539/822	415/817		1·22 (1·13–1·31)
≥55	512/786	337/740		1·38 (1·27–1·51)
Clinical nodal status (χ^2_1=6·3; p=0·01)				
Negative	917/1338	730/1307		1·19 (1·12–1·25)
Positive	461/776	342/793		1·36 (1·24–1·49)
Unknown	126/206	63/218		2·11 (1·67–2·66)
Clinical tumour size (χ^2_1=43·1; p<0·0001)				
1–19 mm	301/382	299/402		1·04 (0·97–1·12)
20–49 mm	1061/1547	746/1551		1·41 (1·33–1·50)
≥50 mm	124/337	71/323		1·68 (1·31–2·15)
Unknown	18/54	19/42		0·71 (0·43–1·15)
Biopsy ER and PR status (χ^2_3=4·5; p=0·10)				
ER+ and PR+	226/343	150/345		1·51 (1·31–1·73)
ER+ and PR–	54/91	25/98		2·28 (1·57–3·31)
ER– and PR–	278/407	165/406		1·61 (1·42–1·84)
Unknown	946/1479	795/1469		1·13 (1·08–1·18)
Biopsy grade (χ^2_2=2·5; p=0·12)				
Well	32/66	17/60		1·67 (1·05–2·67)
Moderate	186/303	84/317		2·32 (1·90–2·84)
Poor	117/189	46/195		2·66 (2·02–3·50)
Unknown	1169/1762	988/1746		1·13 (1·08–1·18)
Biopsy grade and ER status (χ^2_3=13·7; p=0·003)				
Well or moderate, ER+	141/237	77/234		1·78 (1·45–2·19)
Poor, ER+	45/84	22/92		2·30 (1·53–3·47)
Well or moderate, ER–	76/128	21/138		3·86 (2·55–5·83)
Poor, ER–	71/104	24/103		2·85 (1·97–4·11)
Other or unknown	1171/1767	991/1751		1·15 (1·10–1·21)
Type of neoadjuvant chemotherapy (χ^2_2=44·9; p<0·0001)				
No anthracycline or taxane	329/446	292/439		1·07 (0·99–1·16)
Anthracycline, no taxane	891/1436	696/1438		1·24 (1·16–1·31)
Anthracycline and taxane	284/438	147/441		1·95 (1·68–2·25)
Planned local therapy (χ^2_3=121·7; p<0·0001)				
Radiotherapy only	167/200	144/190		1·10 (1·00–1·22)
Lumpectomy	634/724	623/735		1·03 (0·99–1·08)
Mastectomy	252/754	73/757		3·48 (2·74–4·43)
Unknown	451/642	295/636		1·53 (1·38–1·68)
Total	1504/2320 (64·8%)	1135/2318 (49·0%)		1·28 (1·22–1·34)

0·2 1·0 4·0
Lower frequency with NACT Higher frequency with NACT

Figure 1: **BCT rate ratios**
Numbers with BCT or mastectomy after chemotherapy. Excludes local therapy unknown (67 patients with NACT and 51 with adjuvant chemotherapies). BCT=breast-conserving therapy. ER=oestrogen receptor. PR=progesterone receptor. NACT=neoadjuvant chemotherapy.

Age was not associated with the frequency of breast-conserving therapy.

- NACT ++breast-conserving therapy than adjuvant information about response to treatment
- No better than postoperative adjuvant treatment in reducing breast cancer mortality
- Perhaps as a consequence of the reduction of surgery, NACT is associated with moderately increased local recurrence risk, which persists for at least 10 years.

TOTAL around 5000 pts – 1983-2002

Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) - Lancet Oncology 2018*

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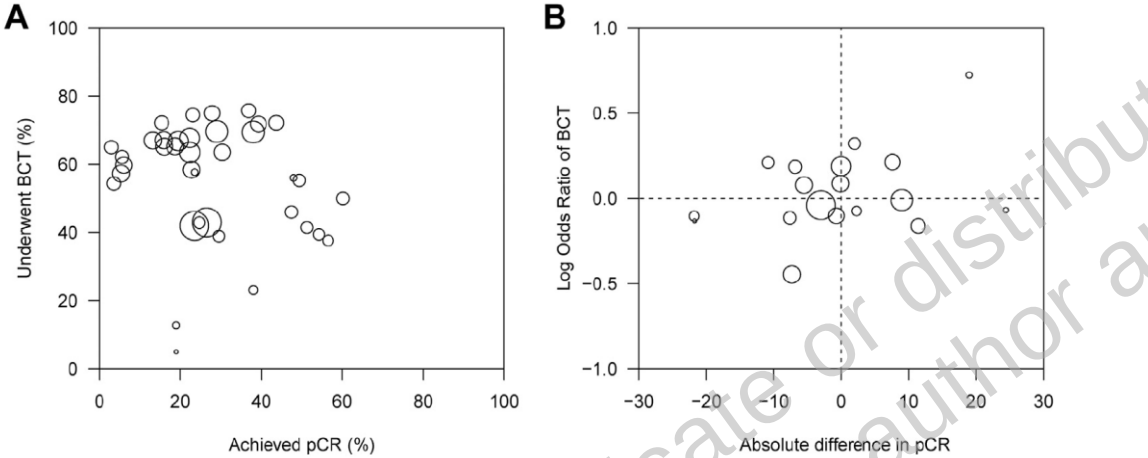
More neo-adjuvant treatments/need to have optimal locoregional control



Increasing pCR, no increase in BCT

Neoadjuvant studies should use BCT as a secondary end-point.

Total 12,311 patients across studies (36) 1997-2016
Grade 3 (0.7% to 72% with a median of 46%)
ER+ (19% to 100% with a median of 40%.)
HER2+ (0 to 100% with a median of 40% (15 studies))
TNBC patients (max of 55% - 12 studies). were clinically
Node positive (15% to 86with a median of 52%) , ranging from % across studies.
Average age: median of 49 years, interquartile range from 48.6 to 50 years.

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Impact of neoadjuvant chemotherapy and pathological complete response on eligibility for breast-conserving surgery in patients with early breast cancer: A meta-analysis. Criscitiello C et Al. Eur J Cancer. 201

- **Choice between more conservative or more radical approaches**
- **Gene testing and integration of results with treatment on time**
- **Impact of locoregional and systemic treatments on QOL**

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Decision-making process

- Risk of ipsilateral breast recurrence (IBR)
- Risk of contra-lateral breast cancer (CBC)
- Potential survival benefit of contralateral prophylactic mastectomy (CPM)
- Factors with impact in IBR or CBC

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Comunicating risk – a difficult task

Numeracy includes minimal statistical literacy

Health numeracy is a person's ability to access, interpret, and use numeric information to make health decisions.

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Main factors influencing young womens choices:

- Disruptions to personal life caused by treatment
- Genetic predisposition
- Surgical preferences
- Distress levels
- Surgical recommendation
- Objective result of genetic test (FAST TESTING)

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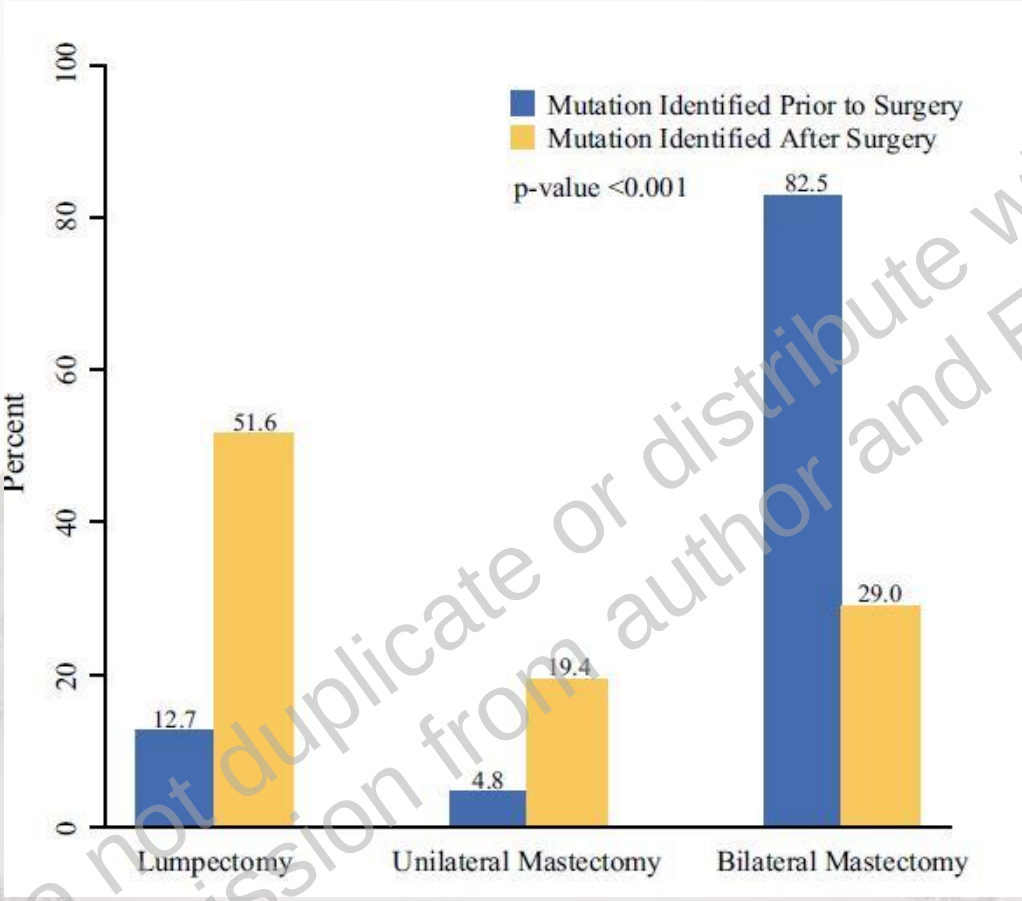

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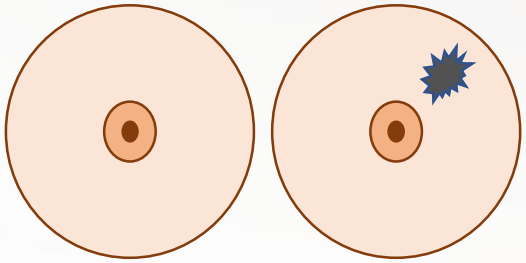
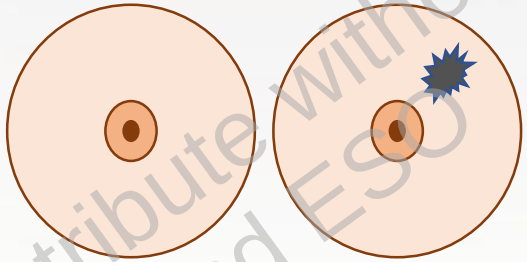
Impact that Timing of Genetic Mutation Diagnosis has on Surgical Decision Making and Outcome for BRCA1/BRCA2 Mutation Carriers with Breast Cancer
Akiko Chiba et al 2016, Ann Surg Oncology





- IBR – 1-2% year <7 Y
  IBR – doubles >7 Y
- CBC – 3% year BRCA1 - 2% year BRCA2

- IBR – 1-2% year
- CBC -0.5% year

NO OVERALL SURVIVAL DIFFERENCES

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Surgery after Neo-adjuvant Chemotherapy

- Initial work-up of locorregional disease
- Monitoring response to treatment
- Axillary approach
- BCS after treatment
- Reconstructive surgery

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Pre-treatment work-up

Comparative Accuracy Studies	Number Studies (2050 patients)	P value	AUC
MRI Clinical	11	0.10	0.89 0.83
MRI Ultrasound	10	0.15	0.93 0.90
MRI Mammography	7	0.02	0.90 0.89

Meta-analysis of Magnetic Resonance Imaging in Detecting Residual Breast Cancer After Neoadjuvant Therapy.

Marinovich ML, Houssami N, Macaskill P, Sardanelli F, Irwig L, Mamounas EP, von Minckwitz G, Brennan ME, Ciatto S.

J Natl Cancer Inst. 2013 Jan 7.

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st gallen oncology conferences

BCC 2017

Surgery of the Primary (IBC) after Neo-Adjuvant Systemic Therapy

10. **In women undergoing breast conserving surgery after neo-adjuvant chemotherapy and proceeding to standard radiation with or without additional adjuvant systemic therapy.**

Which is the ***minimum*** acceptable surgical margin to avoid re-excision (with multifocal residual disease in the pathological specimen)?

(1) No ink on invasive tumor or DCIS? 55,2 %

(2) 2 mm clearance? 27,6 %

(3) > 2 – 5 mm clearance? 6,9 %

(4) > 5mm clearance? 3,4 %

(5) Margin is irrelevant? 0 %

(6) Abstain 6,9 %

15th St.Gallen International Breast Cancer Conference 2017 Consensus

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BCY4

Timing in N0 axilla

SNB before NAC

\+ reliable SNB

identification rate accepted (97%)

false negative rate accepted (SN-/N+; 9.8%)

SNB after NAC

\+ no separate operation needed for SNB

\+ downstaging of the axilla (23-42% in cN+)

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Krag. Lancet Onc 2007
Boughey. JAMA 2013
Alvarado. Ann Surg Onc 2012
Kuerer. Ann Surg 1999
Rouzier. JCO 2002

Current indications for axillary dissection Post neoadjuvant therapy

- Clinically (US) node-positive patients confirmed by staging after NAC – IBC or Locally advanced inoperable (N2/N3)
- SLNB positive after NAC (burden of disease? – ITC/micro- NSABP – B-18)
- If postmastectomy radiation is not indicated by the positive SLN or does not include the regional nodes

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Omission of ALND in clinically N+?
NCCN guidelines 3.2018

Initially positive axilla

- May be restaged after NACT
- Axilla still clinically positive → ALND (US findings*)
- Axilla clinically negative → SLN or ALND
- FNR >10% after NACT, can be reduced by documenting removal of clip, dual tracer, and removing >2 SLN
- Marking of nodes during biopsy with tattoo or clip

***Node positivity: Palpable lymph nodes ; >1 cm in size; reduced fatty deposition; lateral cortical hypertrophy on ultrasonography.**

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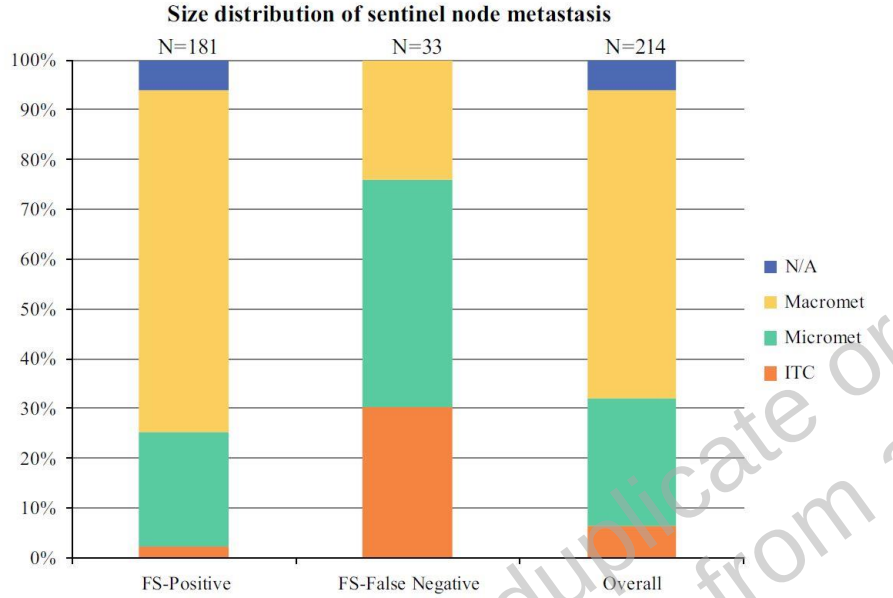
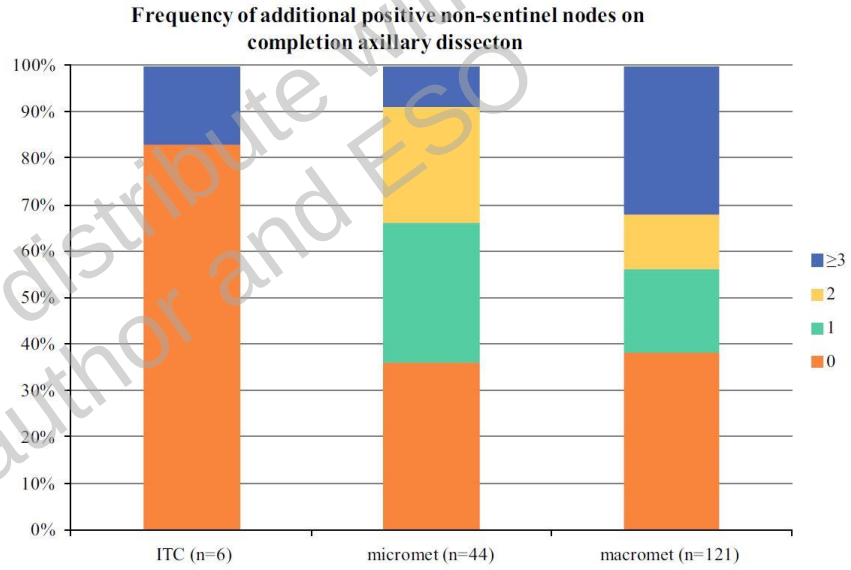
711 SLN after NAC / FS 181 positive 530 negative (33 FN 6,2%)





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Does Low-Volume SLN Disease Require ALND?
T.A. Moo et al. Ann Surg Oncol 2018

Low-volume SLN disease after NAC is not an indicator of a low risk of additional positive axillary nodes and remains an indication for ALND, even when not detected on intraoperative FS.

- Axilla negative at presentation and NAC (except in LABC) – SNB Post NAC
- Axilla positive pre-NAC and negative post NAC (at least 3 negative nodes, dual tracer/clip/tattoo)
- Axilla positive pre-NAC and micro or minimal burden – ALND/RT
- Beware of subtypes associated a higher FNR – Luminal/lobular

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Criteria for mastectomy

- IBC /LABC not responding to PST (NO RECONSTRUCTION)
- Persistence of skin edema
- Residual tumor size (Oncoplastic Techniques) – Tumor/Breast ratio
- Presence of extensive suspicious microcalcifications ->mammography, MRI
- No evidence of multicentricity-> MRI
- Desire of the patient – INFORMATION

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This is when “things” get UNOBJECTIVE AND NON EVIDENCE BASED

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Usability

- Breast cancer conservative treatment
  - Simple
  - With local flaps
  - Therapeutic mammaplasty
  - LD miniflap
  - Perforator flaps
  - FAT injection

- Mastectomy
  - Implants
  - Implants with ADM
  - LD with implant
  - LD autologous
  - TRAM
  - DIEAP, SGAP….
  - FAT injection
  - CL breast

Fashionable surgery

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Objective decision making between conventional and oncoplastic breast-conserving surgery or mastectomy: An aesthetic and functional prospective cohort study.

Pukancsik D, Kelemen P, Újhelyi M, Kovács E, Udvarhelyi N, Mészáros N, Kenessey I, Kovács T, Kásler M, Mátrai Z. Eur J Surg Oncol. 2017 Feb;43(2):303-310.

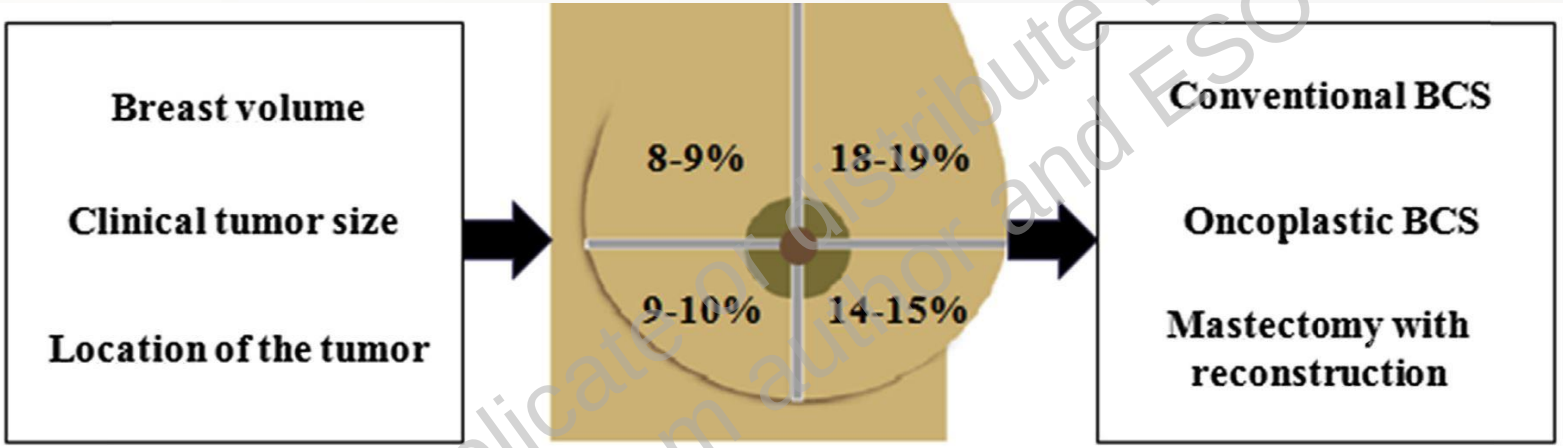
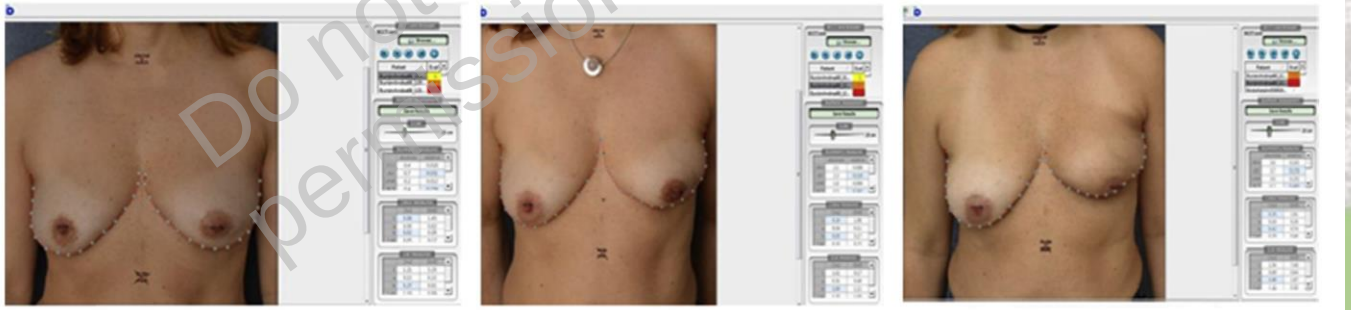


Figure 3. The algorithm used to determine the appropriate surgical strategy, considering the maximal volume of breast volume loss.



Overall classification: "good" - preoperative

Overall classification: "fair"- 4th week

Overall classification: "poor" - 12th postoperative month

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Total mastectomy vs Nipple Sparing Mastectomy

iNSPiRE
INTERNATIONAL NIPPLE SPARING MASTECTOMY REGISTRY

Breast Reconstruction following Nipple-Sparing Mastectomy: Predictors of Complications, Reconstruction Outcomes, and 5-Year Trends.
Colwell AS, Tessler O, Lin AM et al.
Plast Reconstr Surg 2014; 133: 496-506.

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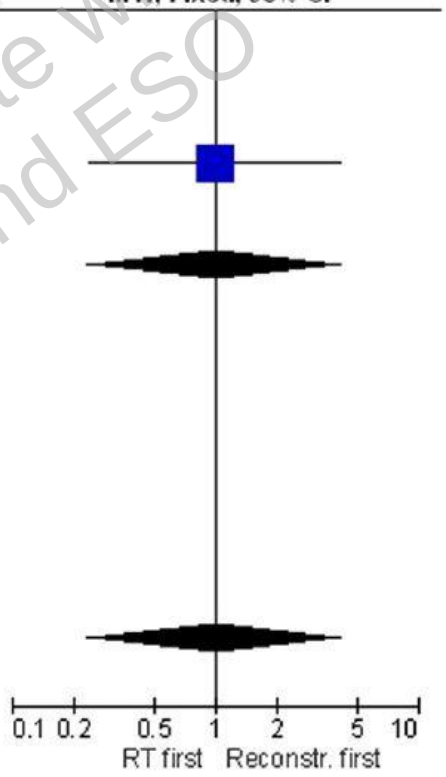
Timing of Reconstruction– when ?

Study or Subgroup	RT first Events	Total	Reconstruction first Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.8.1 Autologous						
Baumann (2011)	19	189	0	0		Not estimable
Halyard (2004)	0	0	1	15		Not estimable
Momoh (2012)	1	100	0	0		Not estimable
Nahabedian (2008)	4	53	4	53	100.0%	1.00 [0.24, 4.23]
Temple (2005)	2	100	0	0		Not estimable
Tran (2001)	6	70	0	0		Not estimable
Subtotal (95% CI)		512		68	100.0%	**1.00 [0.24, 4.23]**
Total events	32		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.8.2 Implant						
Subtotal (95% CI)		0		0		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		512		68	100.0%	**1.00 [0.24, 4.23]**
Total events	32		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



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J. Berbers et al. / European Journal of Cancer 50 (2014) 2752–2762
Reconstruction: Before or after postmastectomy radiotherapy?' A systematic review of the literature

Outcomes of Oncoplastic Surgery

- Oncological – recurrences (local and systemic)
- Reinterventions /conversion to mastectomy
- Complications –delay in adjuvant treatments
- Radiotherapy planning
- Cosmetic outcome (PROMs and Cosmesis)

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Outcomes

Seventeen articles were identified that met the inclusion criteria,representing 1312 patients and 1324 oncoplastic cases (Table 1). Reported median follow-up ranged from 20 to 73 months.

TABLE 2. Articles Reporting Local-Regional and Distant Recurrence Rates

Reference	Patients/Cases	Mean/Median Follow-up, mo	Stages Included	Local-Regional Recurrence Rate	Distant Recurrence Rate
Caruso et al[21] (2008)*	61/63	68	I to III	1 (1.6%)	6 (9.8%)
Caruso et al[22] (2011)*	50/52	72.6	0 to IIIB	1 (1.9%)	1 (2%)
Chang et al[10] (2004)	37/37	NR	NR	0	0
Chang et al[6] (2012)	79/85	39	0 to IV	2 (2.3%)	2 (2.3%)
Clough et al[4]	175/175	49	NR	3 (1.7%)	11 (6.3%)
Currie et al[23]	20/20	36	I and II	0	0
Denewer et al[24]*	50/50	20	I and II	0	0
Eaton et al[35]	86/86	54	0 to III	6 (7%)	1 (1.2%)
Grubnik et al[17]*	251/251	50	NR	6 (2.4%)	3 (1.2%)
Gulcelik et al[20]	106/106	33	I to III	1 (0.9%)	NR
Imahiyerobo et al[25]	64/64	34.6	0 to III	5 (7.8%)	2 (3.1%)
Losken et al[26]	63/63	40	0 to III	2 (3.2%)	0
McCulley and Macmillan[18]	50/50	NR	≥III	0	0
Munhoz et al[15]*	106/106	47	NR	7 (6.6%)	NR
Santanelli et al[19]	11/11	26.5	I and II	0	0

*Studies that utilized intraoperative frozen section.

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Outcomes Following Oncoplastic Reduction Mammoplasty: A Systematic Review.
Piper ML, Esserman LJ, Sbitany H, Peled AW.
Ann Plast Surg. 2016 May;76 Suppl 3:S222

Outcomes

Seventeen articles were identified that met the inclusion criteria,representing 1312 patients and 1324 oncoplastic cases (Table 1). Reported median follow-up ranged from 20 to 73 months.

TABLE 1. Articles Included in Systematic Review

Reference	Year	Patients/Cases	Mean/Median Follow-up, mo	Oncologic Outcomes Described	Patient or Aesthetic Outcomes Described
Barnea et al[1]	2014	20/22	34.7	No	Yes
Caruso et al[21]	2008	61/63	68	Yes	No
Caruso et al[22]	2011	50/52	72.6	Yes	No
Chang et al[10]	2004	37/37	NR	Yes	Yes
Chang et al[6]	2012	79/85	39	Yes	No
Clough et al[4]	2012	175/175	49	Yes	Yes
Currie et al[23]	2013	20/20	36	Yes	No
Denewer et al[24]	2012	50/50	20	Yes	Yes
Eaton et al[35]	2014	86/86	54	Yes	No
Grubnik et al[17]	2013	251/251	50	Yes	Yes
Gulcelik et al[20]	2013	106/106	33	Yes	No
Imahiyerobo et al[25]	2014	64/64	34.6	Yes	No
Losken et al[26]	2007	63/63	40	Yes	No
Losken et al[9]	2014	83/83	NR	No	No
McCulley and Macmillan[18]	2005	50/50	NR	Yes	Yes
Munhoz et al[15]	2011	106/106	47	Yes	Yes
Santanelli et al[19]	2009	11/11	26.5	Yes	Yes

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Outcomes Following Oncoplastic Reduction Mammoplasty: A Systematic Review.
Piper ML, Esserman LJ, Sbitany H, Peled AW.
Ann Plast Surg. 2016 May;76 Suppl 3:S222

Outcomes

- No standardized outcome evaluation

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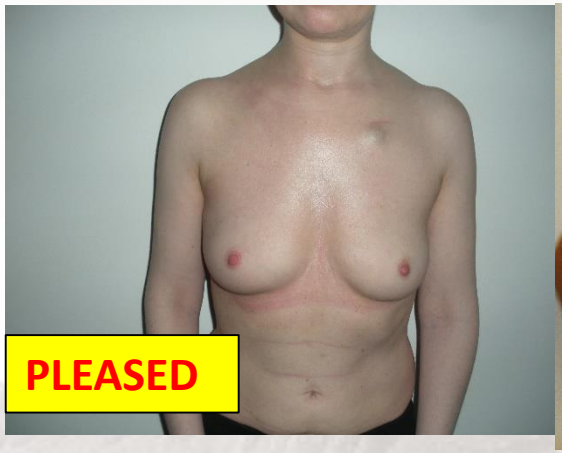
CINDERELLA trial

Compar**in**g patients **de**cision on aesthetic outcome with the BCCT.co**re** objective evaluation after control**l**ed te**a**ching in patients proposed to breast cancer locoregional treatment. A prospective randomized trial.



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Aesthetics in breast conserving therapy: do objectively measured results match patients' evaluations?
Heil J, Dahlkamp J, Golatta M, Rom J, Domschke C, Rauch G, Cardoso MJ, Sohn C.
Ann Surg Oncol. 2011

CONCLUSIONS

- Challenges for the surgeon (oncoplastic) are huge
- Young women are usually well informed and seek for second opinions
- Young women will hopefully live longer with the consequences of the treatment
- Due to longer life span - expected higher rate of LRR
- Due to longer life span – body changes additional need for corrective surgery
- More information on risk and impact on day to day life of choices
- Inclusion of young patients in trials

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THANK YOU