Malignant Disease of the Breast – Part One

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September 28th, 2016

Objectives

Medical Expert:

Etiological factors, genetics and epidemiology of breast cancer

Anatomy of breast, blood supply, lymphatic drainage, surrounding neuro-vascular structures.

Presentation, histology and management of DCIS

Presentation, histology and management of LCIS

Histological classification of invasive breast carcinoma

Grading and tumor prognosis

Role of hormone receptors in breast carcinoma

Staging of breast carcinoma

Surgical management of breast cancer , SLNB role

Collaborator:

Imaging and diagnostic techniques of malignant breast disease

Health Advocate:

Role of screening mammography

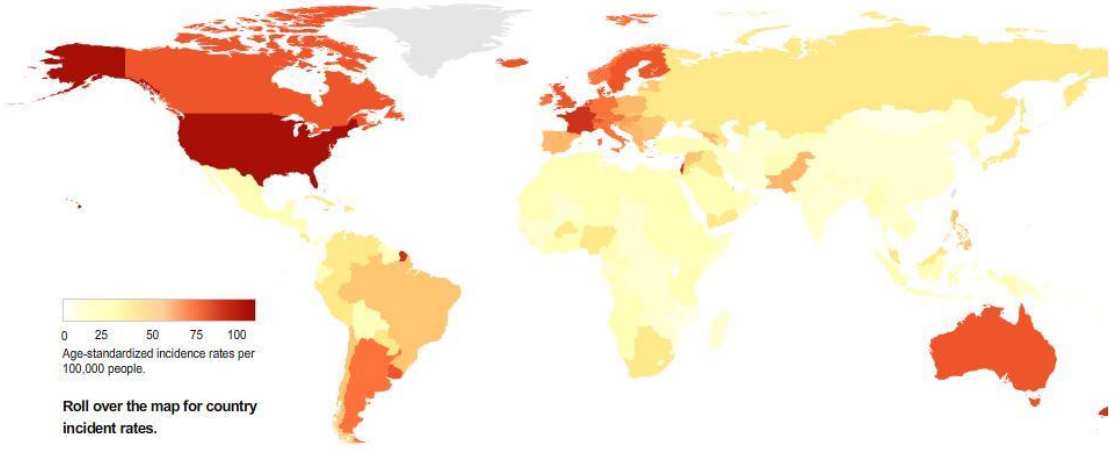
Manager:

Breast cancer screening

Genetic screening for breast cancer

Epidemiology

- Most commonly diagnosed cancer worldwide
- 280,000 new cases diagnosed in the USA annually, with approximately 40,000 deaths per year
- The American Cancer Society estimates that 1 in 8 women will be diagnosed with breast cancer in their lifetime
- Highly heterogeneous in tumour biology



TIME graphic by Feilding Cage
Source: International Agency for Research on Cancer

Risk Factors

- Increasing Age
- Gender (100 times greater risk in women)
- Race
- Weight
- Height
- Estrogen
- Breast Density
- Age of menarche
- Nulliparity
- Family history
- Lifestyle (Smoking, fat intake, alcohol all show weak relationships)
- Abortion DOES NOT increase risk

Risk Prediction Models

- There are three leading models for risk prediction in breast cancer: BRCAPRO, IBIS and BOADICEA
- IBIS has the best predictability of the models
- IBIS accounts for both genetic and nongenetic factors, and is useable in clinic and family practice settings
- It may overestimate risk in women with atypical hyperplasia
- http://ibis.ikonopedia.com/

Breast Cancer Genetics

- Majority of breast cancers are sporadic
- 5-10% of women presenting with breast cancer will have a hereditary form
- Most commonly identified genetic loci are BRCA1/2 mutations
- Breast cancers may also be associated with inherited syndromes (Li-Fraumeni, Cowden)
- Risk assessment, testing and management of patients with these mutations is different than average risk patients

Estimated risks for cancer with BRCA mutations

Cancer type	Risk in carriers to age 70 years*	Lifetime risk in general population	Comments
Breast	*BRCA1:* 55 to 70% *BRCA2:* 45 to 70%	~12%¶[1]	In most studies, risk in *BRCA1* carriers is higher than that observed in *BRCA2* carriers. The incidence of breast cancer diagnosed younger than 50 years of age is higher in *BRCA1* carriers compared with *BRCA2* carriers, but both groups have an increased risk of premenopausal breast cancer, as well as increased lifetime risks.
Contralateral (opposite) breast	Up to 63% at 25 years post-diagnosis but highly age-dependent	7% at 25 years post-diagnosis[2]	Risk is affected by other factors such as tamoxifen use and oophorectomy. Mutation carriers who have had lumpectomy have increased ipsilateral risks over long follow-up periods.
Ovarian	*BRCA1:* Approximately 40% *BRCA2:* Approximately 15%	~1%[1]	The incidence of ovarian cancer diagnosed younger than 50 years of age is higher in *BRCA1* carriers, and overall rare in all carriers younger than 40 years old. Risk of fallopian tube cancer is also substantially elevated.
Colon	Unclear	~5%[1]	Studies have not been consistent about whether risk is elevated. If elevated, risk is likely to be small.
Prostate	Elevated; absolute risk not well defined	~14% Whites ~19% African Americans	Risk appears to be higher in *BRCA2* carriers and in men younger than 65 years old.
Male breast	*BRCA1:* 1% *BRCA2:* 8%	0.1%[3]	Risk before age 50 is very low.
Pancreatic	*BRCA1:* Unclear *BRCA2:* 5%	1.5%[1]	Risk in *BRCA2* carriers is higher versus *BRCA1* carriers.
Other sites	To be determined	Varied	These sites may include cancer of the stomach and skin (melanoma), and uterine papillary serous carcinoma.

Based on Ontario Ministry of Health and Long Term Care guidelines, individuals with a personal or family history of cancer as described below may be eligible to be seen for genetic counselling:

1. Multiple cases of breast cancer (particularly where diagnosis occurred at less than 50 years) and/or ovarian* cancer (any age) in the family – especially in closely related relatives in more than one generation.
2. Age at diagnosis of breast cancer less than 35 years.
3. A family member diagnosed with both breast and ovarian* cancer.
4. Breast and/or ovarian* cancer in Jewish families.
5. Family member(s) with primary cancer occurring in both breasts, especially if one or both cancers were diagnosed before age 50.
6. A family member diagnosed with invasive serous ovarian* cancer.
7. Presence of male breast cancer in the family.
8. Family member with an identified BRCA1 or BRCA2 mutation.
9. Presence of other associated cancers or conditions suggestive of an inherited cancer syndrome.

*includes cancer of the Fallopian tubes and primary peritoneal cancer

Breast Screening

You are speaking to your mother. She has just received her notice from the Ontario Breast Screening Program recommending that she go for a screening mammogram. She is reluctant to attend. A recent article she read indicates there are concerns with mammographic screening in average risk women and that screening may cause more harm than good. She wants to know your opinion.

What are the breast screening guidelines for average risk women in Ontario?

What would you tell her regarding the benefits of mammographic screening?

OBSP

The OBSP screens two groups of women, which include the following:

- Ontario residents at average risk for breast cancer who are 50 to 74* years of age and have:
  - no acute breast symptoms
  - no personal history of breast cancer
  - no current breast implants
  - not had a mammogram within the last 11 months

  * Women over age 74 can be screened within the OBSP; however, they are encouraged to make a personal decision about breast cancer screening in consultation with their healthcare provider. The OBSP will not recall women over age 74 to participate in the program. There isn't enough high-quality scientific evidence to support screening women older than age 74 regularly. To continue screening through the OBSP, a healthcare provider will need to provide a referral.

ME SEARCH

The New York Times

TheUpshot

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HEALTH POLICY PERSPECTIVE

Universal Mammograms Show We Don't Understand Risk

Aaron E. Carroll @aaronecarroll MAY 6, 2014

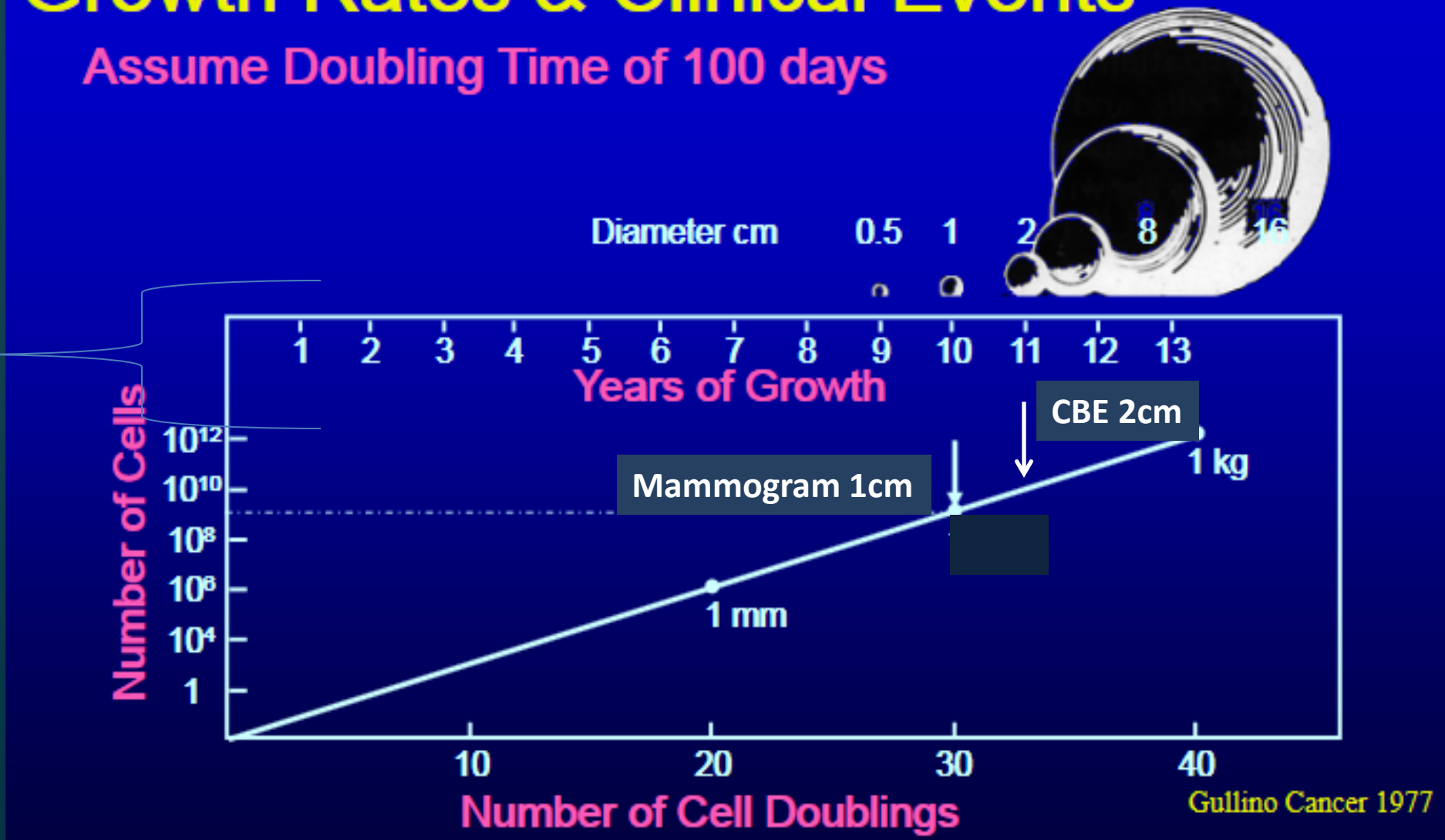
162

Out of any group of 1,000 50-year-old women today, about five are likely to die of breast cancer in the next 10 years.

If all 1,000 women received mammograms at age 50 and every two years for the next decade, though, the number of deaths might decline by only one — to four, the collected research shows.

Growth Rates & Clinical Events

Assume Doubling Time of 100 days



Gullino Cancer 1977

The Canadian Task Force on Preventive Health Care CMAJ 2011

For *(average-risk)* women aged 50–69 years, we recommend routinely screening with mammography every two to three years. (Weak recommendation; moderate-quality evidence)

Weak recommendations result when:

- the balance between desirable and undesirable effects is small
- the quality of evidence is lower
- there is more variability in the values and preferences of patients.

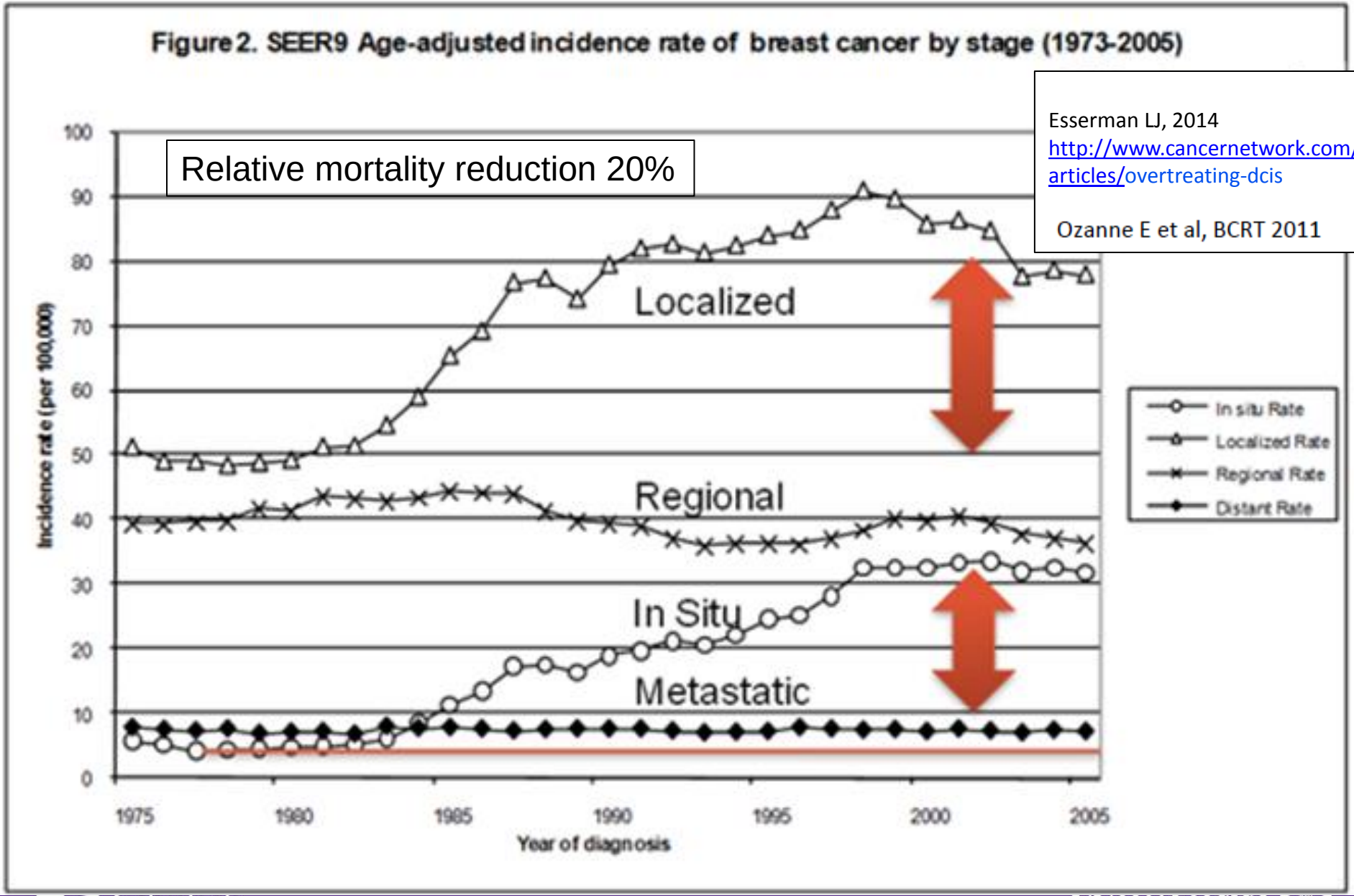


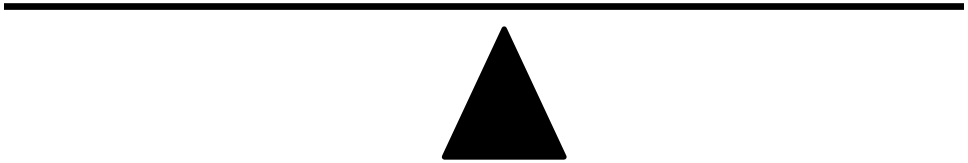
Figure 2. SEER9 Age-adjusted incidence rate of breast cancer by stage (1973-2005)
Relative mortality reduction 20%
Esserman LJ, 2014
http://www.cancernetwork.com/articles/overtreating-dcis
Ozanne E et al, BCRT 2011
Localized
Regional
In Situ
Metastatic
In situ Rate
Localized Rate
Regional Rate
Distant Rate
Incidence rate (per 100,000)
Year of diagnosis
0
10
20
30
40
50
60
70
80
90
100
1975
1980
1985
1990
1995
2000
2005

What do you discuss?

Screening 230 average risk women 50-69 over 20 years would*:

- avert 1 BC death
- *? less treatment*

- ~ 100 false positives
- ~ 40 biopsies
- 3-(5) over-diagnoses



•15-20 women will develop breast cancer

Independent UK Panel on Breast Cancer Screening, Lancet. 2012;380

Canadian Task Force on Preventive Health Care, CMAJ. 2011;183

The New York Times

HEALTH

Vast Study Casts Doubts on Value of Mammograms

By GINA KOLATA FEB. 11, 2014

One of the largest and most meticulous studies of mammography ever done, involving 90,000 women and lasting a quarter-century, has added powerful new doubts about the value of the screening test for women of any age.

Breast Screening

- Breast self-exam
  -not recommended Preventive health care, 2001 update: Should women be routinely taught breast self-examination to screen for breast cancer?N Baxter, Canadian Task Force on Preventive Health CareCanadian Medical Association Journal 164 (13), 1837-1846

- Physician routine breast exam
  -not recommended
  - Canadian breast screening studies

    - 50-60 randomized to PE + mammography vs PE
    - 40-50 randomized to PE + mammography vs observation

- Screening MRI

  – No evidence
  – Only in Ontario for lifetime risk >25%

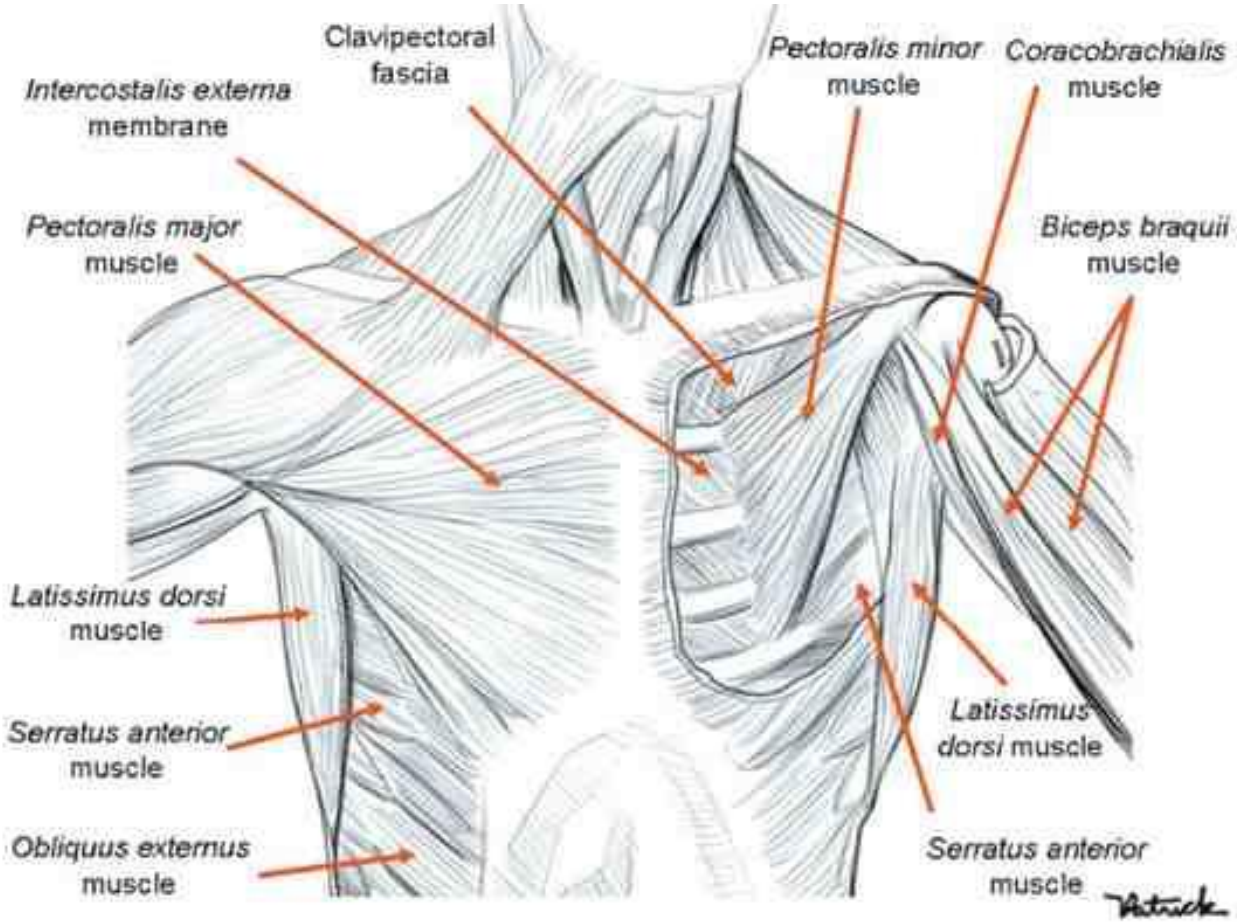
Breast MRI

- Identify occult primary in patient with axillary-positive disease
- Identify residual disease in cases of positive margins after lumpectomy
- Biopsy-proven Paget's disease and normal US and mammography

Anatomy

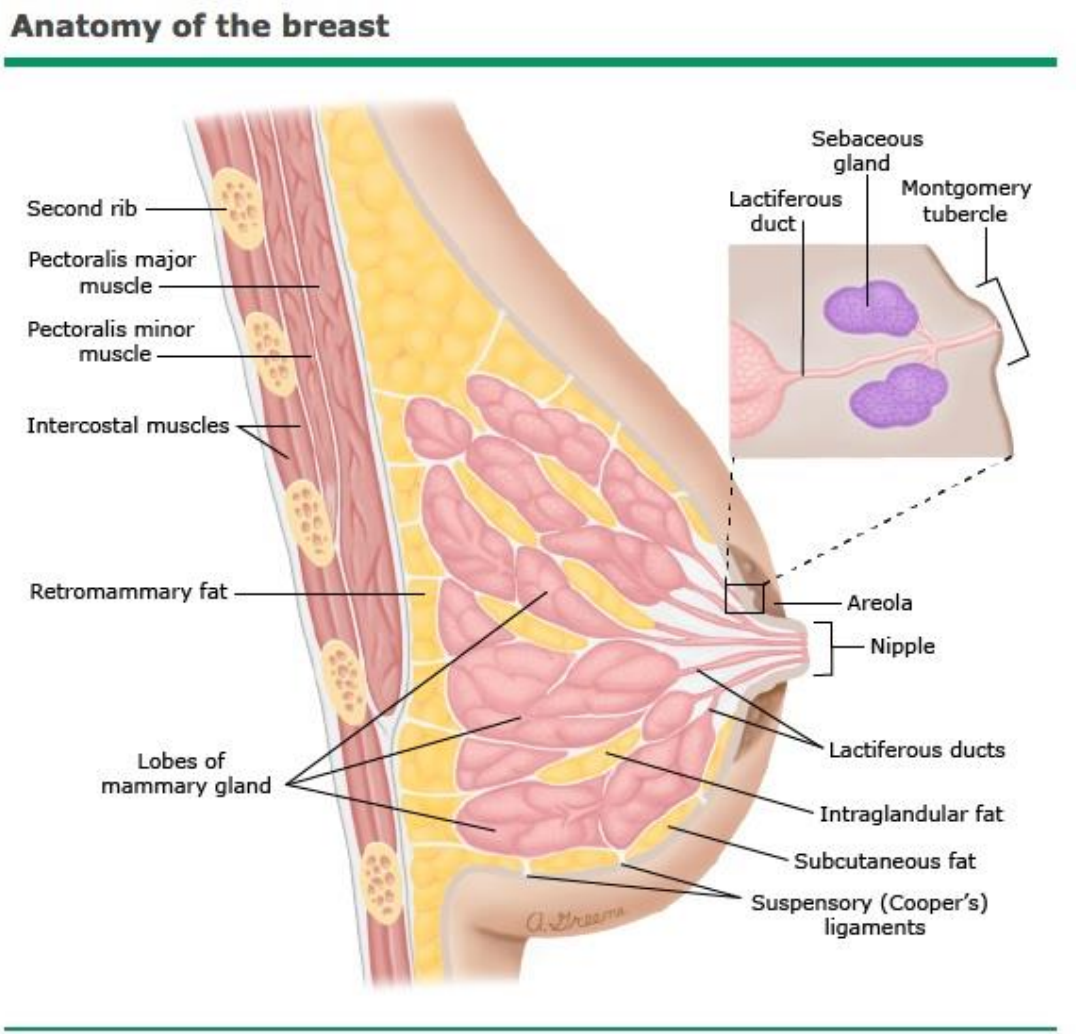
- Skin - Margins of the breast
- Muscles
- Nodal Basins
  - Axillary
  - Supraclavicular
  - Internal mammary
- Axilla
  -Nerves
    - Intercostal
    - Lateral pectoral nv bundle
    - Thoracodorsal nv bundle
    - Long thoracic

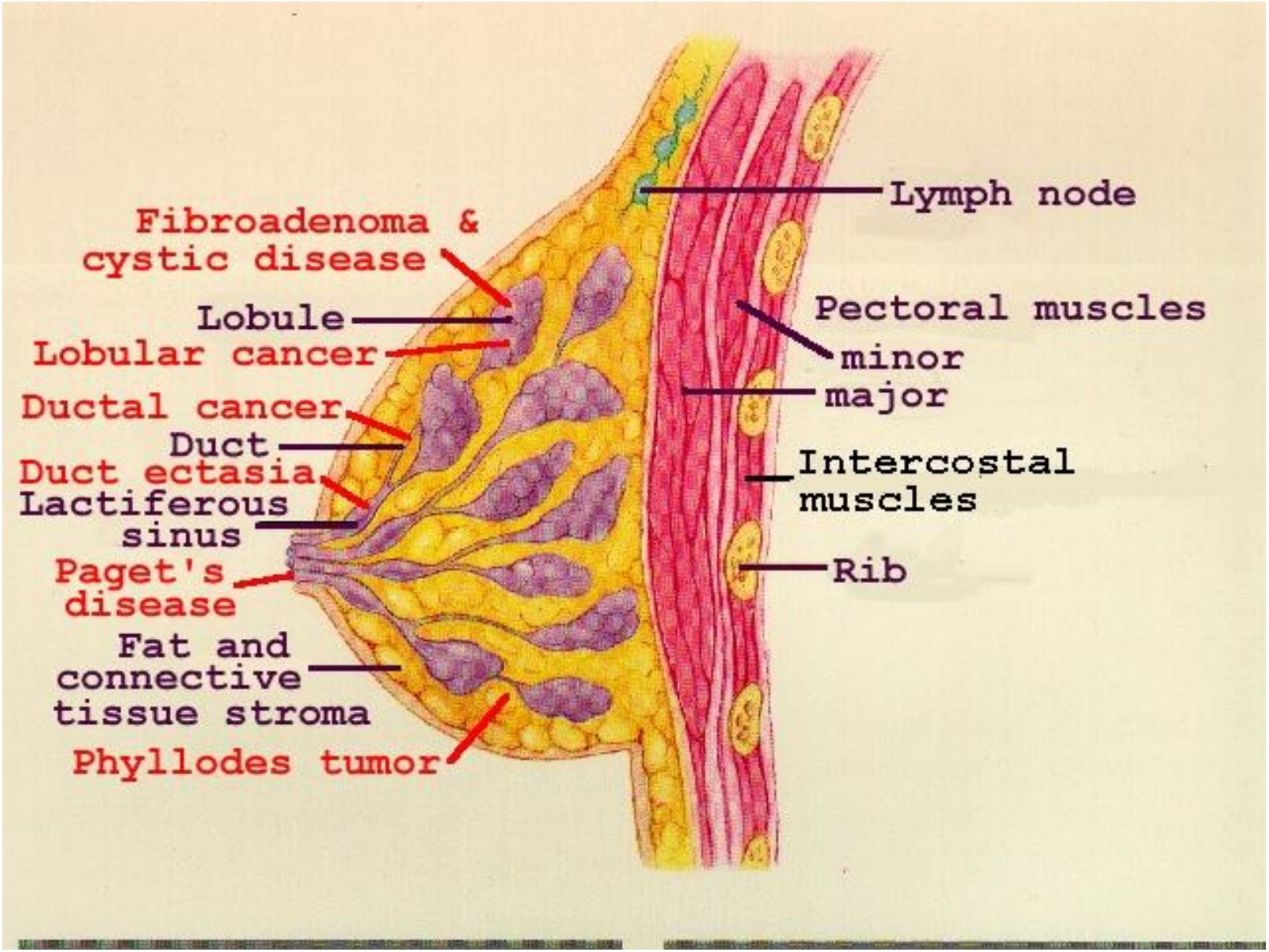
Local, regional, systemic



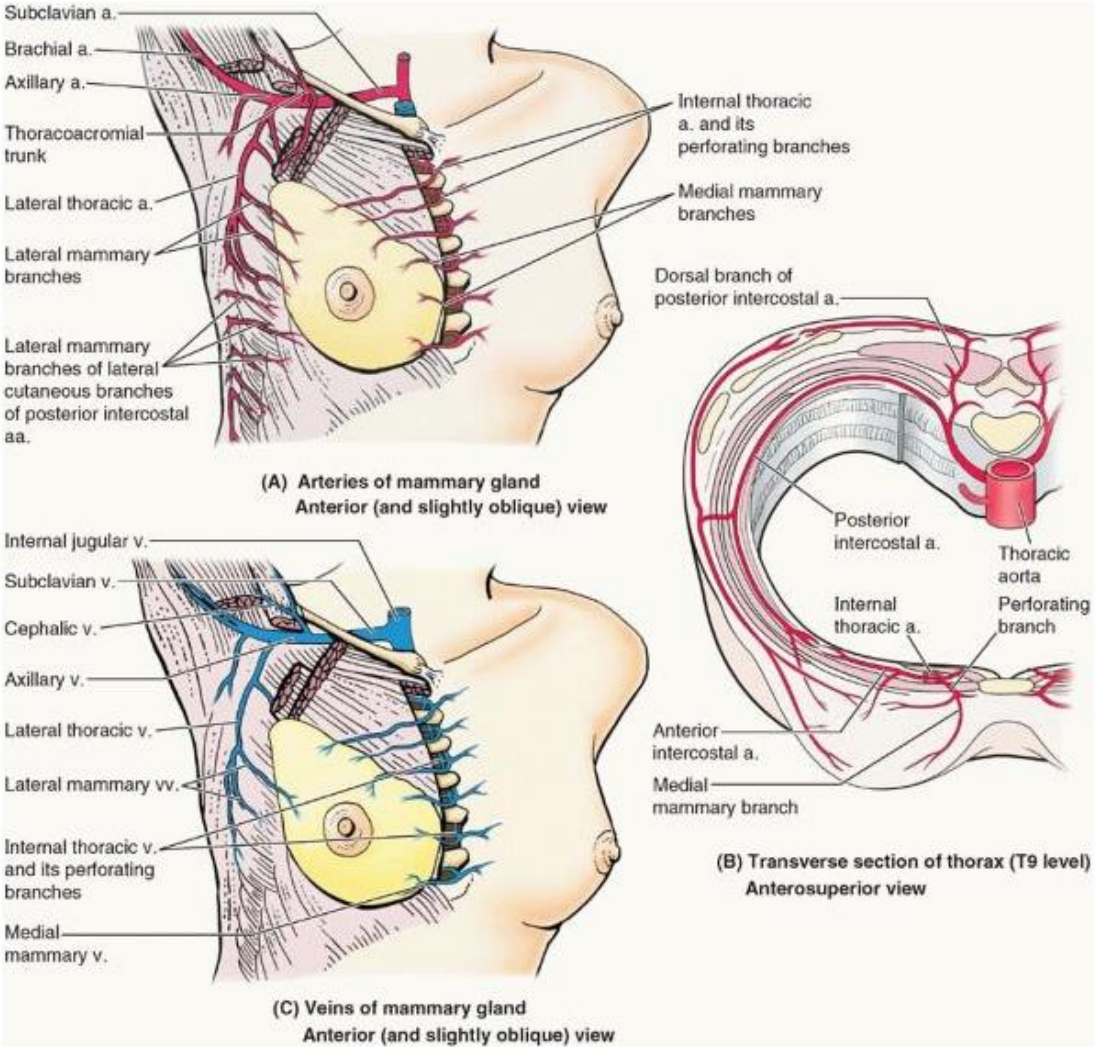
Muscles of the chest

Breast Anatomy



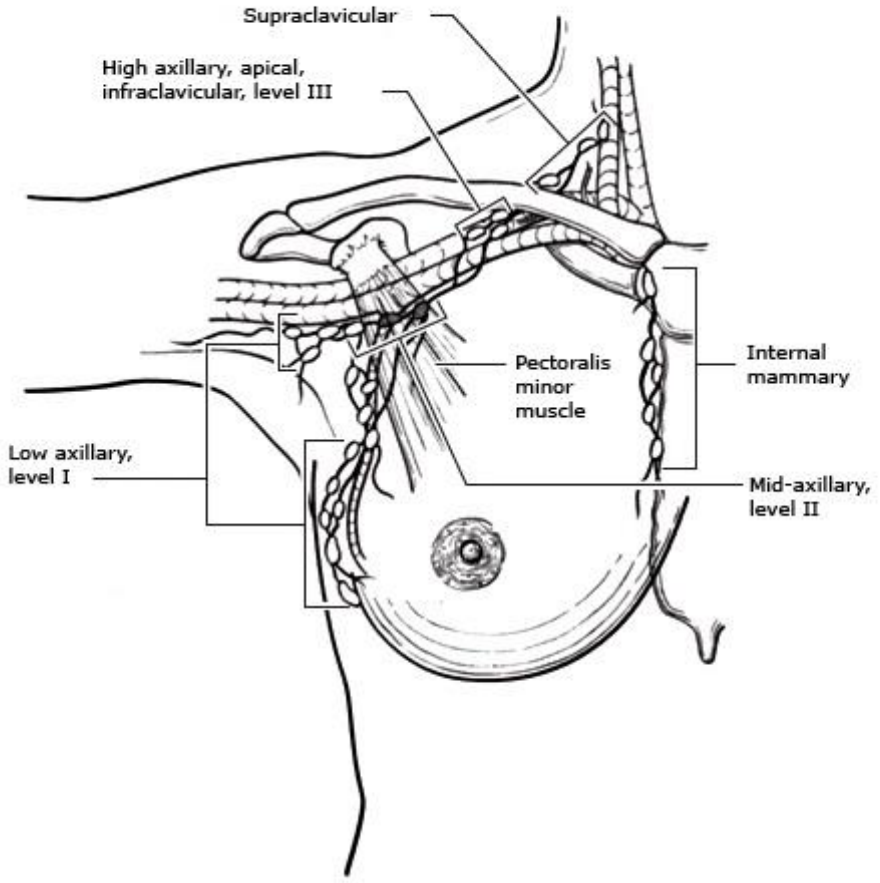

Fibroadenoma & cystic disease
Lobule
Lobular cancer
Ductal cancer
Duct
Duct ectasia
Lactiferous sinus
Paget's disease
Fat and connective tissue stroma
Phyllodes tumor
Lymph node
Pectoral muscles
minor
major
Intercostal muscles
Rib

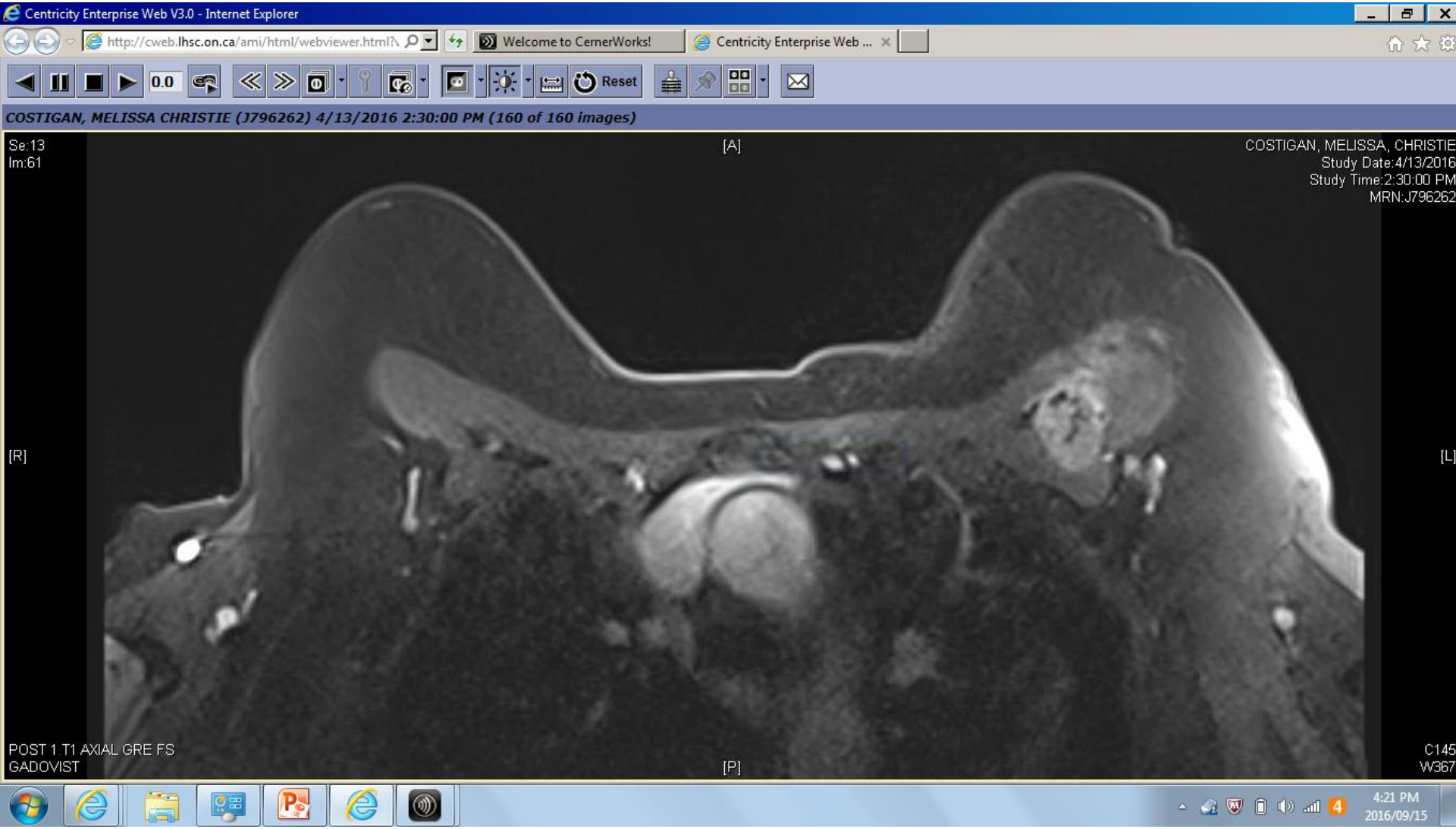
Breast Anatomy



Breast Anatomy

Schematic of the breast and regional lymph nodes

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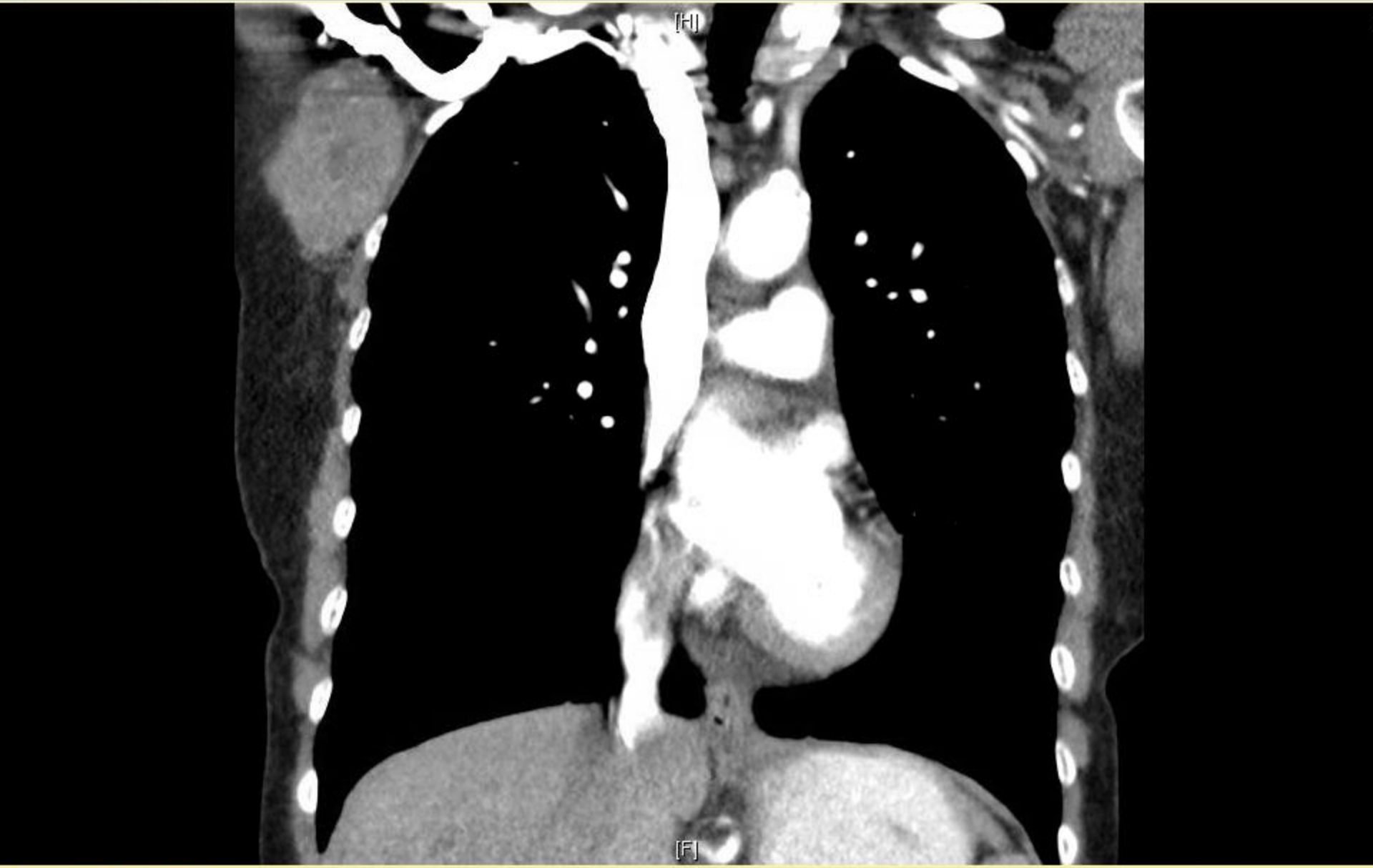


Case

- 42 year old woman, otherwise healthy, woman is referred to you for a suspicious lesion (BIRADS 4) in her left breast
- She undergoes stereotactic biopsy and the pathology is LCIS
- Plan?

LCIS

- Non-invasive lesions that arise from lobules and terminal breast ducts
- Not identified clinically, radiographically or by gross pathology
- Serves as an indicator of increased risk of breast cancer development in either breast
- 80-90% of LCIS diagnosed in pre-menopausal women

LCIS

- Absolute risk of breast cancer development is 1% per year and double that of average-risk women
- Chemoprevention with tamoxifen over 5 years has been shown to reduce cancer risk by half over 10 years in trials

High risk breast lesions

TABLE 1. Summary of Benign Breast Disease Lesions by Histology, Relative Breast Cancer Risk, and Mammographic Abnormality

Category (relative cancer risk)	Mammographic findings
Nonproliferative (RR, 1.2-1.4×)	
Simple cyst	Circumscribed mass
Fibrosis	Mass, focal asymmetry
Fibroadenoma (simple)	Circumscribed mass
Columnar alteration (simple)	Calcifications
Apocrine metaplasia (simple)	Mass, focal asymmetry
Mild ductal hyperplasia	Calcifications
Proliferative disease (RR, 1.7-2.1×)	
Usual ductal hyperplasia	Calcifications
Sclerosing adenosis	Calcifications, focal asymmetry, architectural distortion
Columnar hyperplasia	Calcifications
Papilloma	Mass, calcifications
Radial scar	Architectural distortion
Proliferative disease with atypia (RR, ≥4×)	
Atypical lobular hyperplasia	None, calcifications
Lobular carcinoma in situ	None, calcifications
Atypical ductal hyperplasia	Calcifications
Unclear risk	
Mucocele-like tumor	Calcifications, mass
Apocrine atypia	Calcifications, mass
Secretory atypia	Calcifications

RR = relative risk.

High risk breast lesions

TABLE 2. Management of Breast Lesions Identified on Core Needle Biopsy

Breast lesion	Management	Surveillance
Atypical ductal hyperplasia	Surgical consultation with excision	CBE every 6-12 mo; annual mammogram
Lobular neoplasia, ALH/LCIS	Surgical consultation	CBE every 6-12 mo; annual mammogram
Flat epithelial atypia	Surgical consultation	CBE every 6-12 mo; annual mammogram
Papillomas	Surgical consultation for lesions with atypia, size >10 mm, multiple or peripheral	CBE every 12 mo; annual mammogram
Radial scar/complex sclerosing lesion	<10 mm: observation if adequately sampled >10 mm: surgical consultation	If excised, annual CBE and mammogram
Fibroadenoma	Surgical consultation if atypical features or enlarging	Annual CBE and mammogram
Complex fibroadenoma	Observation	Annual CBE and mammogram
Sclerosing adenosis	Observation	Annual CBE and mammogram
Fat necrosis	Observation	Annual CBE and mammogram
Columnar cell hyperplasia	Observation	Annual CBE and annual mammogram
Phyllodes tumor	Surgical consultation	CBE every 12 mo Annual mammogram
Desmoid tumor/mammary fibromatosis	Surgical consultation	CBE every 12 mo Annual mammogram
PASH	Surgical consultation if large or symptomatic	Annual CBE and mammogram
Apocrine metaplasia	Surgical consultation if atypia present or discordant	Annual CBE and mammogram if excised

ALH = atypical lobular hyperplasia; CBE = clinical breast examination; LCIS = lobular carcinoma in situ; PASH = pseudoangiomatous stromal hyperplasia.

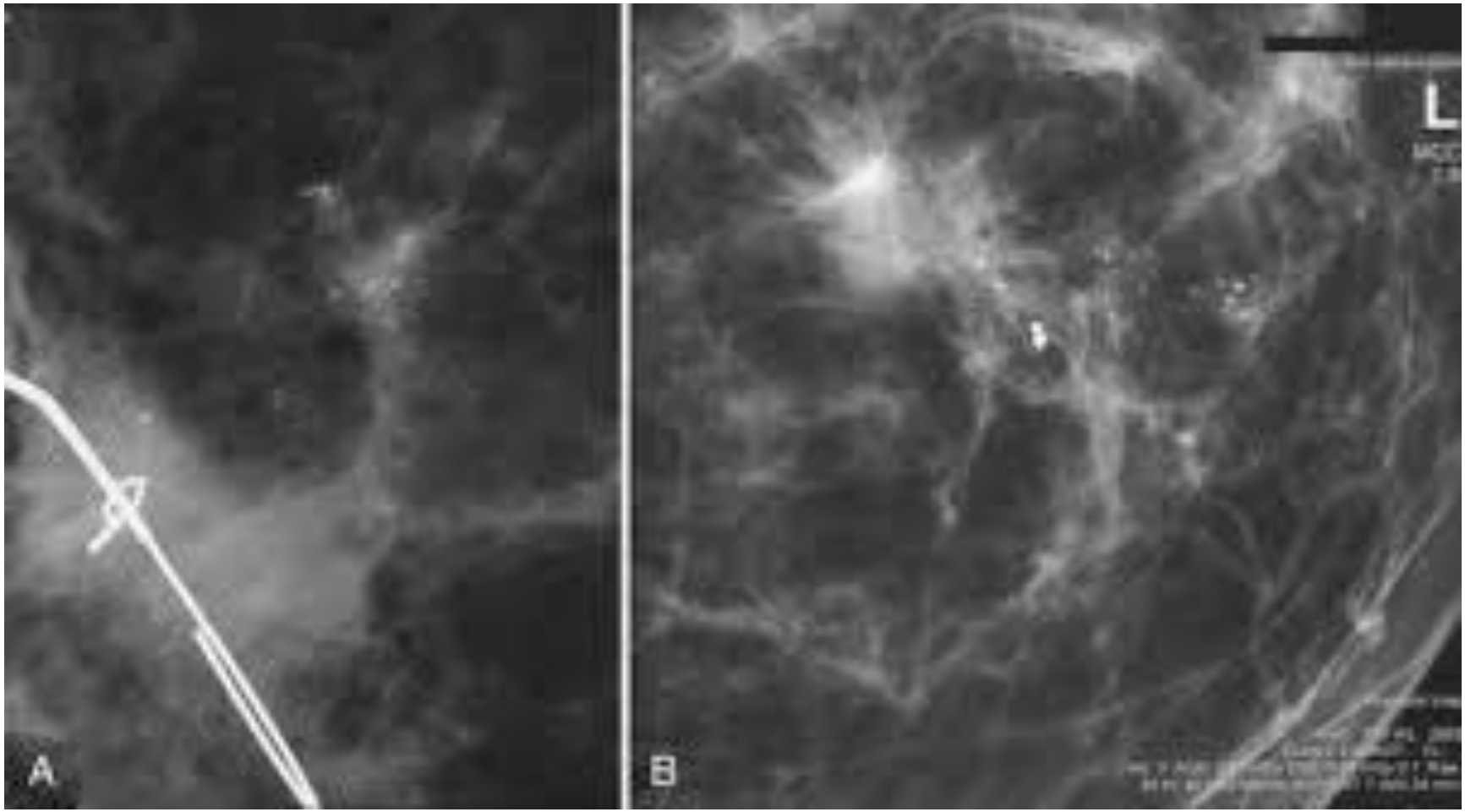
Case

- 54 year old women referred to your clinic for a small cluster of microcalcifications in right breast picked up screening mammography
- Medical history is HTN, Hypothyroidism
- Her mother was diagnosed with breast cancer at the age of 68, no other family history
- Plan?

Case

- Biopsy reveals ER/PR positive DCIS
- She has been reading about the treatment options online and is concerned about needing surgery, and is also asking what are the chances she will need radiotherapy
- How do you counsel this woman?

DCIS



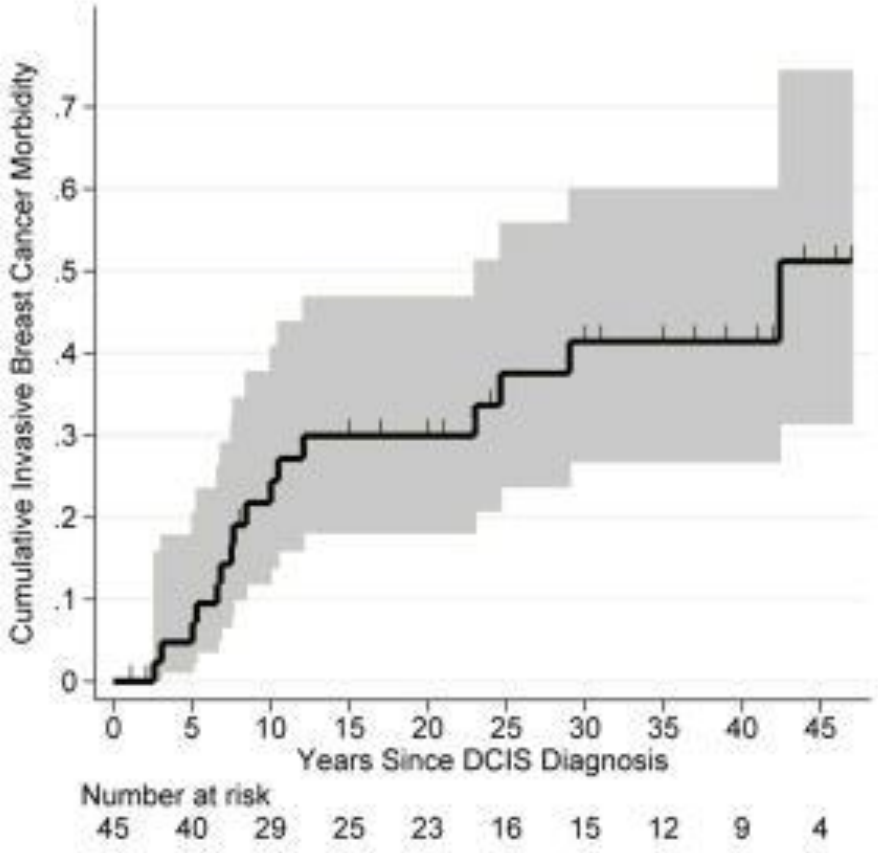
DCIS and MRI

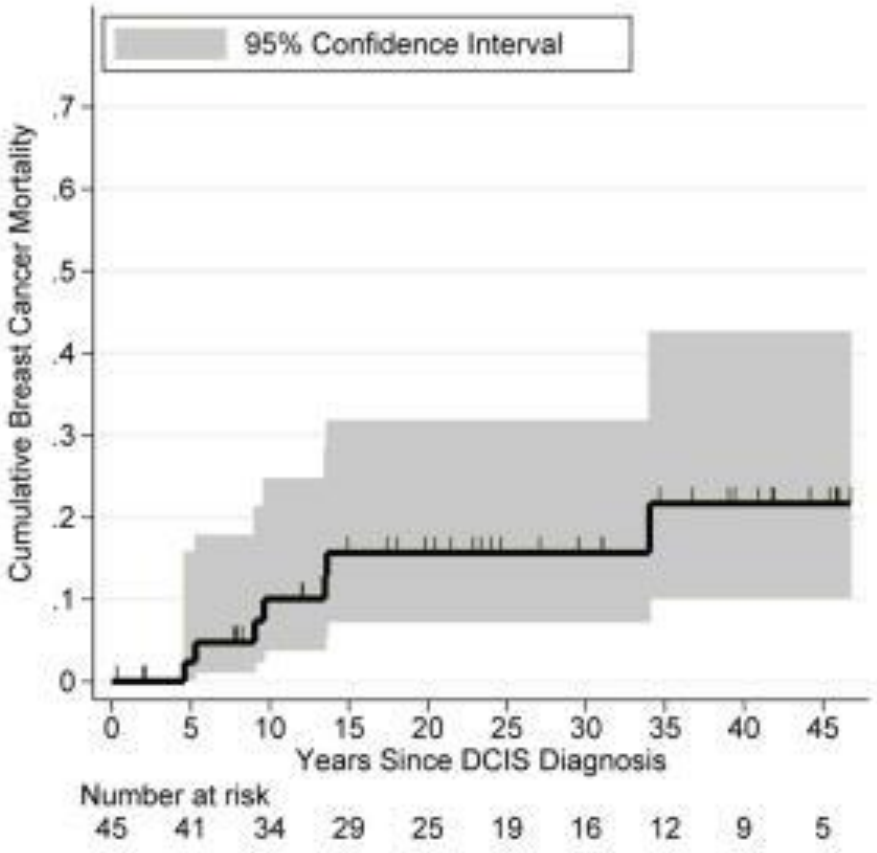
TABLE 3. Summary of the Literature Evaluating the Impact of MRI on Surgical Outcomes in Patients With DCIS

Reference	Patients With MRI/Total No. of Patients	Re-excision Rate: MRI	Re-excision rate: No MRI	*P*	Mastectomy Rate: MRI	Mastectomy Rate: No MRI	*P*
Allen 2010[61]	63/98 (64%)	21.2%	30.8%	.41	20.3%[a]	25.7%[a]	.62
Itakura 2011[62]	38/149 (26%)	16.0%	11.0%	.42	45.0%[b]	14.0%[b]	<.001
Kropcho 2012[63]	60/158 (38%)	30.7%	24.7%	.40	17.7%[c]	4.1%[c]	.0004
Davis 2012[65]	154/218 (71%)	34.1%	39.2%	.52	27.9%[a]	23.4%[a]	NS
Pilewskie 2013[64]	217/352 (62%)	14.3%	20.0%	.19	34.6%[b]	27.4%[b]	.20

Pilewski, Cancer 2014;

Natural History of Low grade DCIS





Dupont, Mod Pathol. 2015 May; 28(5): 662–669

DCIS Surgery

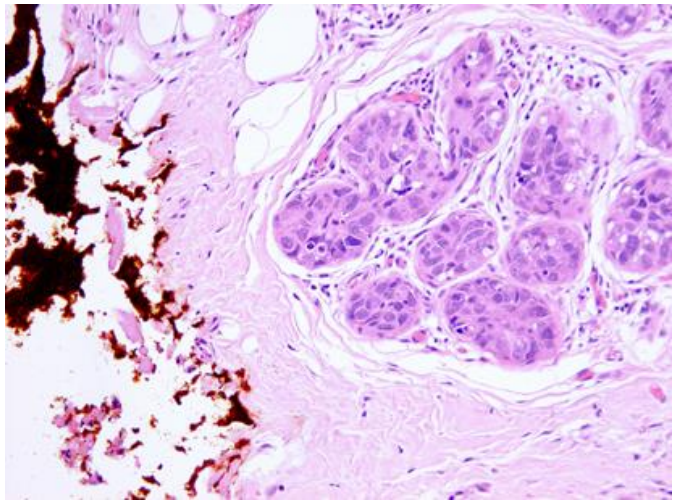
- Lumpectomy +/- radiation preferred

- Margins - *SSO, ASTRO JCO August 15, 2016*
  - 0-2mm recurrence 18%, 2mm 9%
  - 2mm recommended

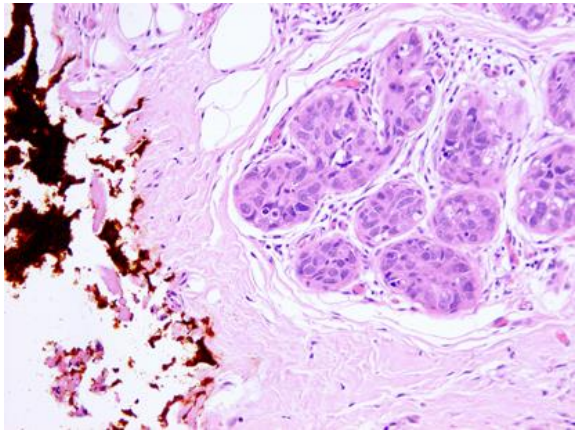
The “holy grail” of margins

>1cm are achieved in <10%

of patients



DCIS Margins



- ‘gaps’, most commonly seen in low grade DCIS, whereas high grade tends to have a continuous growth pattern

Suggestion:

- No tumour at the inked margin is OK
- Minimum 3mm margin if want to try and avoid radiation based on recent trials (low + intermediate grade)

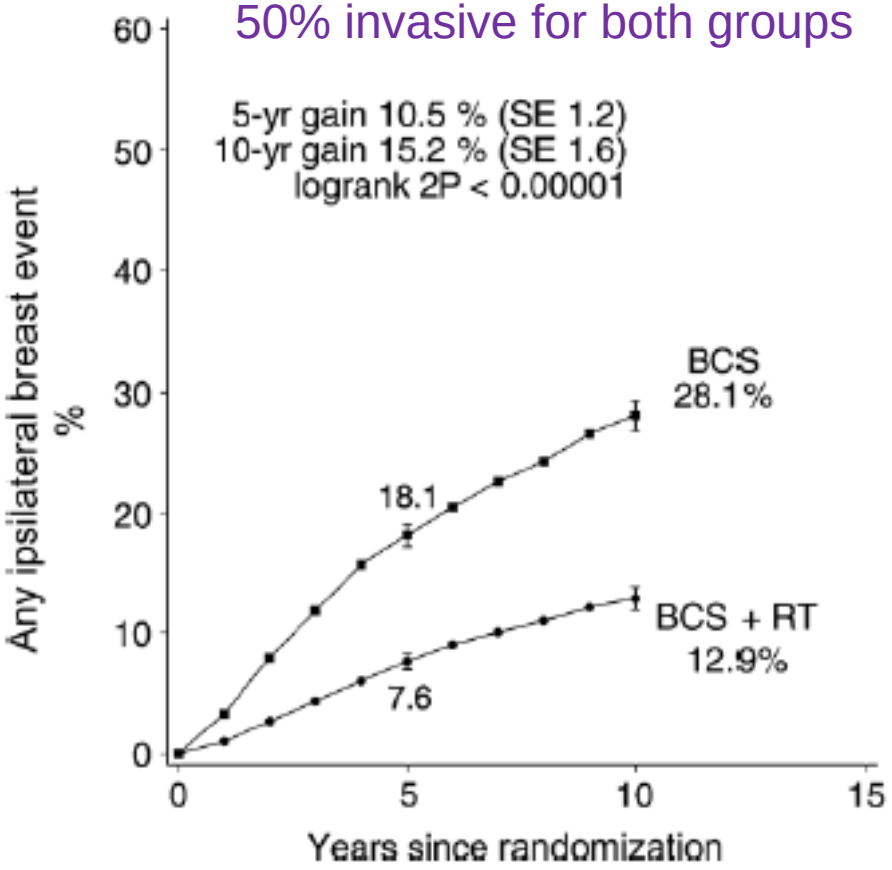
Van Nuys Prognostic Index (VNPI)

Factor			3
Size	≤1	mm	>40 mm
Margin	≥ 10	9 mm	<1 mm
Pathology	grade 1/ no necrosi	grade 2 necrosis	grade 3
Age	>60 ye	-60 years	<40 years

Silverstein MJ, Lagios MD, *J Natl Cancer Inst Monogr*. 2010;41:193-6.

DCIS lumpectomy +/- radiotherapy

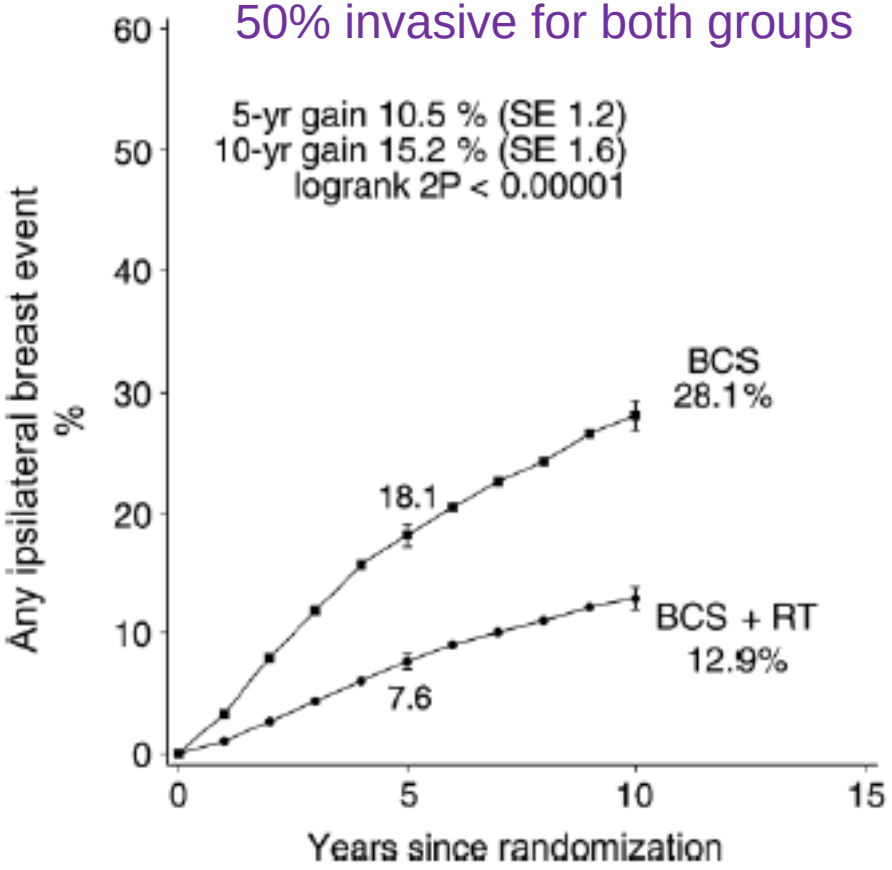
50% invasive for both groups

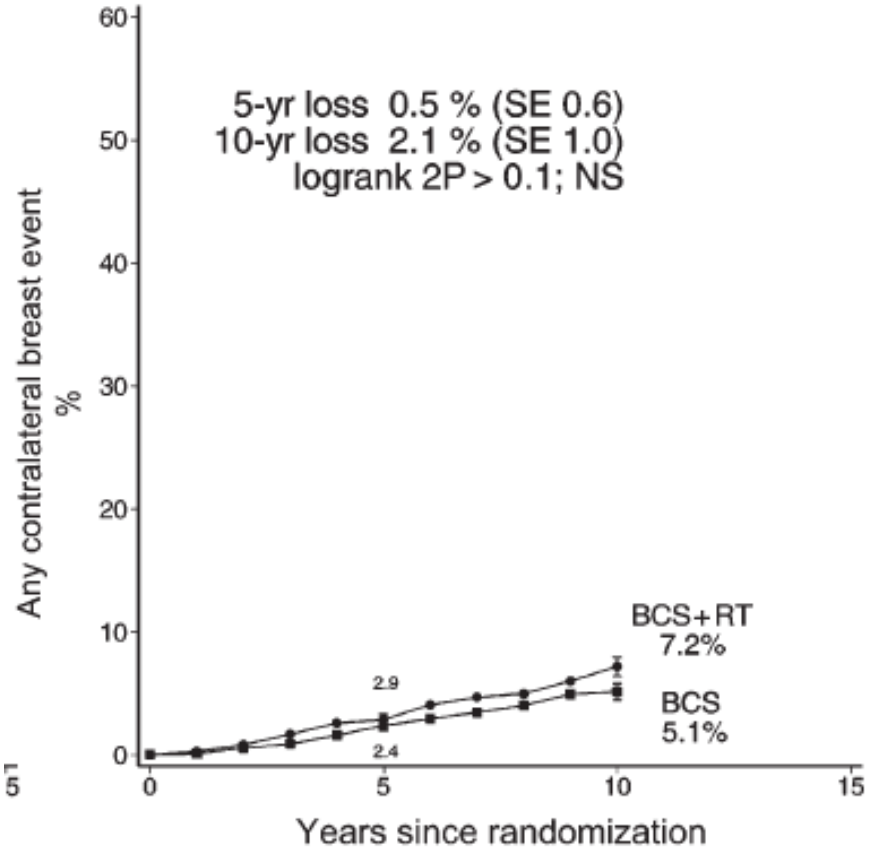


EBCTCG, JNCI Monograph 2010; 41

DCIS lumpectomy +/- radiotherapy

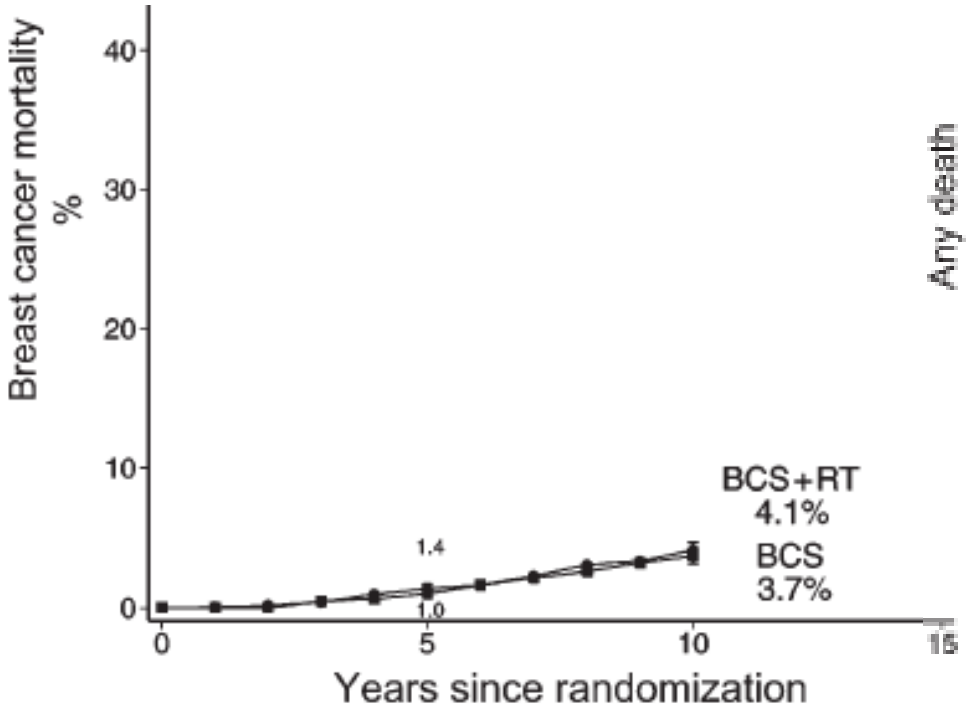
50% invasive for both groups

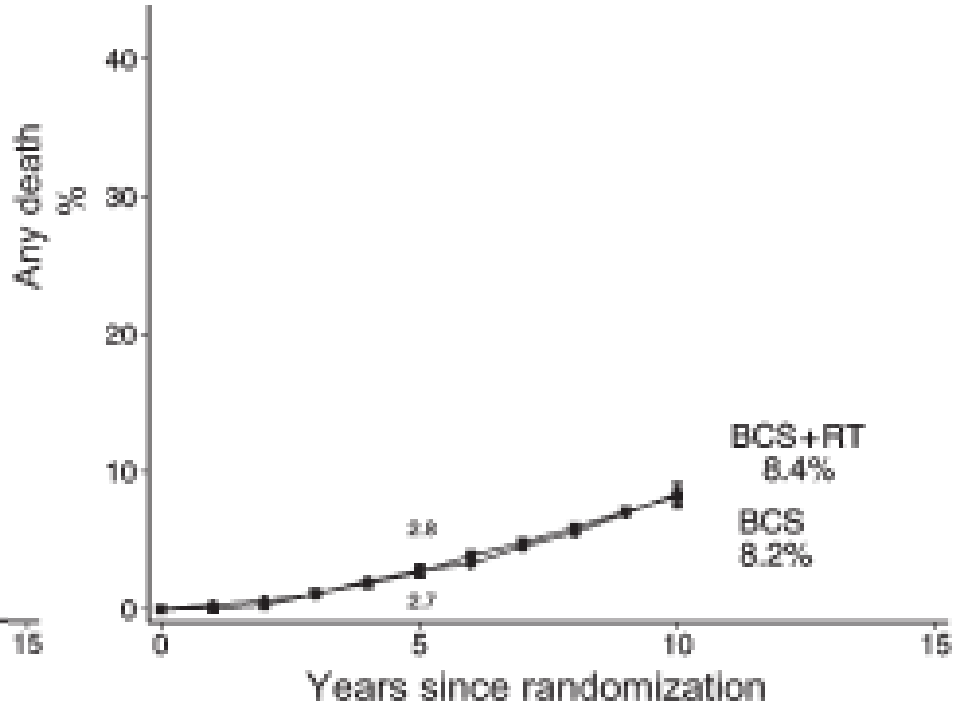




EBCTCG, JNCI Monograph 2010; 41

DCIS lumpectomy +/- radiotherapy





EBCTCG, JNCI Monograph 2010; 41

DCIS lumpectomy +/- radiotherapy

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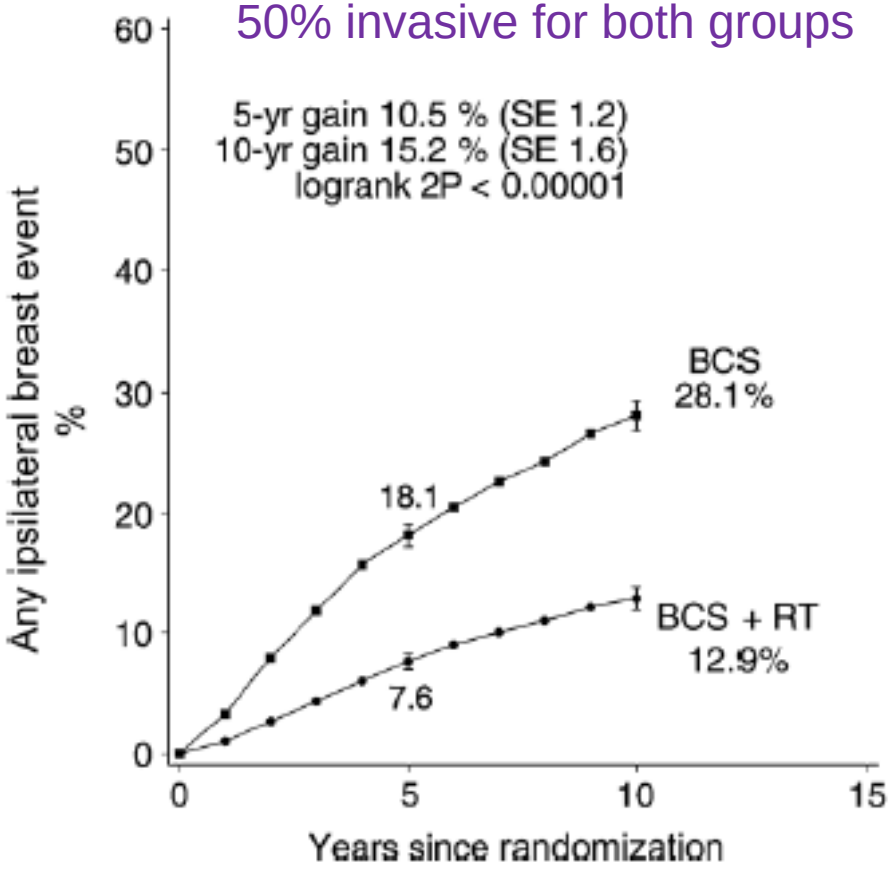
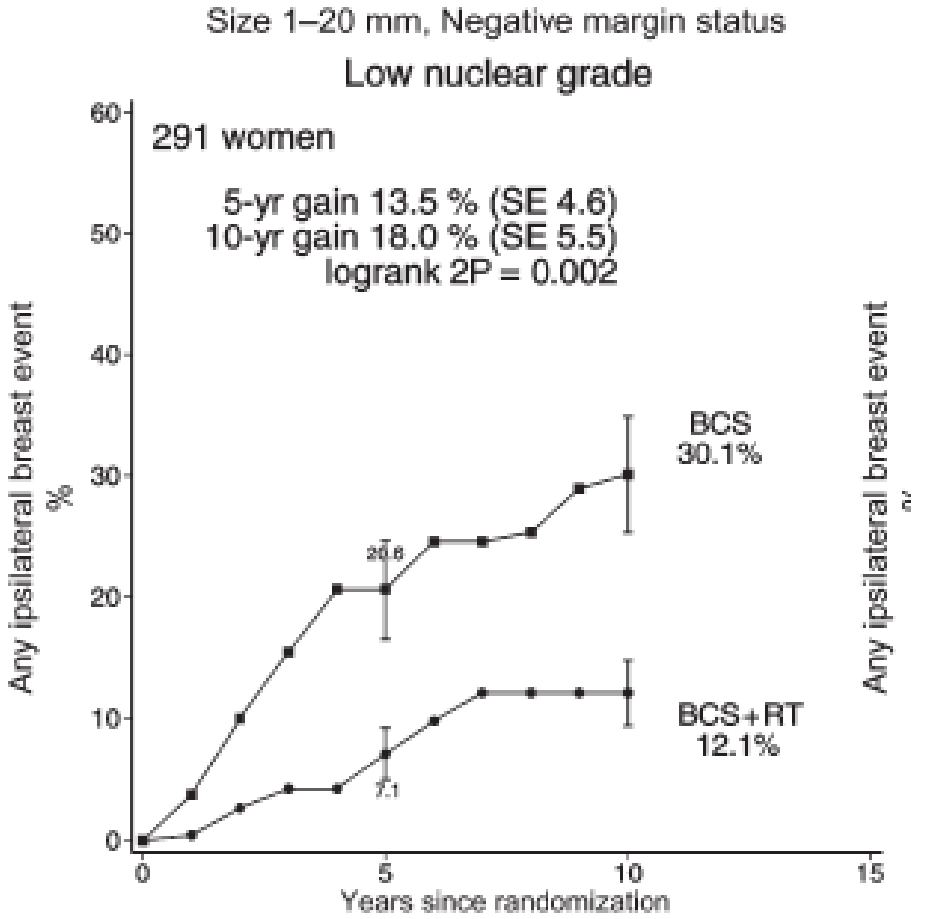
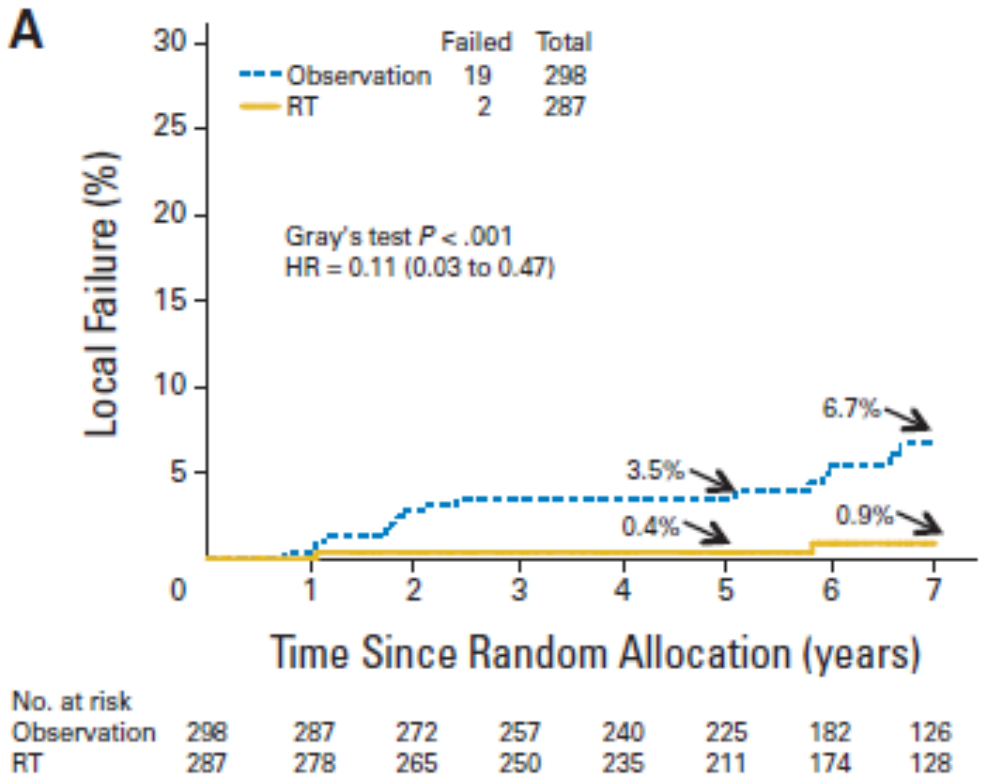
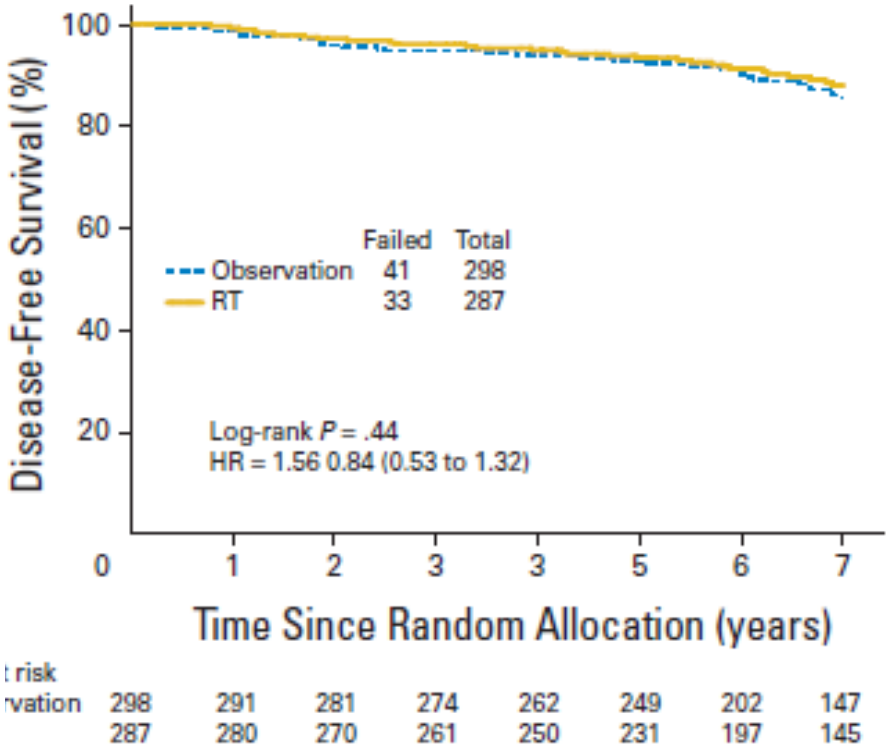




EBCTCG, JNCI Monograph 2010; 41

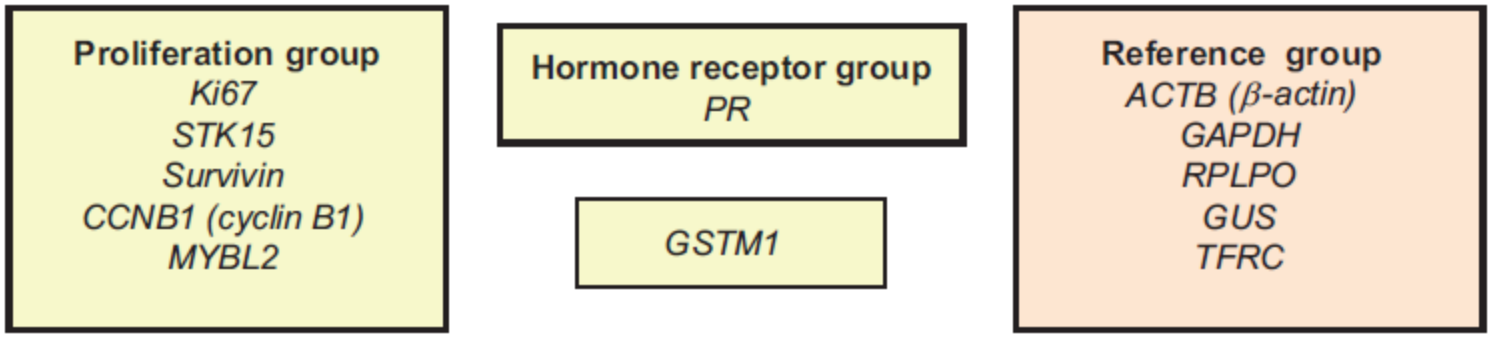
BCS Alone: RTOG 9804





McCormick, JCO 2015; 33

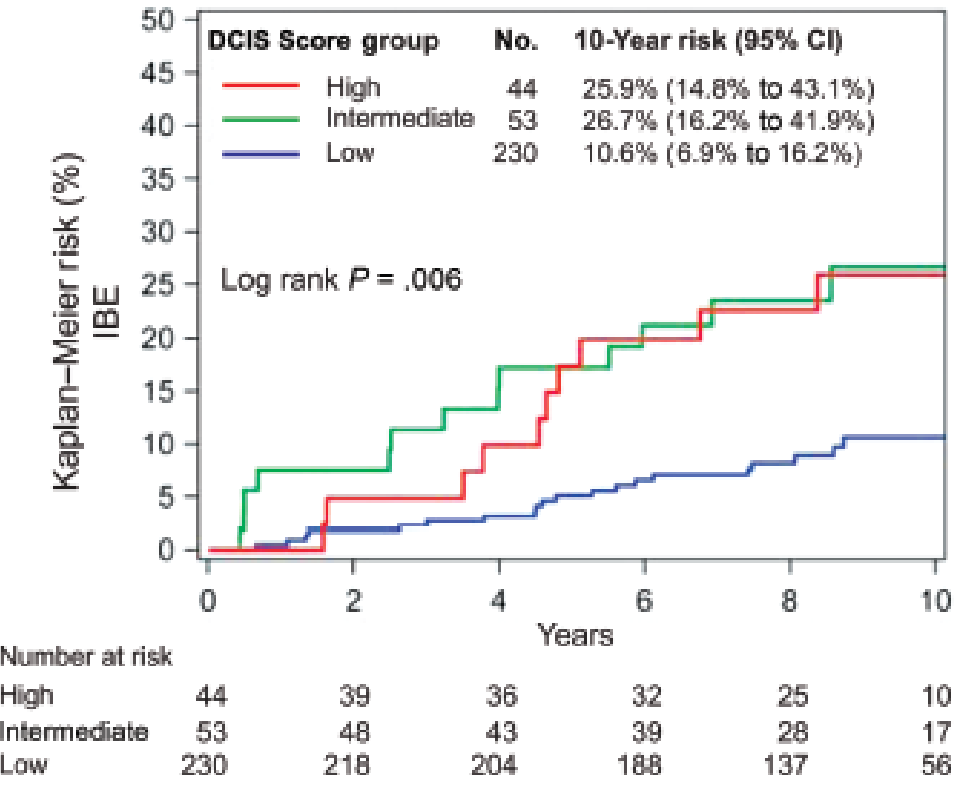
DCIS Score



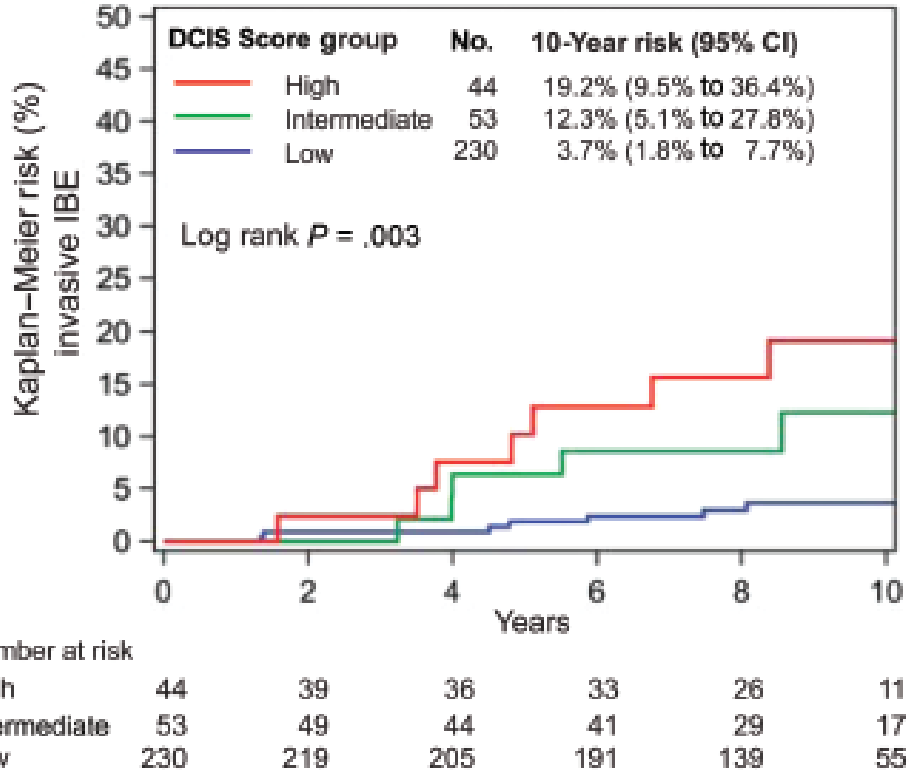
Solin, JNCI 2013;105

Recurrence Score

Ipsilateral Breast Events



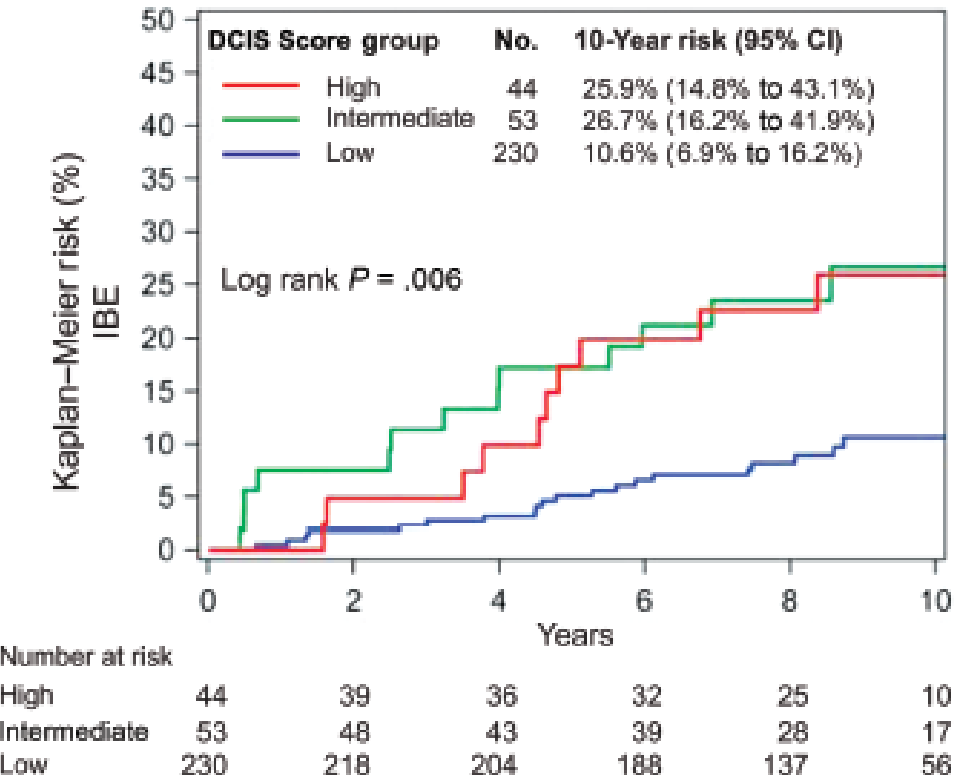
Ipsilateral Invasive Breast Events

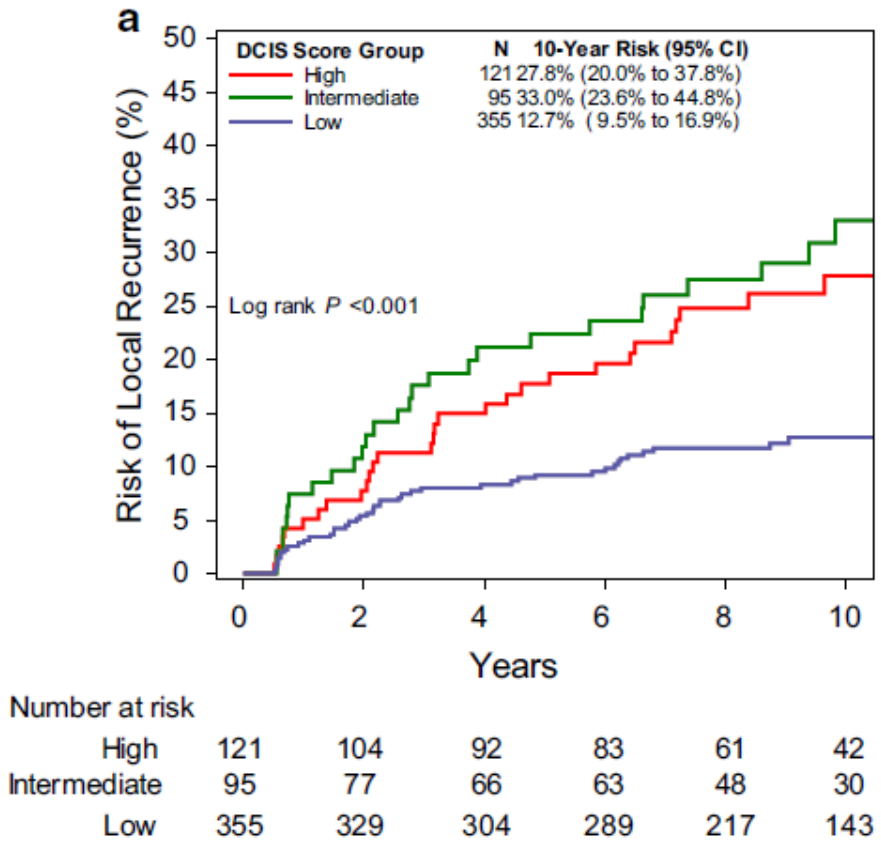


Solin, JNCI 2013;105
Rakovitch, SABCS 2014

DCIS Recurrence Score

Ipsilateral Breast Events





Solin, JNCI 2013;105

Rakovitch, BCRT (2015) 152:389–398

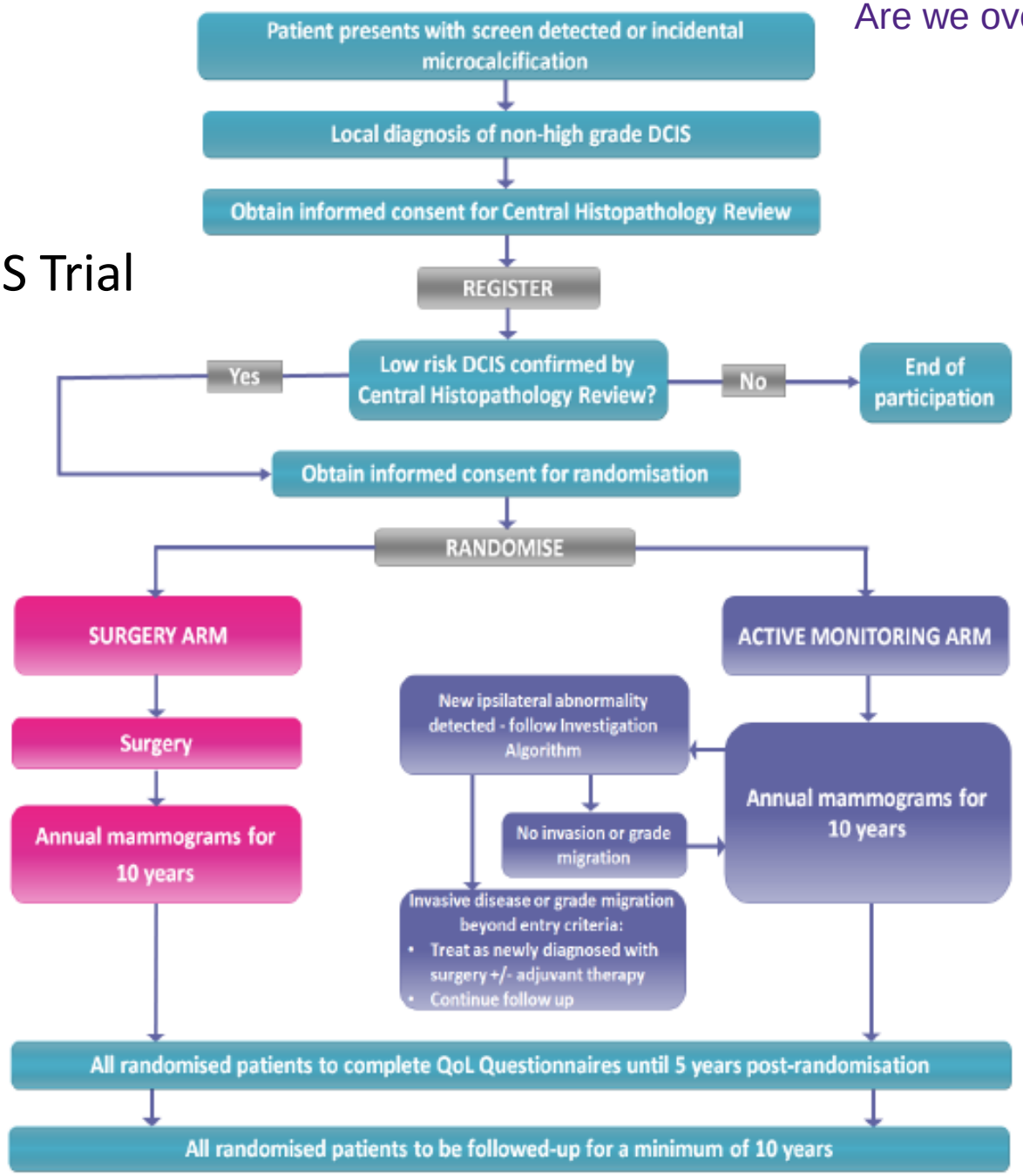
Tamoxifen and DCIS

	NNT to Prevent 1 Breast Event	**NNT to Prevent 1 Invasive Breast Event**
BCS alone	13	28
BCS + Radiation	17	33

Staley, The Breast 2014; 23

Low Risk DCIS Trial (LORIS)

A Francis



DCIS + SN Biopsy

- recommended for mastectomy patients
- can be considered in BCS patients with palpable or larger high grade lesions.

		SLN in DCIS with BCS
Chin-Lenn, Ann Surg Onc 2014; 21	Alberta	61%
Nicholson, EJSO 2015; 41	UK (Sloane project)	24%

Tamoxifen and DCIS

	NNT to Prevent 1 Breast Event	**NNT to Prevent 1 Invasive Breast Event**
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Staley, The Breast 2014; 23

Classification of Breast Ca

- Infiltrating ductal – 76%
- Infiltrating lobular – 8%
- Ductal/lobular – 7%
- Mucinous (colloid) – 2.5%
- Tubular/Medullary/Papillary – 1% each

Infiltrating ductal

- Vast majority of breast cancers
- Pathologically graded into 3 categories: well, moderately and poorly differentiated
- Often associated with DCIS, and the amount of DCIS present is an important prognostic factor in patients treated with breast-conserving surgery

Infiltrating lobular

- Second most common breast cancer
- Rates rising in NA, may be associated with post-menopausal hormone use
- Appear later and usually are well-differentiated
- Some evidence suggests a better prognosis for most sub-types compared to ductal

Mucinous (Colloid)

- Rare (1-2% of all breast cancers)
- Soft gelatinous appearance, usually a well-circumscribed lesion
- Better prognosis than ductal

Medullary

- Account for ~1% of breast cancers
- Often are poorly-differentiated, are common in younger women, and are associated with BRCA1
- Despite their aggressive appearance, prognosis is more favourable compared to ductal

TNM Staging

Tumor node metastases (TNM) staging system for carcinoma of the breast

Primary tumor (T)*¶Δ	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease (Paget disease) of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4◇	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma§

TNM Staging

Pathologic (pN)†**	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including isolated tumor cell clusters (ITC))
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)¶¶
pN0(mol+)	Positive molecular findings (RT-PCR)¶¶, but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected ΔΔ
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected ΔΔ
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected◇◇ internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected◇◇ internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected◇◇ ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected ΔΔ; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected◇◇ ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected ΔΔ
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

TNM Staging

Anatomic stage/prognostic groups§§			
0	Tis	N0	M0
IA	T1¥¥	N0	M0
IB	T0	N1mi	M0
	T1¥¥	N1mi	M0
IIA	T0	N1‡‡	M0
	T1¥¥	N1‡‡	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1¥¥	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Hormone Receptors

- ER/PR receptor positive disease accounts for ~75% of breast cancers
- Adjuvant hormone therapy has demonstrated benefit in these patients
- Agents used are tamoxifen and aromatase inhibitors

Tamoxifen

- Selective Estrogen Receptor Modulator (SERM)
- Agent of choice for premenopausal women
- Important side-effect is risk of venous thrombosis

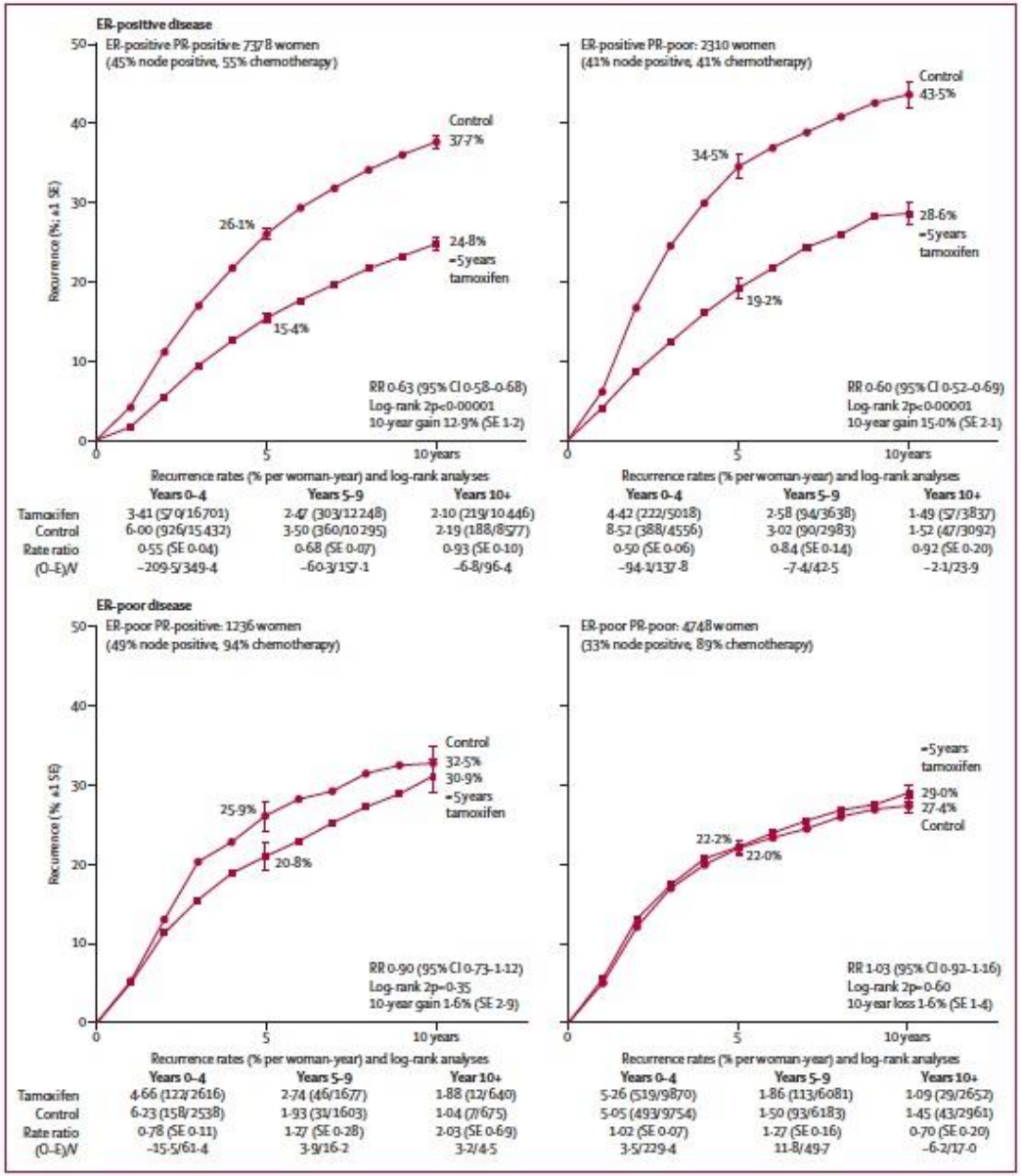


Figure 1: **Relevance of measured ER and PR status to the effects of about 5 years of tamoxifen on the 10-year probability of recurrence**
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain (and its SE) is absolute difference between ends of graphs. ER=oestrogen receptor. PR=progesterone receptor. O–E=observed minus expected, with variance V.

Aromatase Inhibitors

- Inhibit peripheral conversion of androgens to estrogen
- In post-menopausal women, is superior to tamoxifen for both recurrence and mortality
- Side-effects include AI-associated MSK syndrome and long term bone density decrease
- Anastrazole, Letrozole, Exemestane

Tratuzumab (Herceptin)

- Interferes with HER2/neu receptor, stopping cells that overexpress HER2 from proliferation
- Administered for 12 months with adjuvant chemotherapy and has overall survival benefit for patients with HER2 positive disease

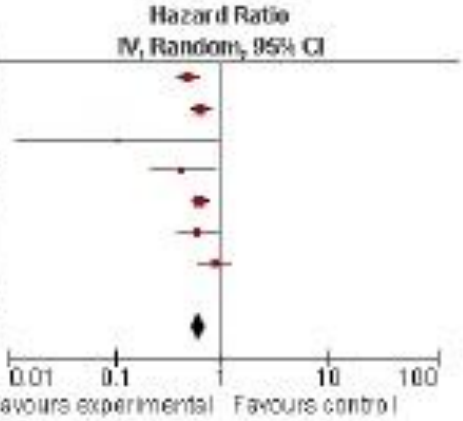
Herceptin

Figure 7. Disease-free survival: all studies.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.73	0.11	1672	1679	21.8%	0.48 [0.39, 0.60]
BCIRG006	-0.45	0.1	1074	1073	23.2%	0.64 [0.52, 0.78]
Buzdar	-2.27	1.11	23	19	0.6%	0.10 [0.01, 0.91]
FinHer	-0.87	0.35	115	116	5.2%	0.42 [0.21, 0.83]
HERA	-0.46	0.09	1703	1698	24.7%	0.63 [0.53, 0.75]
NOAH	-0.53	0.22	117	118	10.7%	0.59 [0.38, 0.91]
PACS-04	-0.15	0.18	260	269	13.8%	0.86 [0.60, 1.22]
Total (95% CI)			4964	4971	100.0%	0.69 [0.50, 0.71]

Heterogeneity: Tau² = 0.02; Chi² = 12.25, df = 6 (P = 0.06); P = 51%
Test for overall effect: Z = 6.99 (P < 0.00001)

(1) B31+N9831



“Surgical” Management (Duff School Case)

- 50 yo F
- New right breast mass . Routine normal mammogram 9 months before. Core biopsy shows invasive mammary carcinoma. Grade 3 ER 10%, PR -, Her2 +. Node positive
- Mother BC 48 died. Maternal aunt BC 54 died.
- Otherwise well, no operations.
- On exam, moderate-large breasts, nothing on inspection, 4 cm mobile mass RUQ, 3cm palpable node, no supraclavicular lymphadenopathy.
- She wants bilateral mastectomies + reconstruction

Further Investigations

- CT Scan
- Bone scan
- MRI of breast?
  - COMICE trial for affected breast

    Turnbull, Lancet 2010; 375: 563–71
  - Contralateral breast?
- Genetics referral
  - If BRCA negative will affect decision making?

"What tormented Ivan Ilych most was the deception, the lie, which for some reason they all accepted, that he was not dying but was simply ill, and that he only need keep quiet and undergo a treatment and then something very good would result."

Leo Tolstoy, The Death of Ivan Ilych 1886

Prognosis

- 25,000 breast cancer cases/year
- 5,000 breast cancer deaths/year
- 1 out of 5 women die of breast cancer

predict



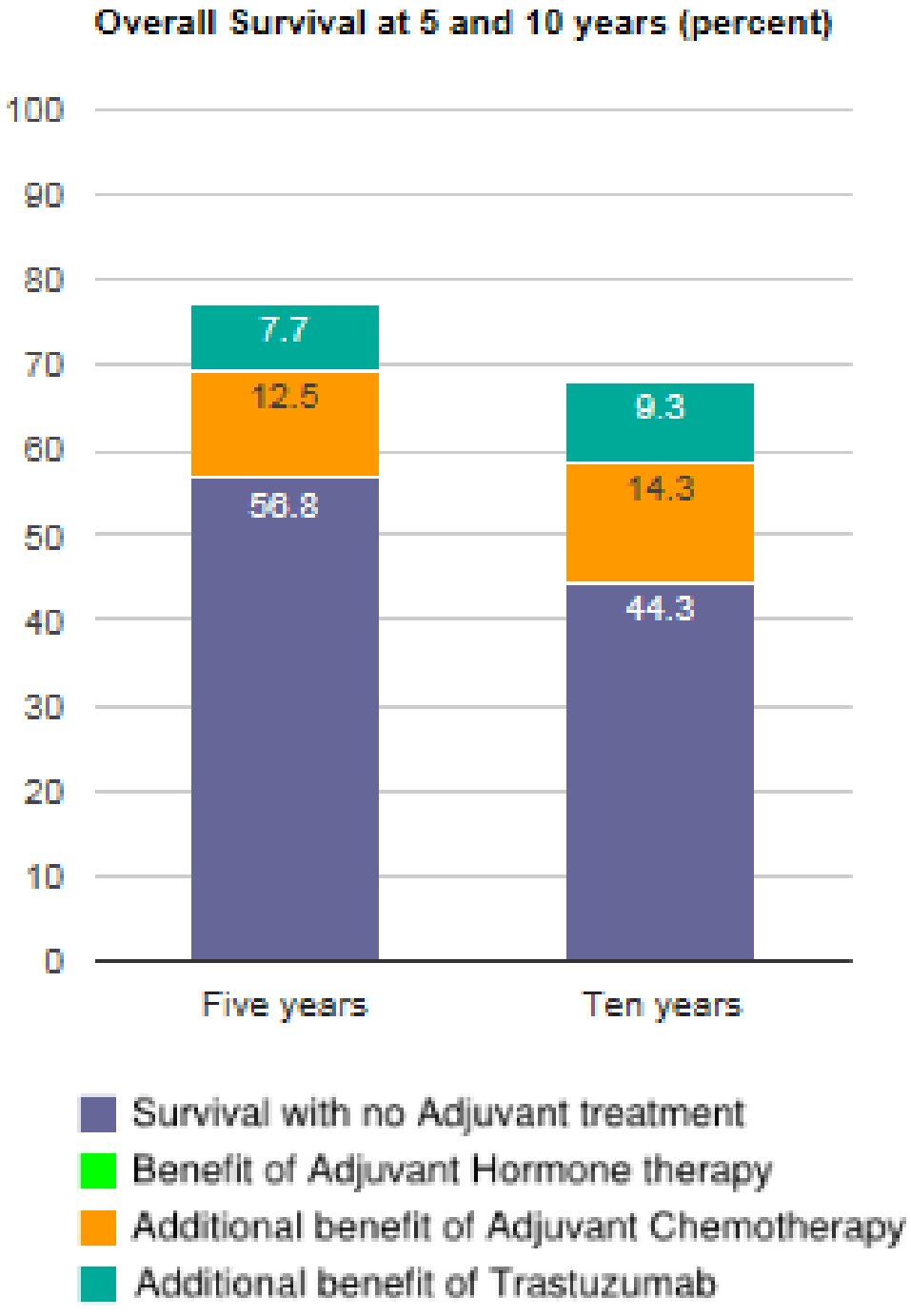

Google™ Custom Search | Search

PREDICT Tool Version 2.0: Breast Cancer Survival; Input

Age at diagnosis:	50		
Mode of detection:	○ Screen-detected	◉ Symptomatic	○ Unknown
Tumour size in mm:	40 (blank if unknown)		
Tumour Grade:	○ 1	○ 2	◉ 3
Number of positive nodes:	2 (blank if unknown)		☐ Micromet
ER status:	○ Positive	◉ Negative	
HER2 status:	◉ Positive	○ Negative	○ Unknown
KI67 status:	○ Positive	○ Negative	◉ Unknown
Gen chemo regimen:	○ No chemo	○ Second	◉ Third

Predict Survival | Clear All Fields | Print Results

PREDICT Tool Version 2.0: Breast Cancer Survival; Results


Overall Survival at 5 and 10 years (percent)
100
90
80
70
60
50
40
30
20
10
0
7.7
12.5
56.8
9.3
14.3
44.3
Five years
Ten years
Survival with no Adjuvant treatment
Benefit of Adjuvant Hormone therapy
Additional benefit of Adjuvant Chemotherapy
Additional benefit of Trastuzumab

Surgery - breast

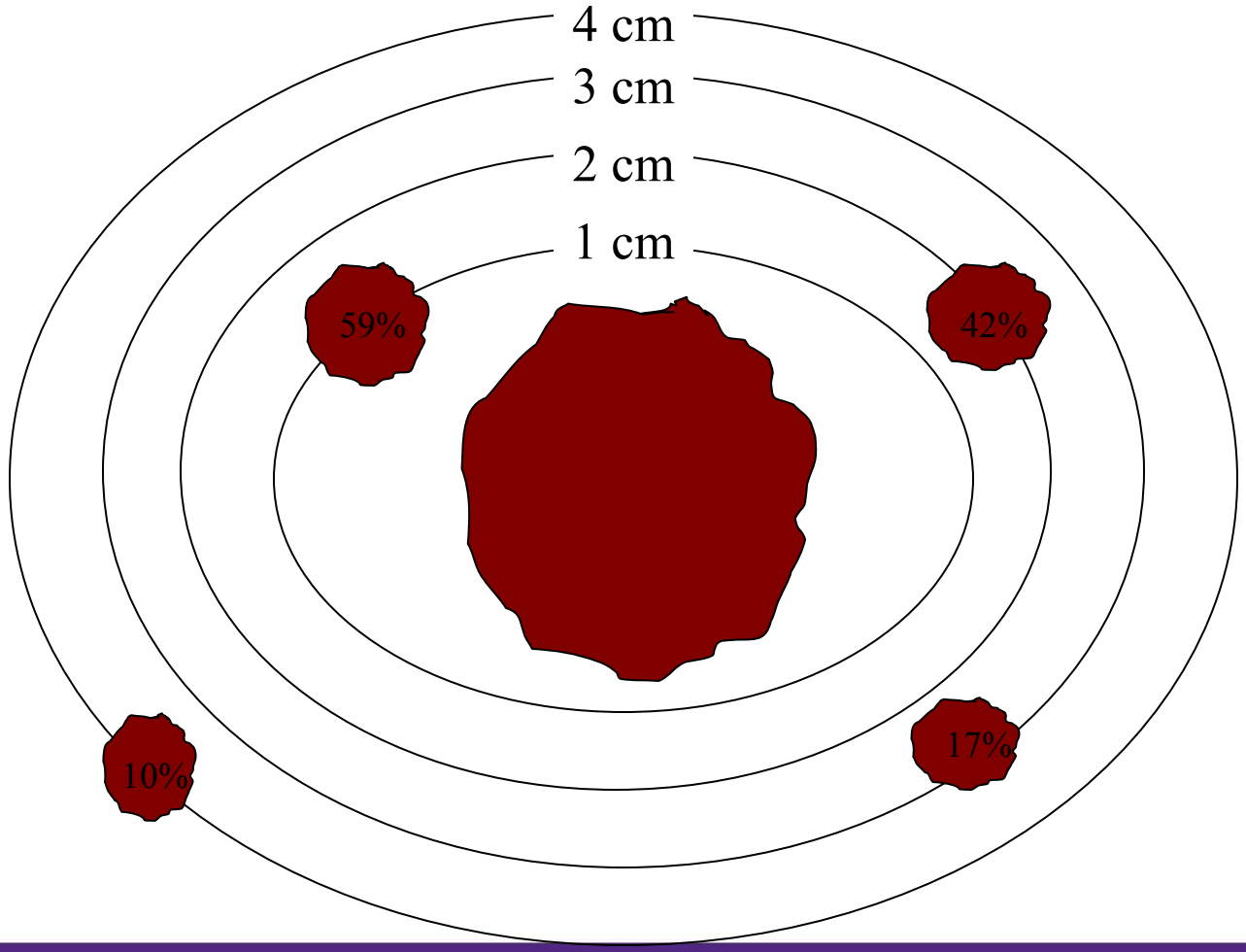
- Mastectomy vs breast conserving therapy
  - NSABP B-07
- Contra-lateral breast?
  - What is the benefit?
- Reconstruction?
  - Immediate vs delayed
  - CCO guidelines for breast reconstruction

	Lumpectomy + Radiation Therapy	Mastectomy +/- Reconstruction
Survival	SAME	
Local Recurrence @ 10 yrs No RT RT If node positive	 40% 10% } NSABP B07* ESSENTIALLY	 <5%, not 0 SAME**
Radiation	Yes	No (Yes if node positive)**
Margin* Re-excision	20%	No
Cosmetic Result	75% Good to excellent	Lousy (flat), 70% Good with reconstruction
Systemic Therapy	SAME	

* Rates are half of historical rates due to use of systemic therapy

** Ragaz, N Engl J Med 1997; 337:956-962, 1997
Overgaarde N Engl J Med 1997; 337:949-955, 1997

Pathologic Extent of Disease



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Systemic Therapy		SAME

Surgery - breast

- Mastectomy vs breast conserving therapy
  - NSABP B-07
- Contra-lateral breast?
  - What is the benefit?
- Reconstruction?
  - Immediate vs delayed
  - CCO guidelines for breast reconstruction

Neo-adjuvant chemotherapy

- Safety – lots of studies, no benefit to chemo first but safe (eg NSABP B-27)
- Clip
- Mastectomy → lumpectomy, better cosmetic result
- Prediction of successful lumpectomy (MD Anderson)
  - Lobular not very successful, triple negative CR 25%
- Prognostic value
- Rare progression on chemotherapy
- Buys time
  Surgical decision making
  -Organizing surgery
- Node negative
  -Medical oncology needs to agree chemotherapy candidate

Surgery - Axilla

- Standard of care in node positive core is AND
  - 6 week recovery
  - 15% chronic lymphedema
  - 10% chronic pain
- If nodes clinically negative after systemic therapy options on study

Radiation

- Will get radiation regardless of breast surgery due to positive nodes
- Radiation to:
  - breast or chest wall
  - regional nodes
    - Internal mammary
    - Supraclavicular
    - Undissected axilla
- Immediate reconstruction – autologous only, implant contra-indicated.

Systemic Therapy

For this patient:

- AC followed by taxane – 4 cycles of each (6mos)
- Herceptin (1 year) – starts with or just after chemo
- Hormonal therapy – 5-10 years after radiation

Nodal Surgery - then until now

- Halstead – 1882 first in NA
- NSABP B04 -Fisher, NEJM,347,2002– first published 1981 - nodal treatment (observation vs radiation vs axillary node dissection) did not seem to make a difference (results ignored)
- Late 1990's Sentinel Node Biopsy – Krag, Giuliani - NSABP B32 completed but taken up as new standard prior to results
- ACOSOG Z11 – Giuliani JAMA. 2011,305(6):569-75 -early stage breast cancer (not stage 3) and <3 positive sentinel nodes do not need AND
- AMAROS – Donkers Lancet 2014 15:12, 1303–1310 -early stage breast cancer and positive sentinel nodes can be given axillary radiation, do not need AND
- MA 20 – Whelan NEJM. 2015;373(4):307-16 - radiation to regional nodes in addition to the breast in patients with node positive disease and BCT.
  - Most patients had AND (no axillary radiation) but those with <10 nodes (sentinel node biopsy) received axillary radiation
- ACOSOG Z1071 – Broughey JAMA. 2013;310(14):1455-61. - node positive patients with neoadjuvant chemotherapy, followed by sentinel node biopsy.
  - False negative rate >10% so recommended against unless 3 or more nodes identified
  - OK if get 3 negative sentinel nodes
- Future for node positive patients, neoadjuvant chemotherapy NSABP B51, Alliance

Lymphedema

	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0.25
1 year	114/410 (28%)	62/410 (15%)	<0.0001
3 years	84/373 (23%)	47/341 (14%)	0.003
5 years	76/328 (23%)	31/286 (11%)	<0.0001
Arm circumference increase >10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0.497
1 year	32/410 (8%)	24/410 (6%)	0.332
3 years	38/373 (10%)	22/341 (6%)	0.080
5 years	43/328 (13%)	16/286 (5%)	0.0009

Data are n/N (%), unless otherwise specified.

AMAROS – Donkers Lancet 2014 15:12, 1303–1310

Thanks for your attention!