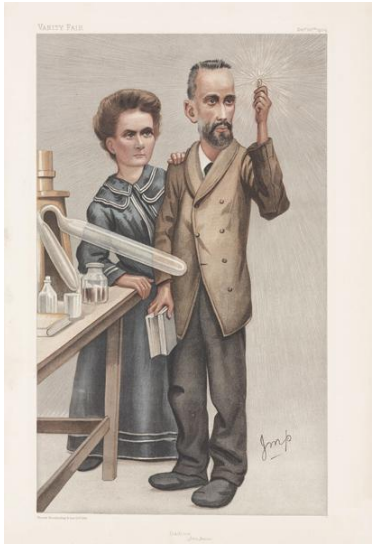
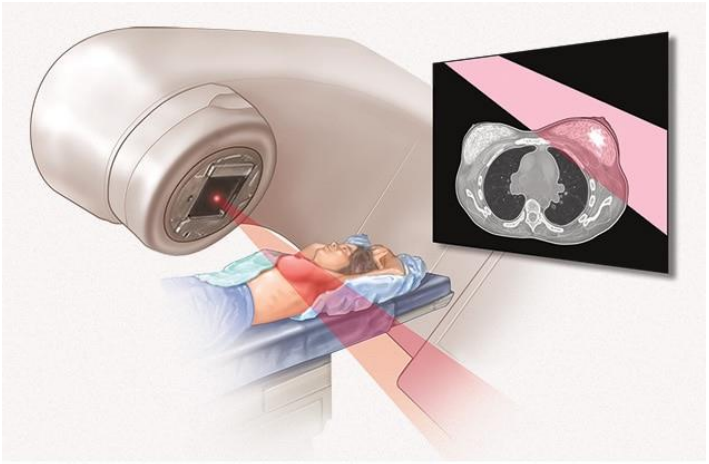
Radiation Therapy and Breast Cancer

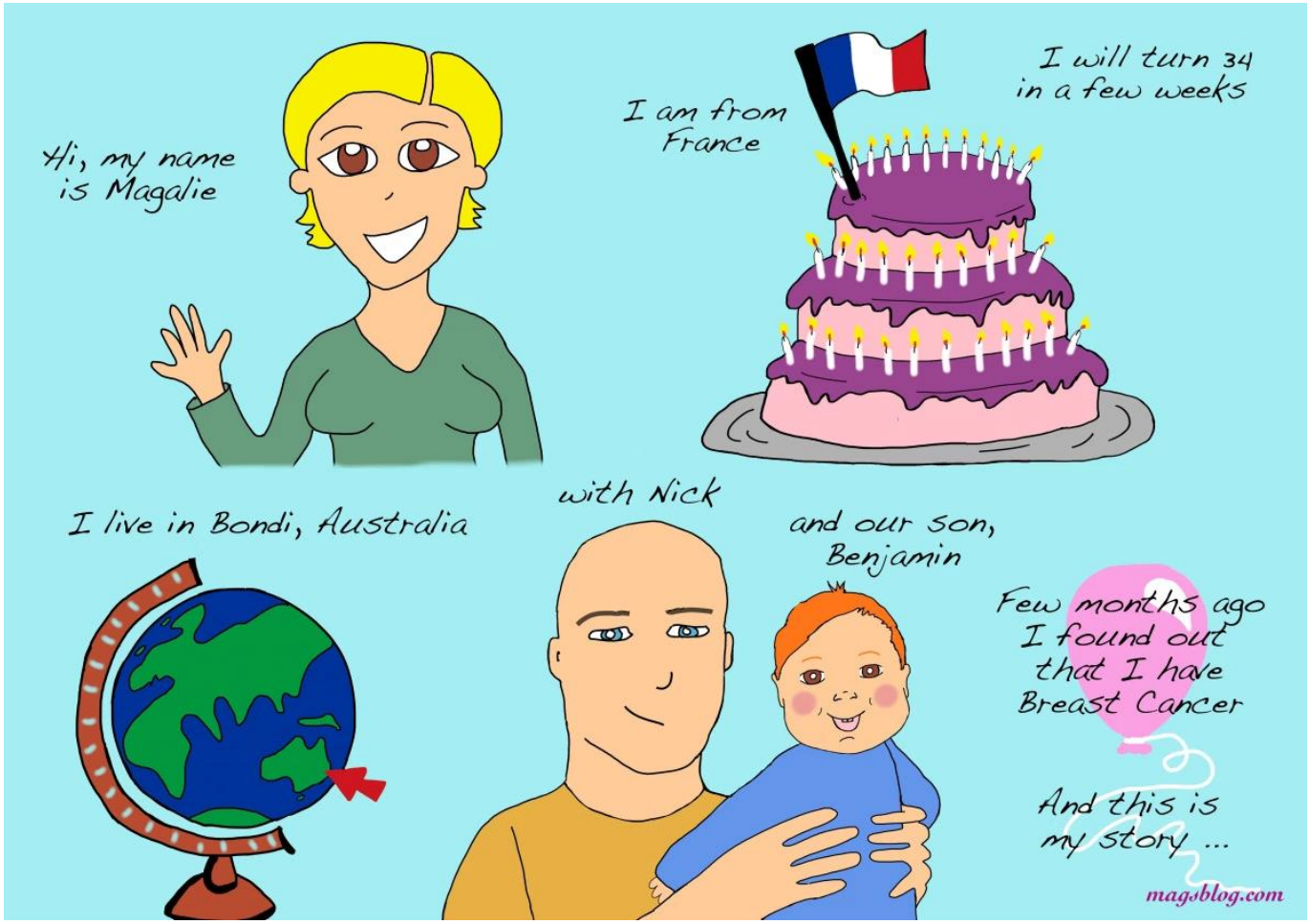
Nick Kummer, MD-PhD
Radiation Oncologist
Confluence Health Medical Group
Wenatchee Valley Hospital & Clinics
Wenatchee, WA





Disclosure: a lot of these material are from the internet, mentors, and medical journals.

A Patient's Perspective



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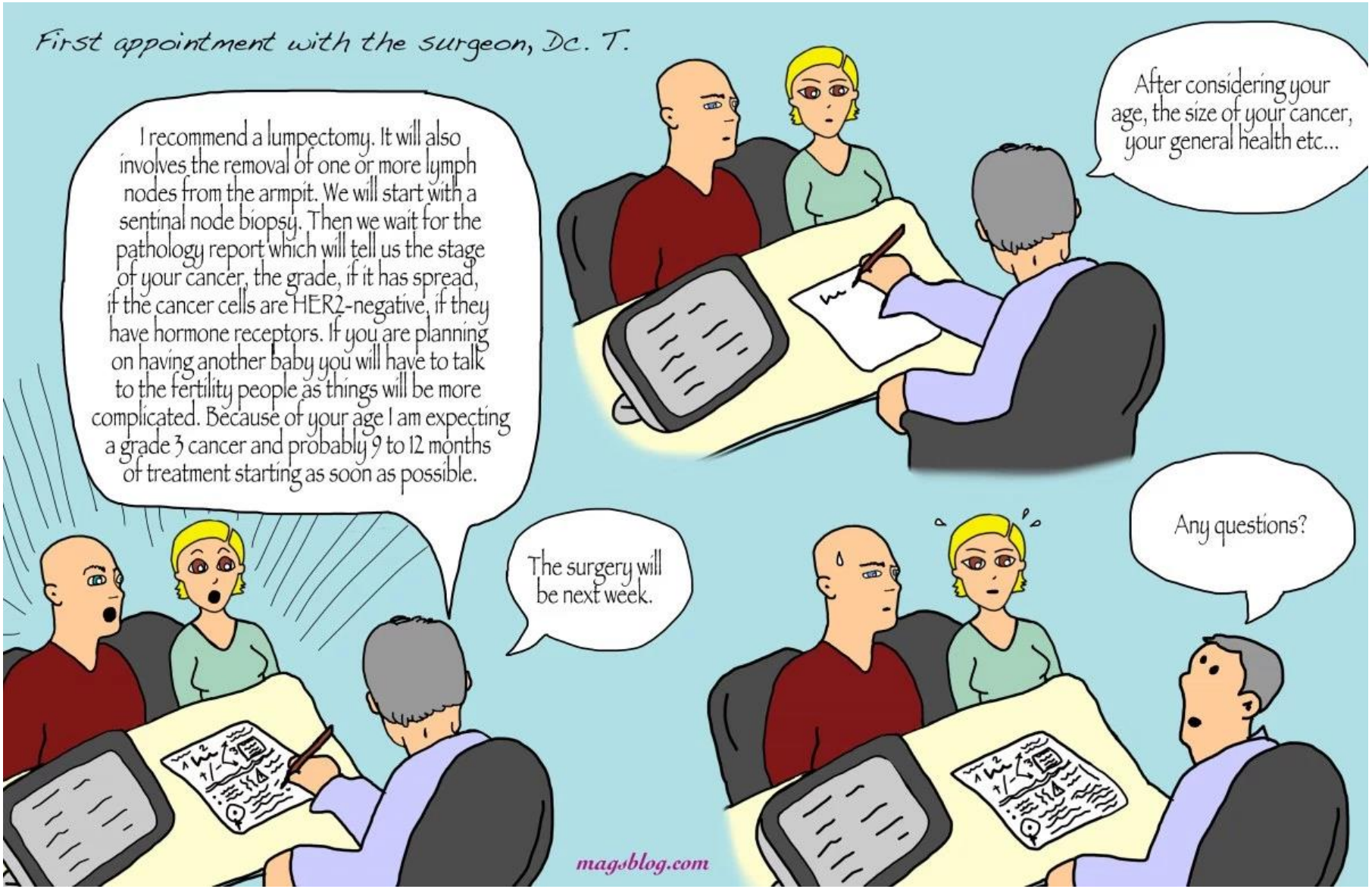
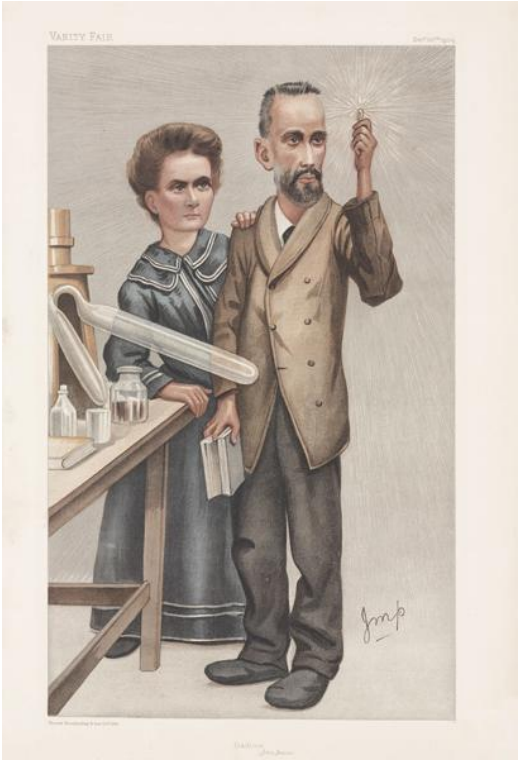


SURGERY -> CHEMOTHERAPY -> RADIATION

Radiation

What is Radiation Therapy



Radiation Therapy 101

The evolution of therapeutic radiation

Roentgen and the New Kind of Ray

1895

Discovery of **x-rays** in 1895 by the German physicist Wilhelm Roentgen.

X-ray image of Bertha Roentgen's Left Hand. November 8th, 1895

- 12/28/1895 Uber Eine Neue Art von Strahlen (On a New Kind of Ray) was presented to the Wurzburg Physical-Medical Society.

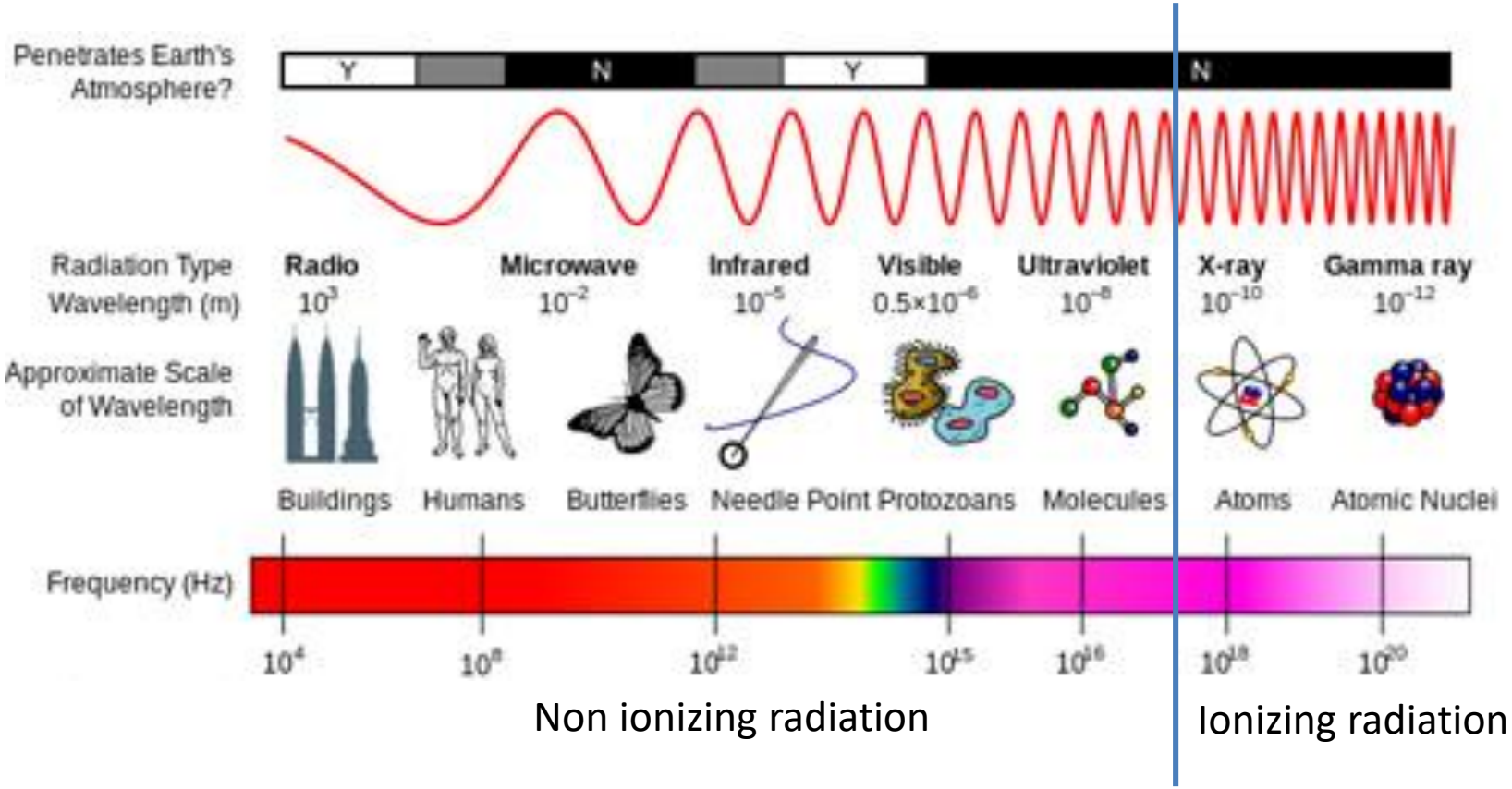
- 1901 Awarded the Nobel Prize in Physics.

EXTERNAL BEAM

Therapeutic Radiation

- Radiation is classified into two main categories:
  - Non-ionizing radiation
  - **Ionizing radiation**

ELECTROMAGNETIC RADIATIONS



Photon E = $h\nu$ (energy = Planck's const x frequency)

= hc/λ (c = speed of light, λ = wave length)

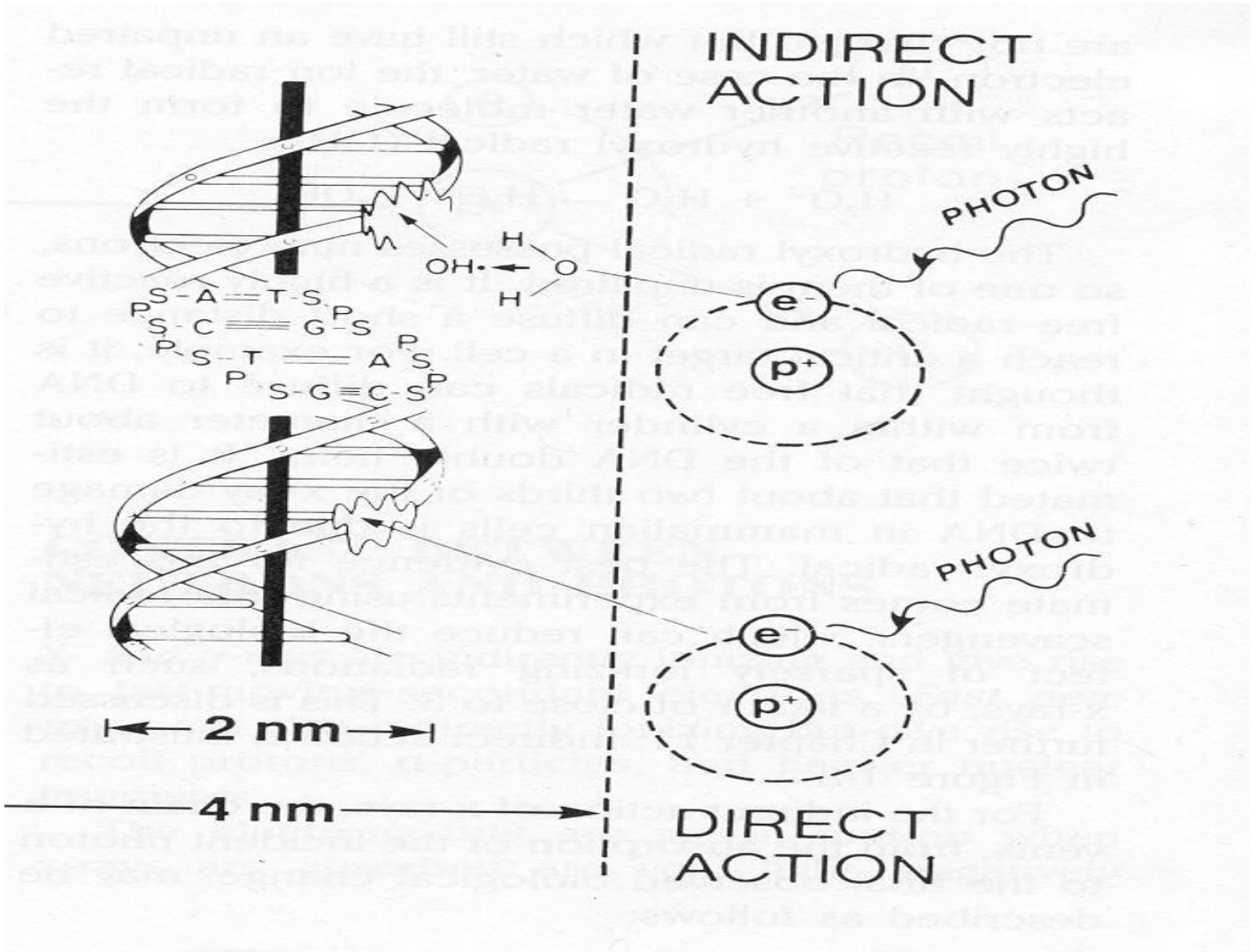
Ionizing Radiation interacts with an atom: X-Ray and Gamma ray

Note: UV is what causes sun burns and skin cancer, it is not ionizing

Mechanism

- Two mechanisms of injury
  - Direct Ionization of the DNA, ≈ 15%
  - Indirect Ionization of the DNA, ≈ 85%
    - DNA damaged by free radicals formed in the micro-environment of the DNA
    - Water is most important source
    - Oxygen is important in fixating injury
    - Sulfhydryl compounds promote repair

Direct vs Indirect Action of Radiation on DNA



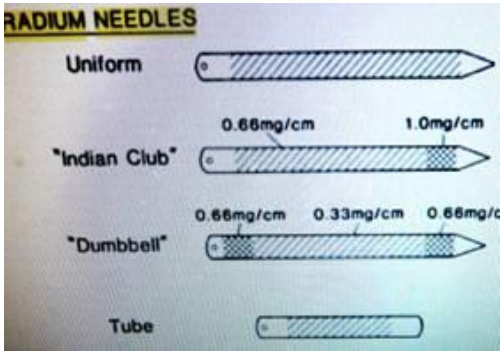
History of Radiation Therapy

Women breaking the glass ceiling

Marie Curie, Radium & Gamma Rays

1898

Becquerel (1895) discovered natural radioactivity and Marie Curie isolated radium (1898) and clinicians started to use it for local treatment of tumors.



- 1903: Nobel Prize in Physics for discovering that radioactive elements emit a natural form of x-rays known as Gamma Rays.
- 1935: Nobel prize for the chemistry of Radium.

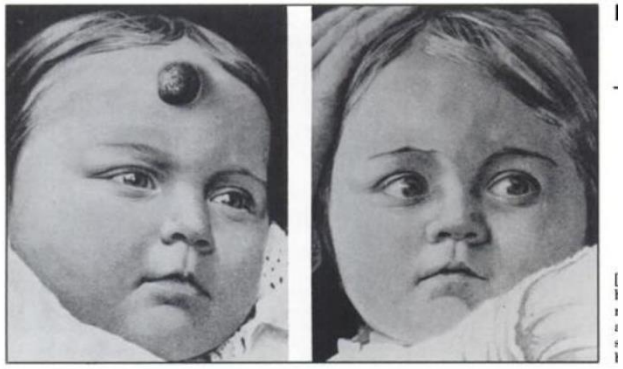
Small tubes containing radium salts are strapped to a woman's face to treat what was either lupus or rodent ulcer, 1905.

The early days of radiation, cures and curses

1895-1915

Rodent ulcer- Lupus

Naevus pigmentosus piliferus treated with x-ray as a child, 70 years later.



Angioma

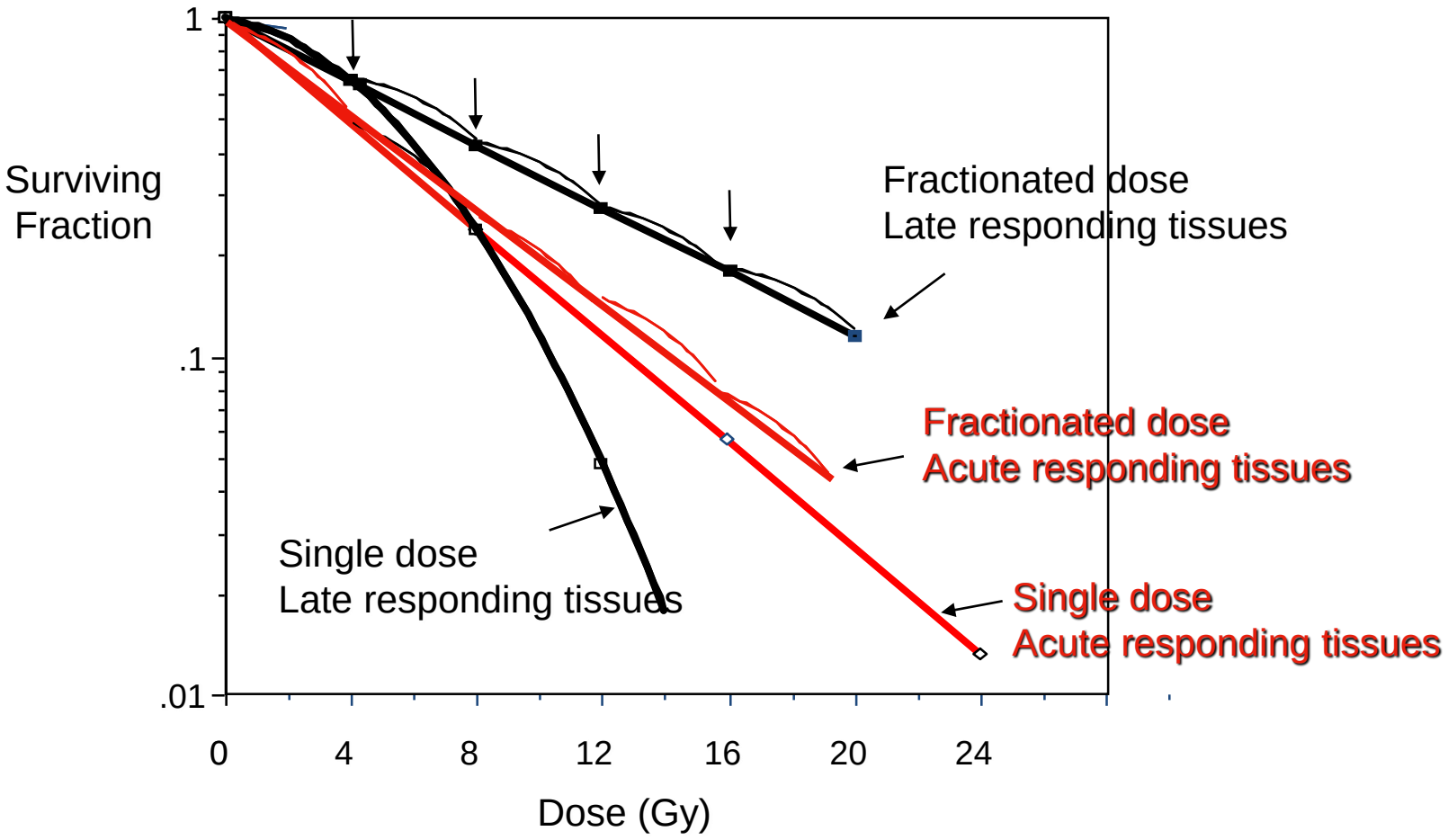
Roentgen's hands in 1903.

RADIATION SHOWED AMAZING RESULTS BUT HAD SIDE EFFECTS

How to treat disease while sparring normal tissue?

Fractionation, a little bit at a time

Dose Fractionation Amplifies Difference



Dose fractionation spares late responding tissues more than acute responding tissues and many tumors

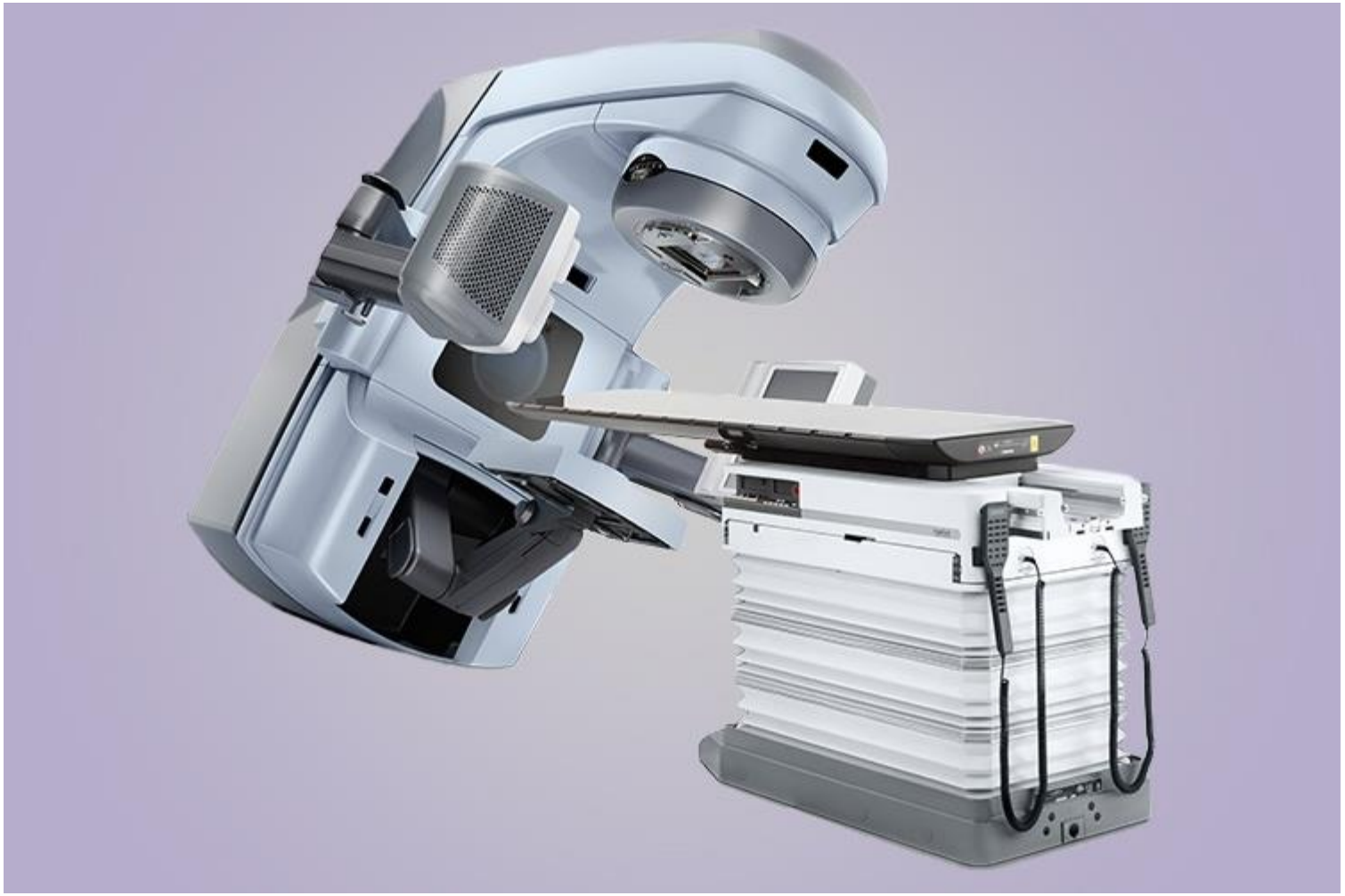
Fractionation

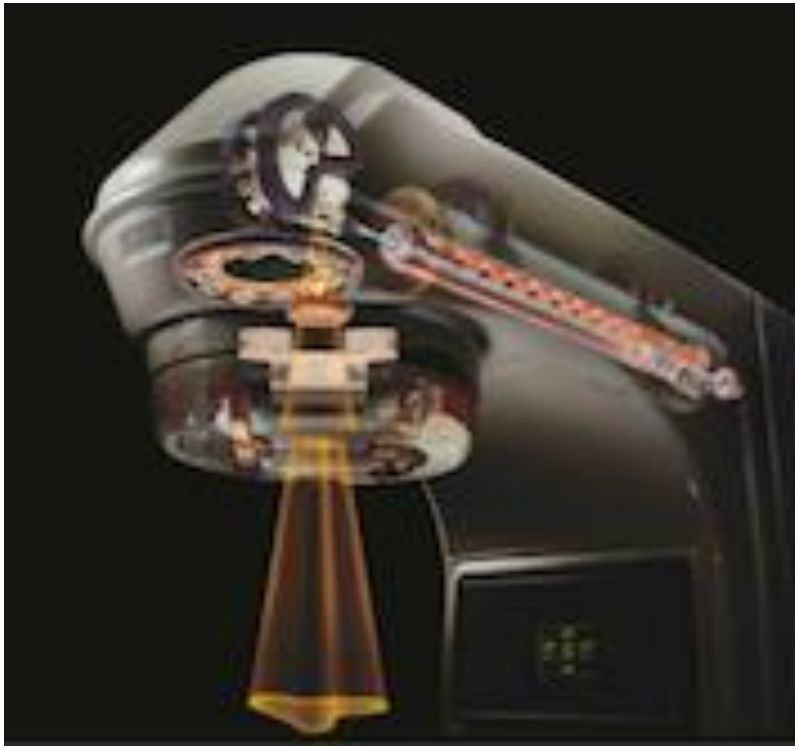
- A little bit of radiation every day allows normal tissue to repair and not cancer
- Roughly 70 Gy of radiation over 35 treatments, with one log kill every 7 Gy = 10 log kill of tumor.

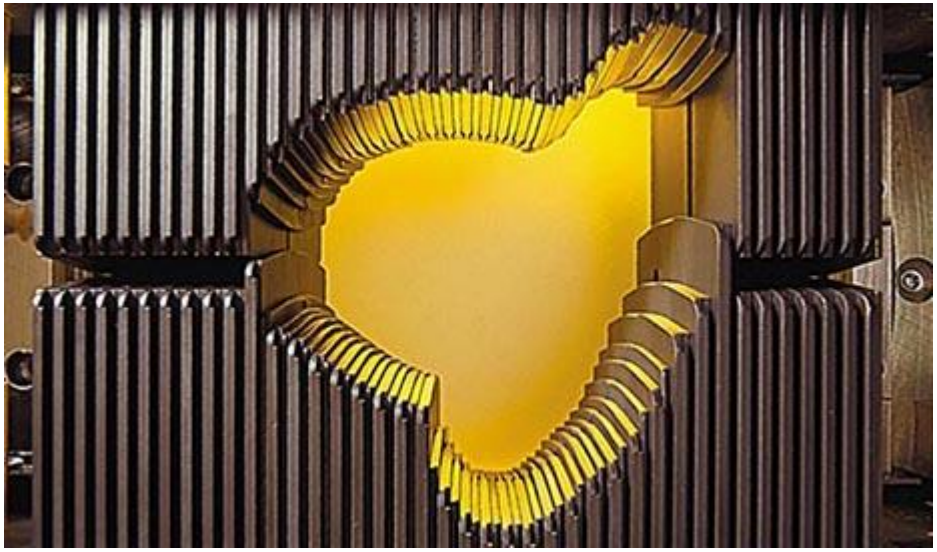
- Spares normal tissue by:
  - » repair of sublethal damage.
  - » repopulation of cells if overall time is long enough. May also spare tumor cells.

- Increases tumor damage by
  - » reoxygenation
  - » reassortment of cells into radiosensitive phases of cell cycle.

Modern Radiation Therapy







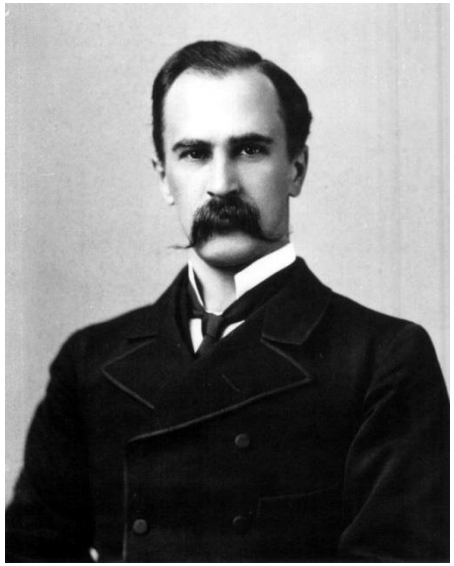
A **multileaf collimator** (**MLC**) is a device made up of individual "leaves" of a high atomic numbered material, usually tungsten, that can move independently in and out of the path of a particle beam in order to block it.

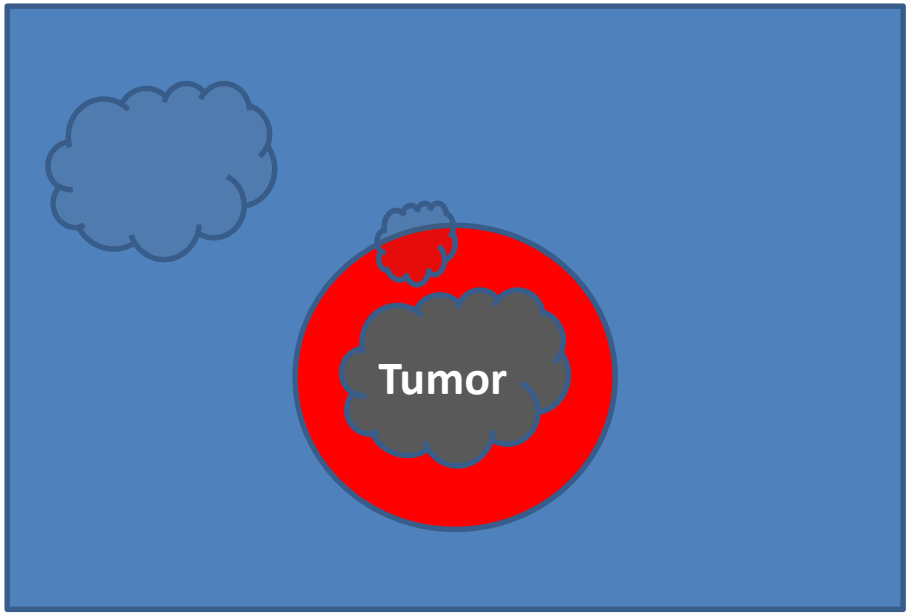
MLCs are used on linear accelerators to provide conformal shaping of radiotherapy treatment beams. Specifically, conformal radiotherapy and Intensity Modulated Radiation Therapy (IMRT) can be delivered using MLCs.

Cancer in a nutshell

- Crab-like disease.
- 1550 BC Ebers Papyrus “tumor against the god”
  - Surgically remove the body of the crab, but it will grow back from the legs-
  - Radiation to get the legs
- Pandora’s box, once it becomes metastatic.
  - Chemotherapy to keep the box closed
- Wolf in sheep's clothing.
  - Immune therapy

“Medicine is a science of uncertainty and an art of probability” Sir William Osler

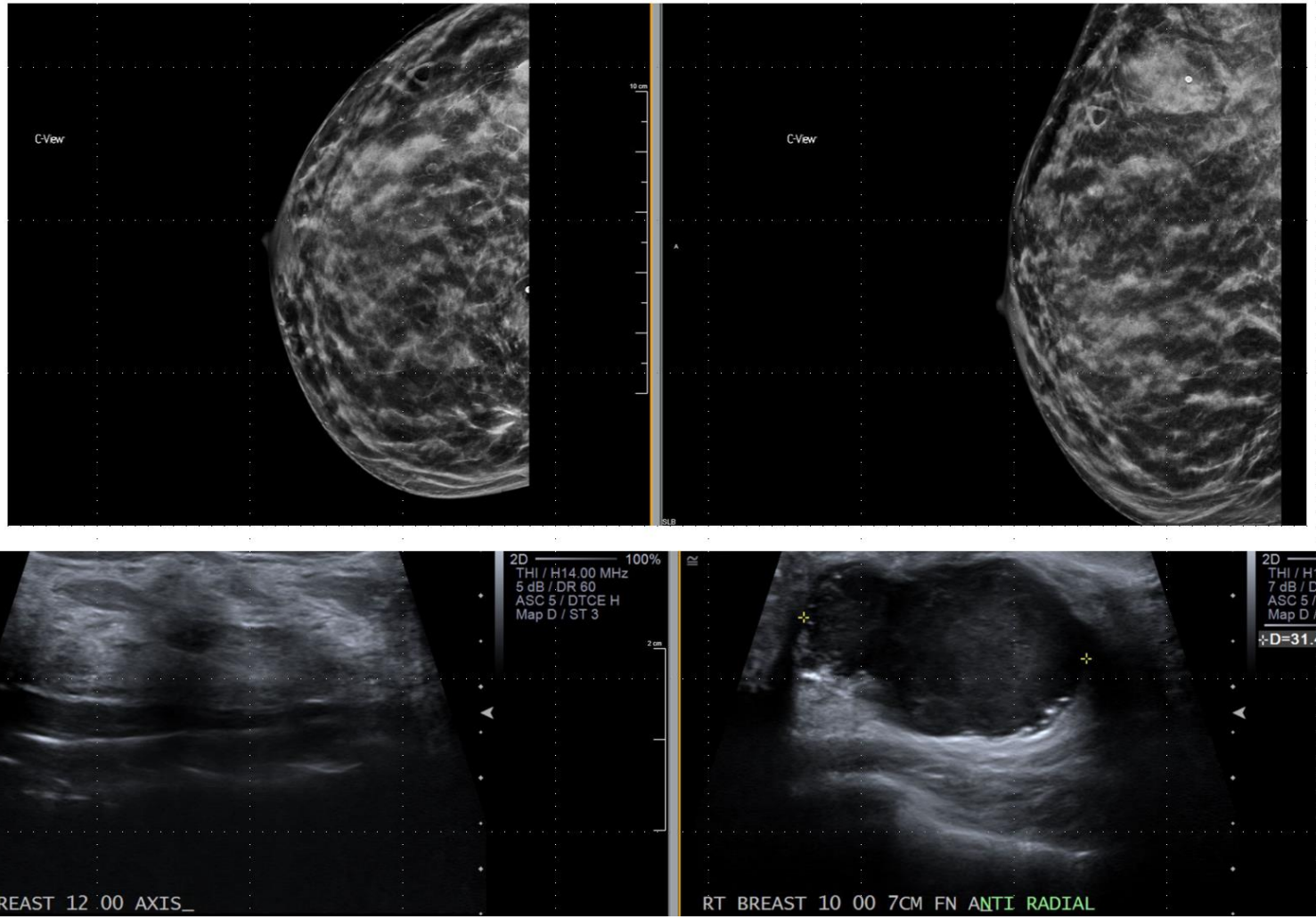




- If you can see it, there are more than 10,000,000,000 cells
- Chemo may kill up to 99% (2 log)= 100,000,000 cells left
- Surgery, easy to miss
- Radiation can kill 10 log (99.9999999%) of cell: less than 1 cell left

A Patient's Perspective

45 yo female G2p2, menarche 12- LMP 9/25/19, no hormone use, maternal GM with BC age 70, non smoker, no ETOH, noted right sided breast mass



3.5 cm spiculate mass with a 2 cm suspicious looking lymph node.

Core needle biopsy of the mass and node

- INVASIVE ADENOCARCINOMA WITH THE FOLLOWING FEATURES:
  1. Histologic type: Invasive ductal carcinoma (supported by patchy GATA3 and CK7 positive immunohistochemical stains).
  2. Histologic grade: Nottingham histologic score:
  a. Glandular (acinar)/tubular differentiation: Score 3.
  b. Nuclear pleomorphism: Score 3.
  c. Mitotic count: Score 3
  d. Overall grade: Grade 3 (of grades 1-3, 9 of 9 possible points).
  3. Extent of invasive adenocarcinoma:
  a. Invasive adenocarcinoma accounts for 80% of the specimen volume.
  b. Invasive adenocarcinoma involves 7 of 7 cores of tissue.
  c. Invasive adenocarcinoma involves up to 11 mm of the length of one of the involved cores.
  4. A. Estrogen receptor (Leica 6f11) POSITIVE (80% of invasive carcinoma nuclei show weak to moderate reactivity) by immunohistochemistry.
  b. Progesterone receptor (Leica 16) NEGATIVE (0% of invasive carcinoma nuclei show reactivity) by immunohistochemistry.
- FISH Analysis HER2 Breast
  Results: Negative
  Interpretation:
  Average HER2 signals/nucleus: 1.8
  Average CEN 17 signals/nucleus: 1.8
  HER2/CEN 17 signal ratio: 1.0
  Number of Observers: 1
  Results show no evidence of HER2 amplification and a HER2/CEN17 ratio of <2.0 with an
  average HER2 copy number <4.0 signals per cell. This is a NEGATIVE result.

cT2 cN0 MX Grade 3 IDC of the right upper outer breast, ER+, PR-, HER2 non amplified

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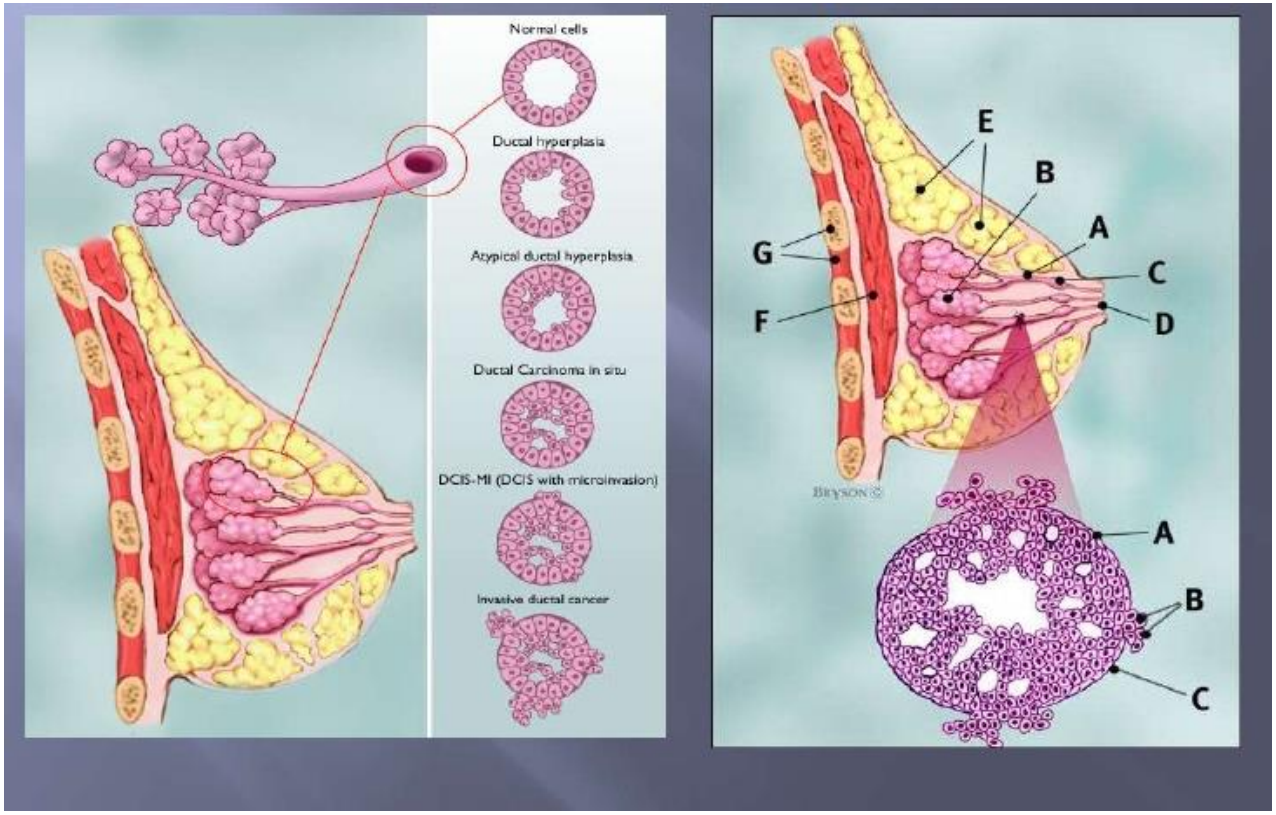
Breast Cancer 101

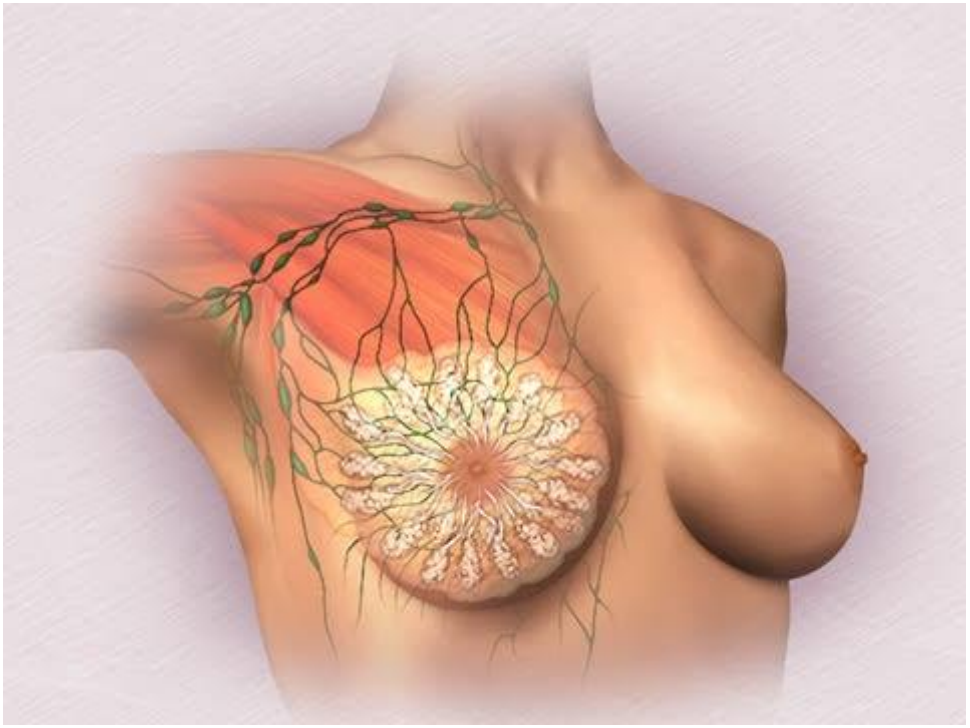
- Most common cancer diagnosed in women
- Incidence: 268,600 cases in 2019 in US along with 62,930 non-invasive breast cancer.
- As of Jan 2019, there are 3.1 million women with breast cancer in the US.
- In US, 1/8 lifetime risk of developing breast ca (12%)
- 2nd leading cause of cancer death in women
- Leading cause of mortality for ages 40-55 yrs
- Risk doubles if you have a first degree relative (only 15% of patients have a first degree relative with BC).
- 5-10% linked to a BRCA mutation.
- 85% occur in women with NO FAMILY HISTORY
- Biggest risk factor is being a women and living.
- If move from low risk→ hi risk area, incidence becomes like hi risk population after 1-2 generations

Breast Cancer 101



Breast Cancer 101

- Pectoralis minor
  - arises from 3-5th ribs + inserts at coracoid process
- Axillary LN levels:
  I- lateral to pec minor
  II- behind pec minor
  III- medial to pec minor
- IMN's
  - Lie in 1st-3rd intercostal spaces
- Rotter's nodes:
  - Interpectoral nodes b/t pec major + minor
- Supraclavicular nodes:
  - Above the clavicle, below the cricoid cartilage.



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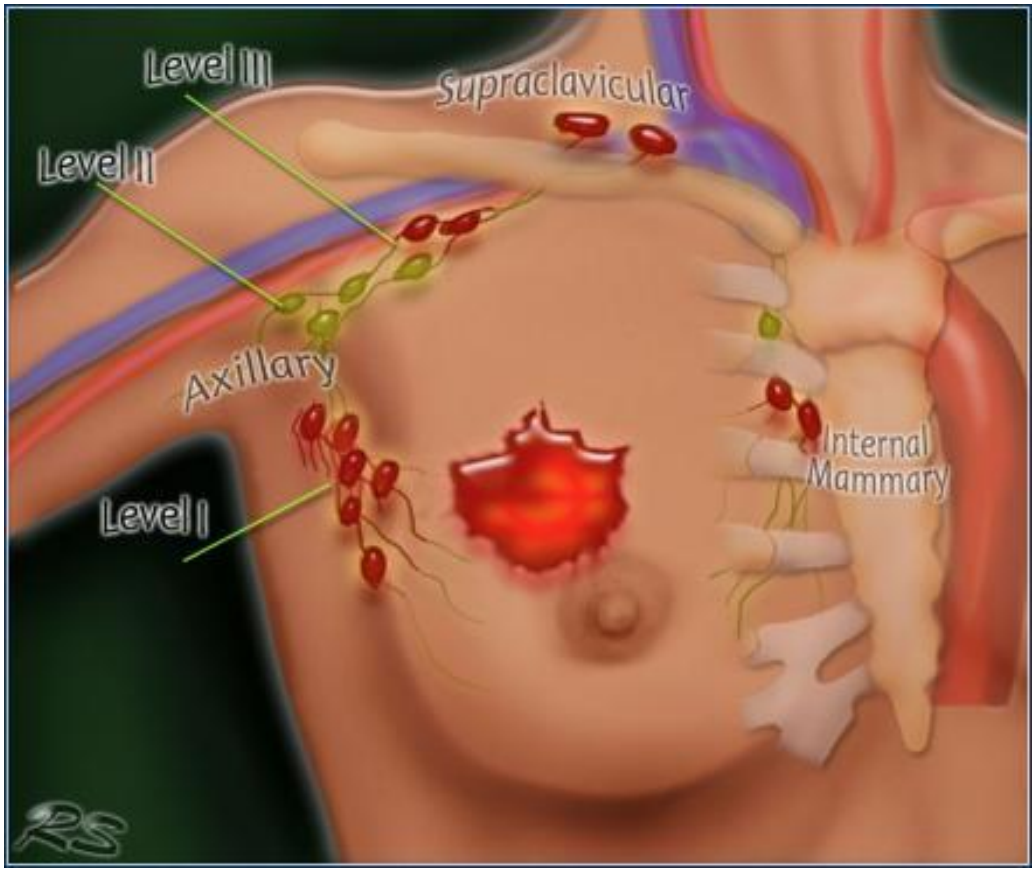


Breast Cancer 101

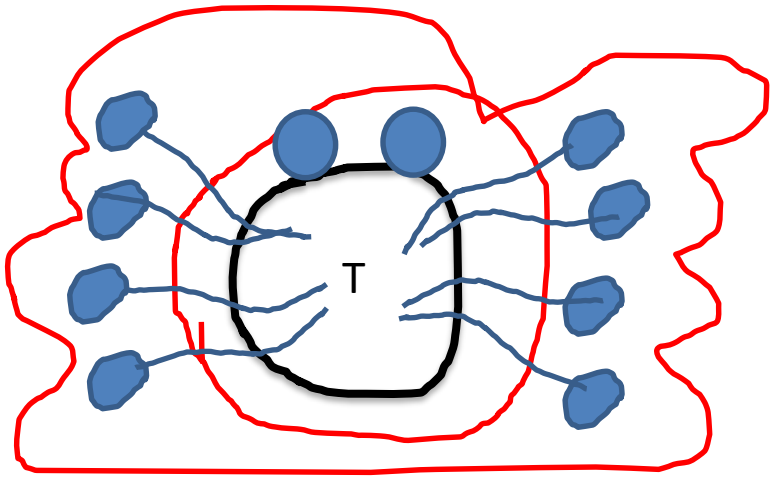
pT	
Tis	DCIS LCIS Paget nipple
T1 mic	≤ 0,1 cm
T1a	≤ 0,5 cm
T1b	> 0,5 - 1 cm
T1c	> 1 cm - 2 cm
T2	> 2 cm - 5 cm
T3	> 5 cm
T4a	Extension to chest wall (does not include pectoralis muscle invasion only)
T4b	Ulceration, ipsilateral satellite skin nodules, or skin oedema - including peau d'orange.
T4c	a+b
T4d	Inflammatory ca

pN	
pN1mi	Micrometastasis > 0,2 mm to 2 mm
pN1a	1-3 axillary nodes
pN1b	Internal mammary nodes with microscopic/macroscopic metastasis by sentinel node biopsy but not clinically detected
pN1c	1-3 axillary nodes and internal mammary nodes and internal mammary nodes with microscopic/ macroscopic metastasis by sentinel node biopsy but not clinically detected
pN2a	4-9 axillary nodes
pN2b	Internal mammary nodes, clinically detected, without axillary nodes
pN3a	≥ 10 axillary nodes or infraclavicular
pN3b	Internal mammary nodes, clinically detected, with axillary node(s) or > 3 axillary nodes and internal axillary mammary nodes with microscopic metastasis by sentinal node biopsy but not clinically detected
pN3c	Supra-clavicular

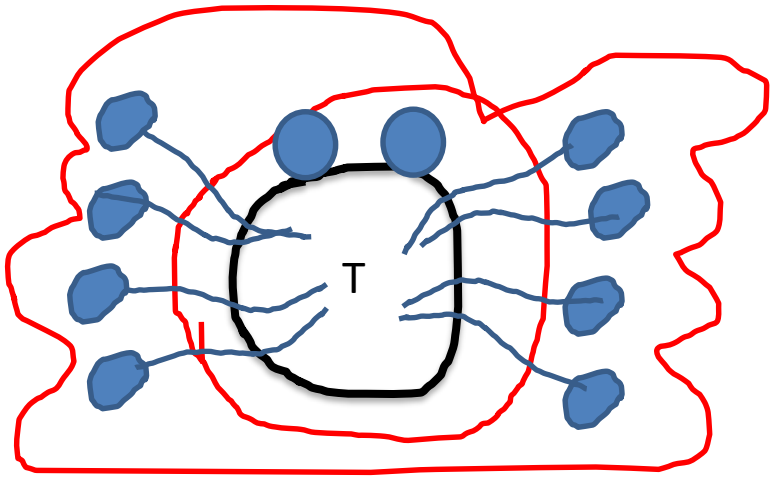
pTNM-Stage	
0	DCIS
IA	T1N0
IB	T0-1N1mi
IIA	T0-1N1 T2N0
IIB	T2N1 T3N0
IIIA	T0-2N2 T3N1-2
IIIA	T4N0-2 T3N1-2
IIIC	anyT N3
IV	systemic

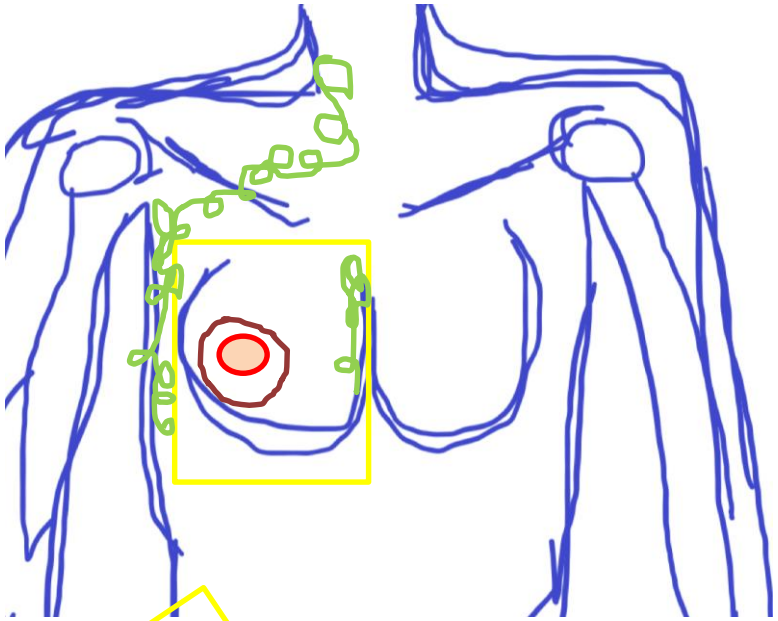
C: clinical P: pathologic Y: post chemotherapy f: by FNA r: recurrent (sn): Sentinel node

Breast Cancer 101



Stage 0 DCIS Breast Only





Stage

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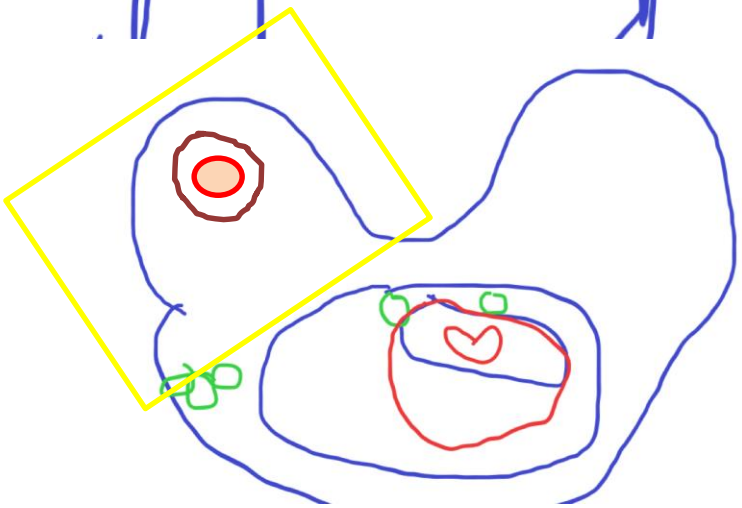
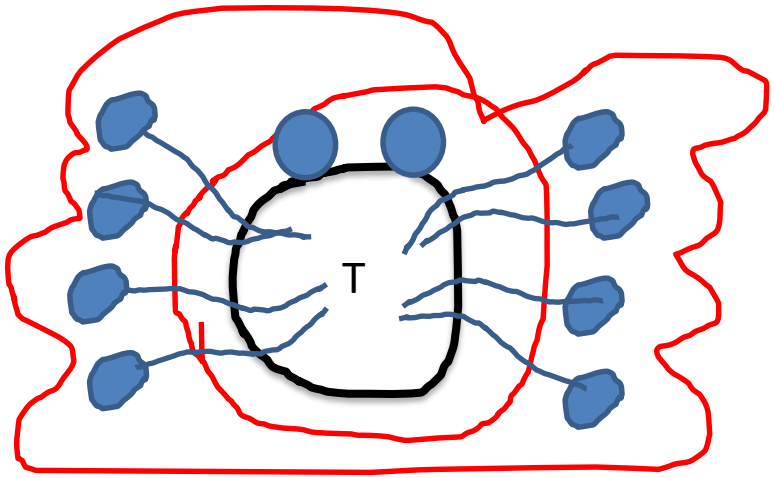
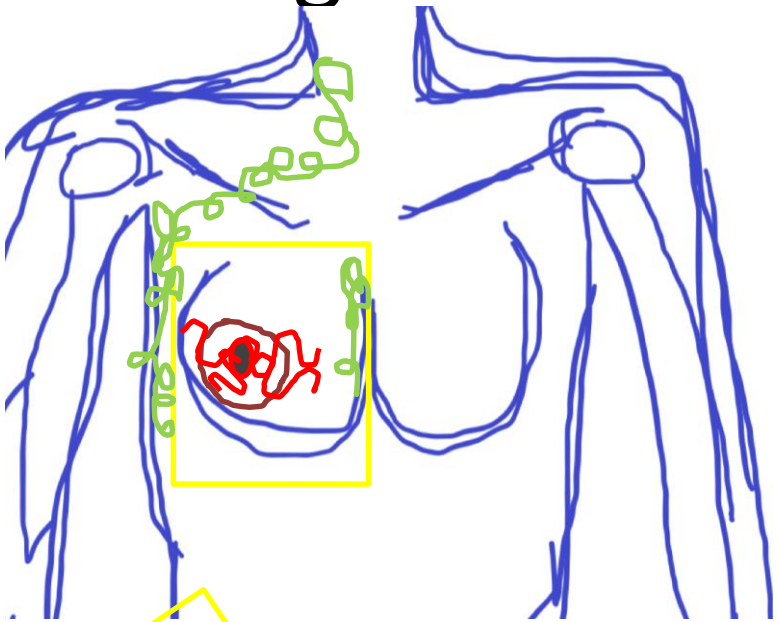
- Lumpectomy to remove the body of the crab
- Radiation for the crab legs
- Hormone therapy as an insurance plan



Stage 1, SLNB
Breast only for stage I





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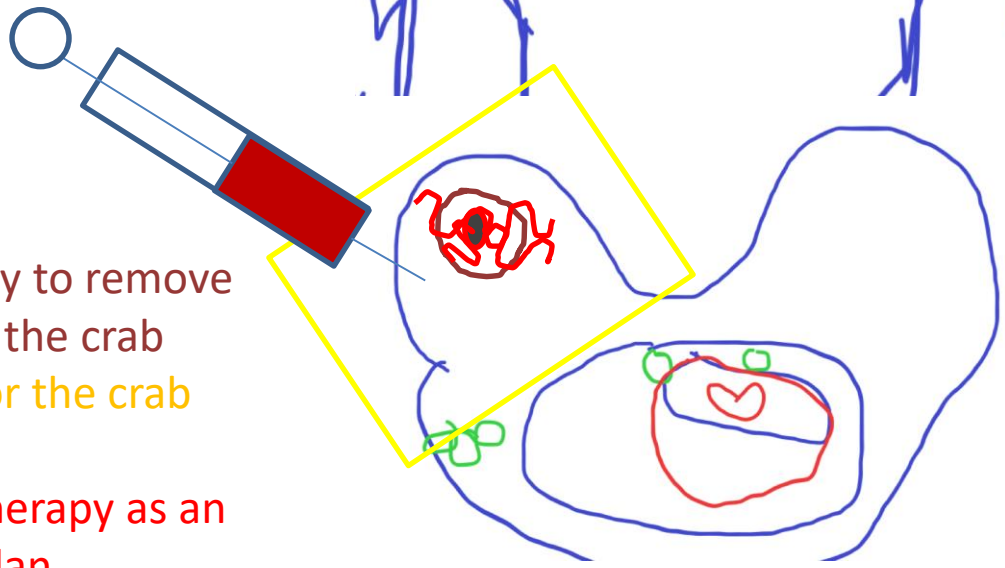
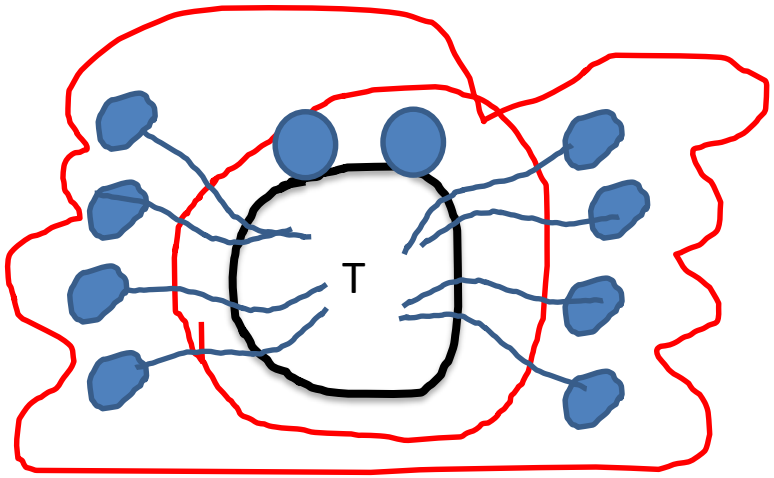
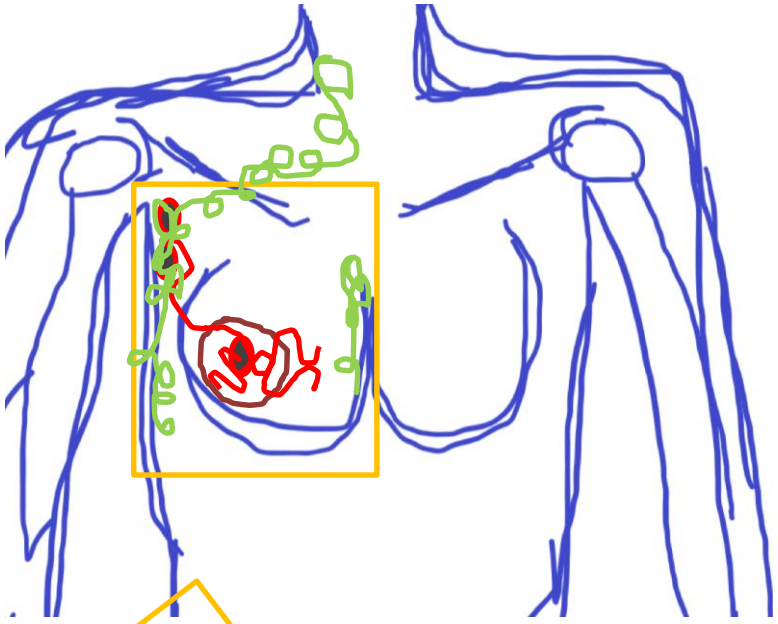


Stage 2, add the Level I/II Axilla





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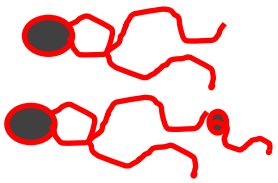
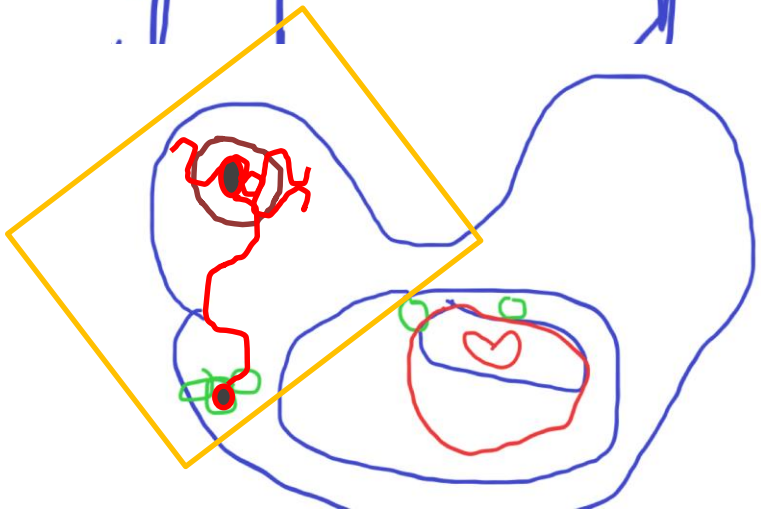
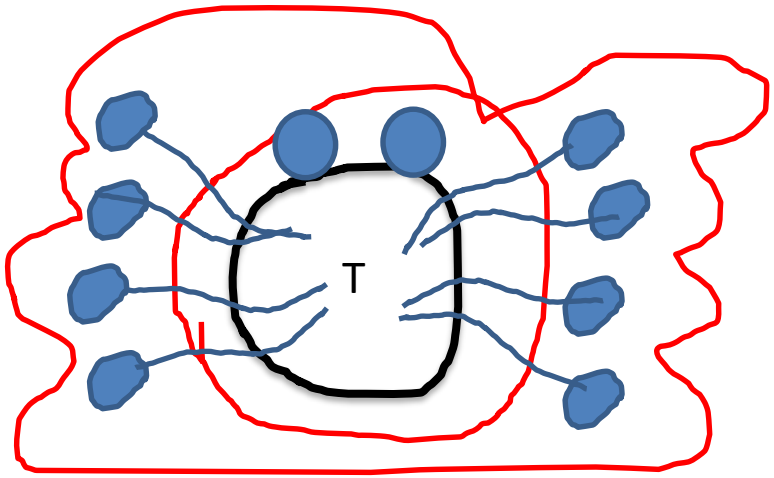
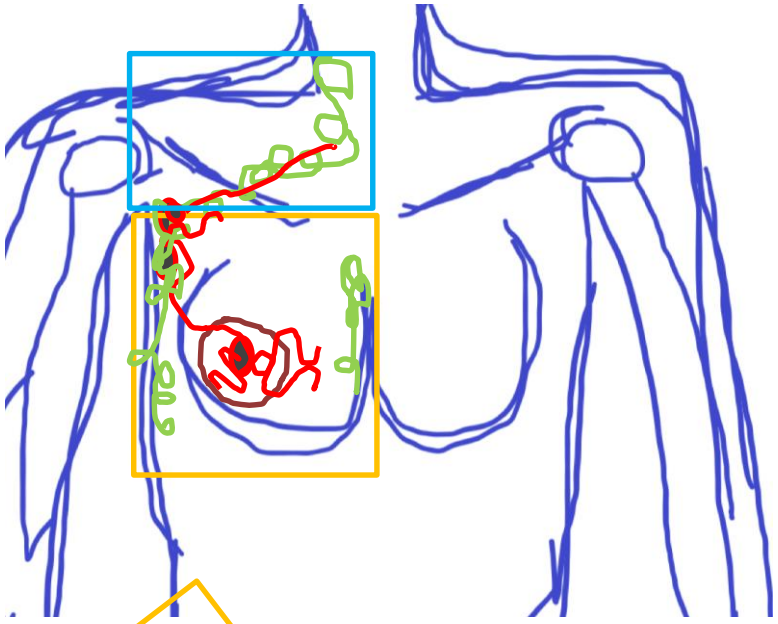




Stage 2 with high level I disease burden, SCLV now at risk





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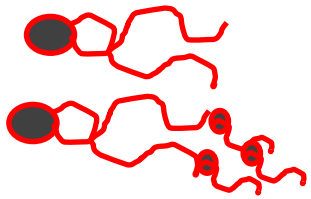
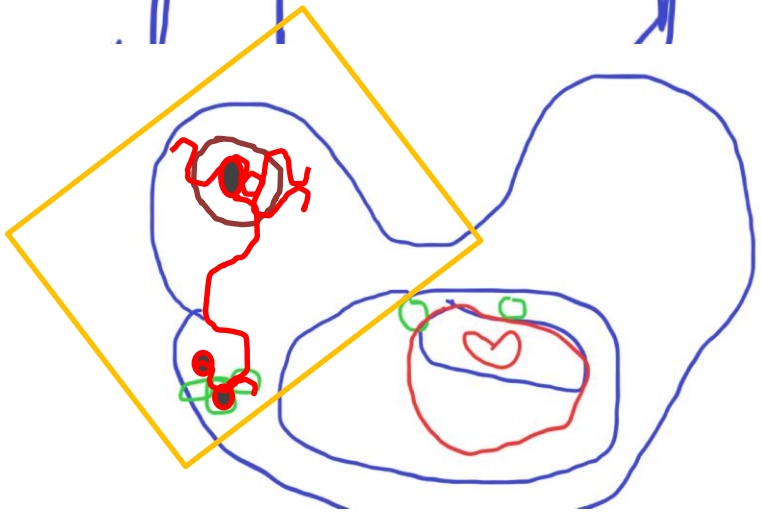
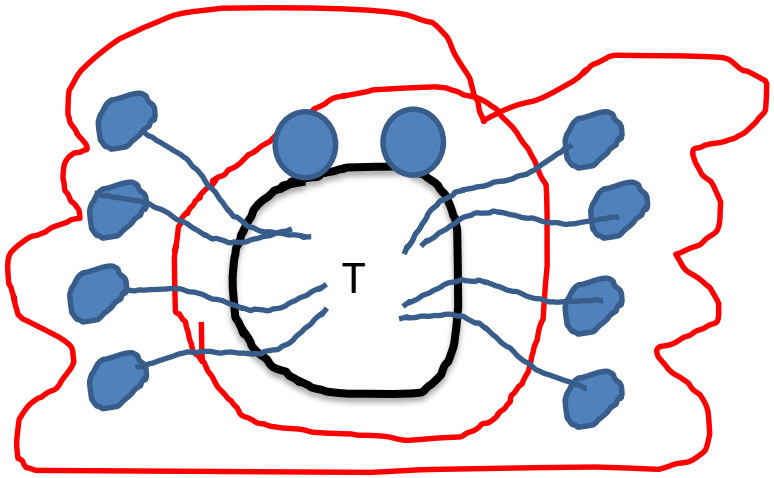
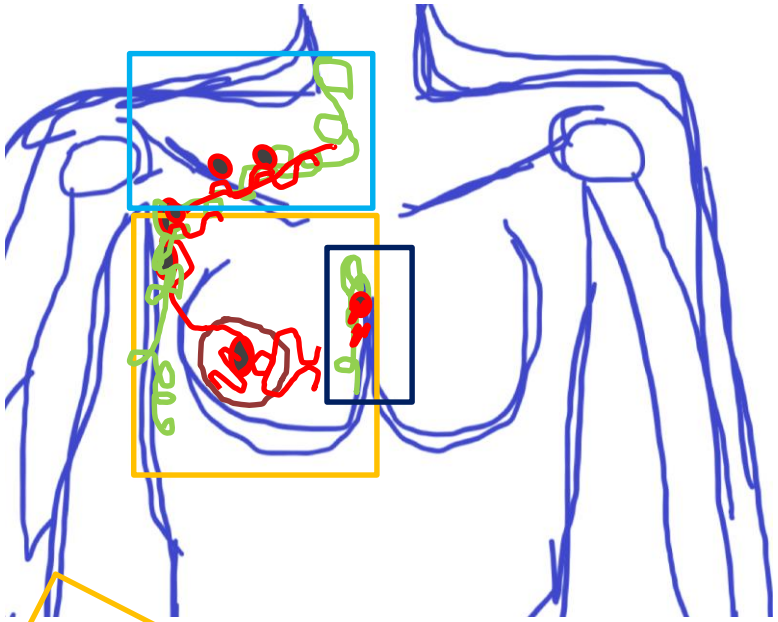




Stage 3, SCLV and IMNs at risk





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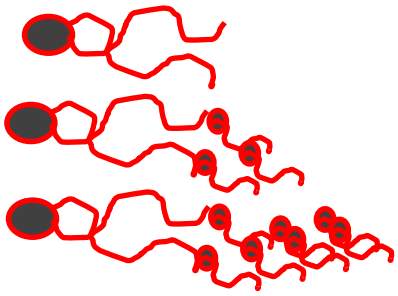
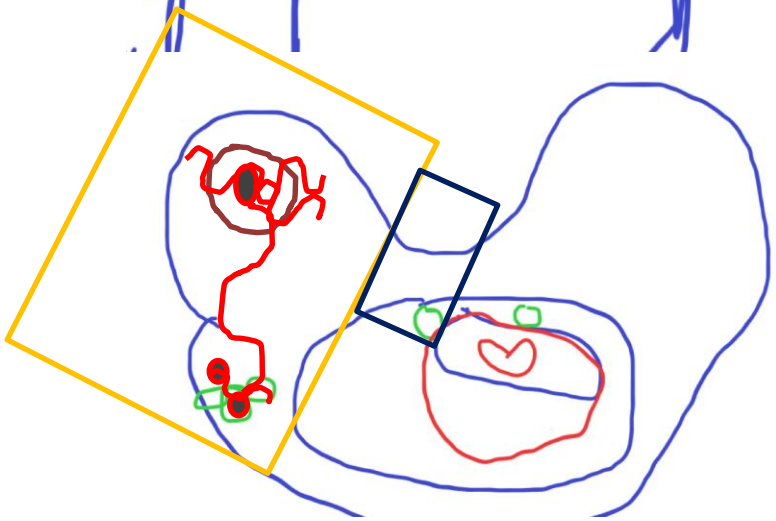
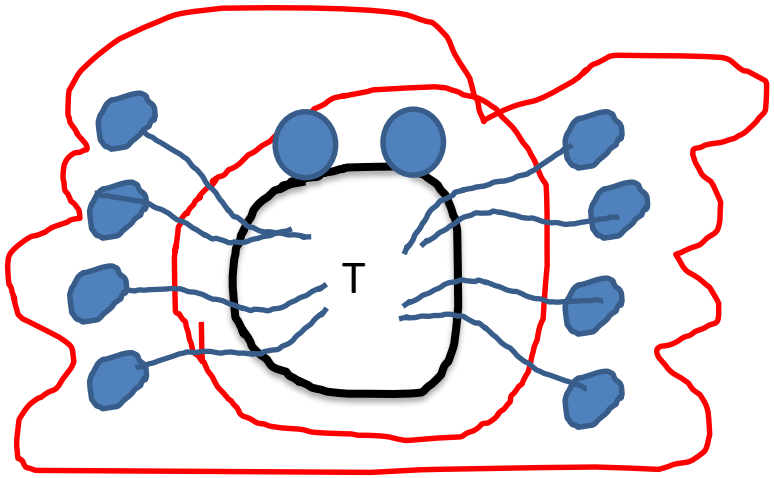
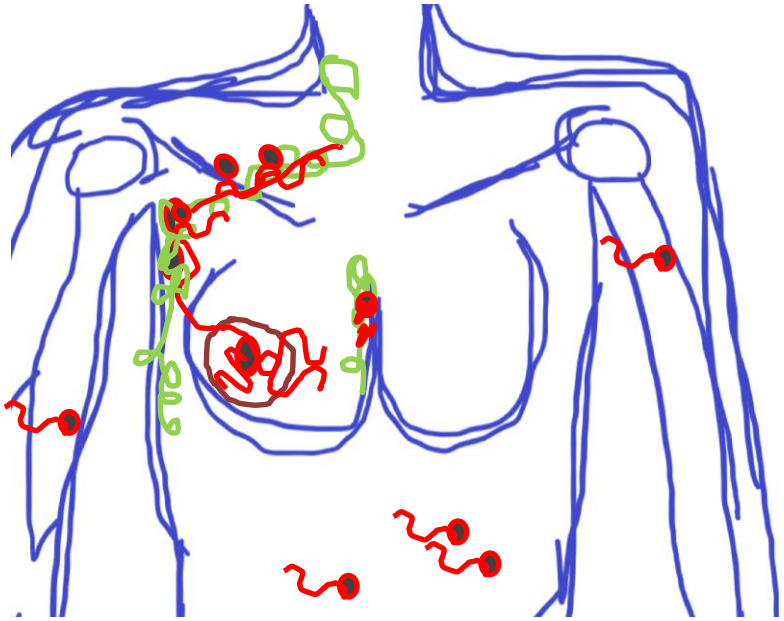




Stage 4, systemic treatment, palliative RT





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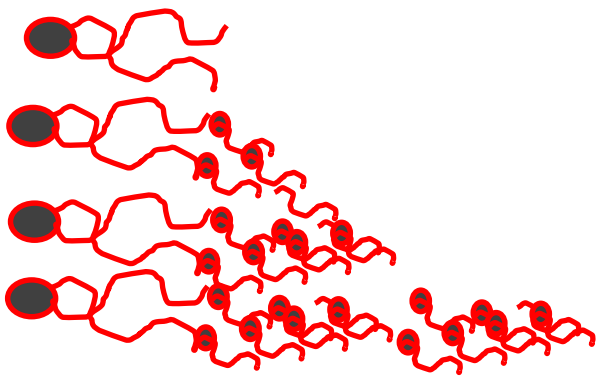
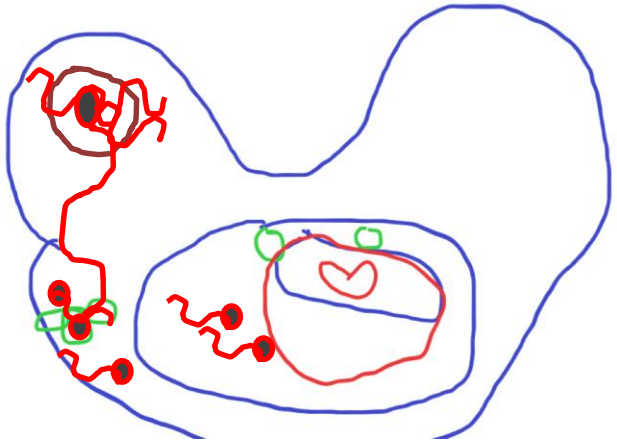
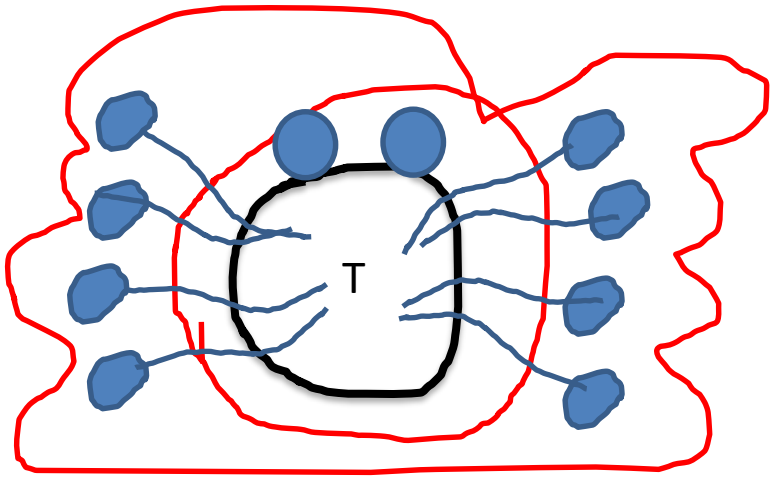
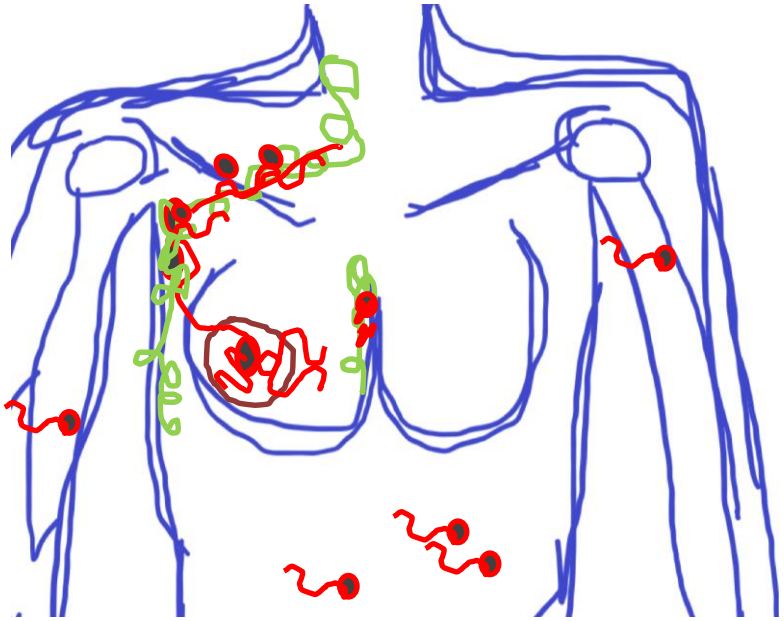




Stage 4, systemic treatment, palliative RT





Tools:

- Surgery: Remove body of the crab (Remove billions of cells)
- Chemotherapy: Prevent and kill seeds that are spreading beyond the regional area. (Kill thousands of cells)
- Radiation: Eradicate the crab Legs. (Kill millions of cells embedded in normal tissue)
- Hormone Therapy: Insurance plan. (Freeze cells in their track)

A Patient's Perspective

45 yo female G2p2, menarche 12- LMP 9/25/19, no hormone use, maternal GM with BC age 70, non smoker, no ETOH, noted right sided breast mass; cT2 cN0 MX Grade 1 IDC of the right upper outer breast, ER+, PR-, HER2 non amplified

Complete staging: Pregnancy test, H&P, CBC, CMP, breast imaging (MRI?), axillary imaging, biopsies, review pathology, genetics counseling, metastatic work-up (PET, brain MRI, bone scan), fertility counseling, assess for distress.

Now What

Surgery, How to Handle the Axilla

- Axillary dissection (more than 10 nodes removed) puts patients at risk for lymphedema.
- The field has been moving away for axillary dissection as studies now show RT and CT can adequately address microscopic disease in the axilla.

Surgery, How to Handle the Axilla

Clinically Node Negative But + on FNA or biopsy; T1-3 N1

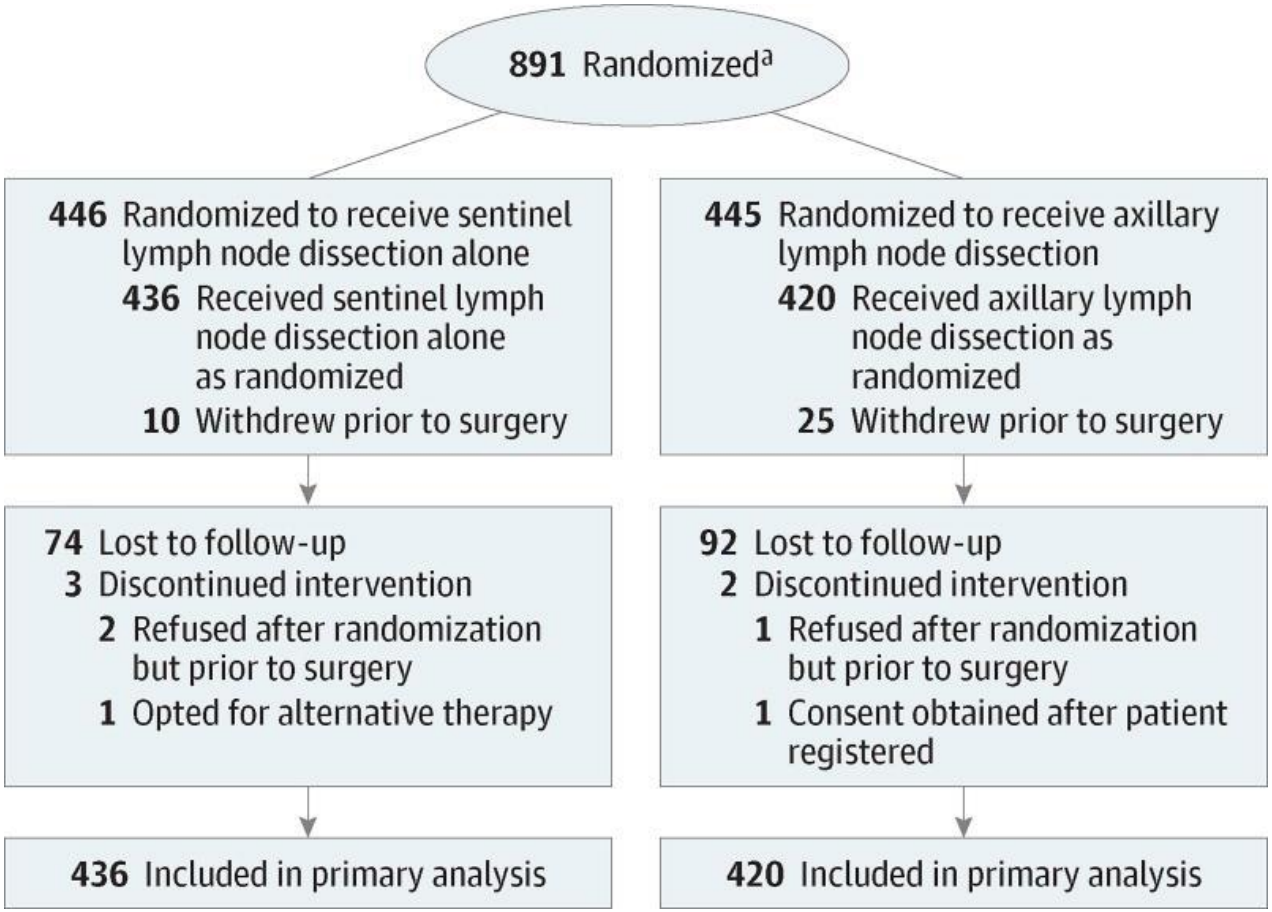
- Axillary dissection (more than 10 nodes removed) puts patients at risk for lymphedema.
- The field has been moving away for axillary dissection as studies now show RT and CT can adequately address microscopic disease in the axilla.
- In my experience, lymph edema is one of the worst toxicity associated with breast cancer treatment.

Surgery, How to Handle the Axilla

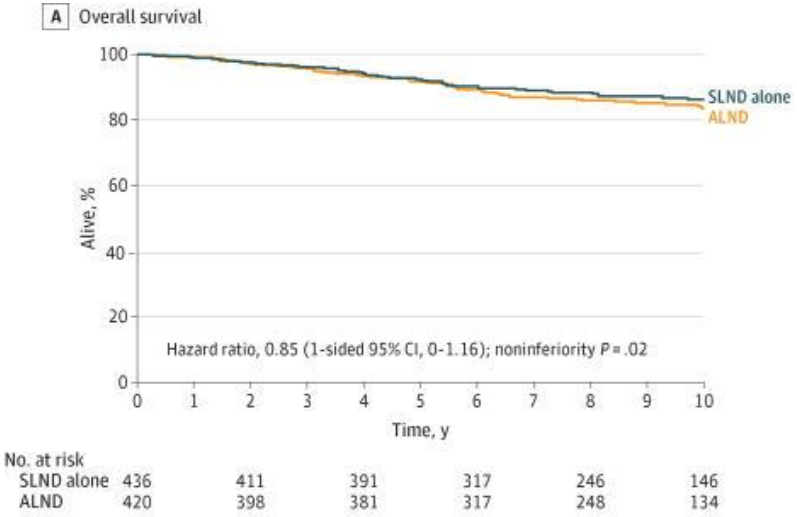
- ALND, or if meets the criteria for ACOSOG Z0011, and low tumor burden, then SLNB.
- Low tumor burden which was image detected disease not apparent on clinical exam and appears to be limited to one or two axillary nodes.
- If SLN is positive, no ALND if:
  - Only micro metastasis (less then 2 mm)
  - T1-T2 tumor with 1-3 positive nodes and whole breast RT is planned and there was no preoperative chemotherapy.
- ALND if the sentinel node was not identified or does not meet the above criteria.

ACOSOG Z0011

- Phase 3 randomized clinical trial enrolled patients from May 1999 to December 2004 at 115 sites
- Eligible patients were women with clinical T1 or T2 invasive breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases

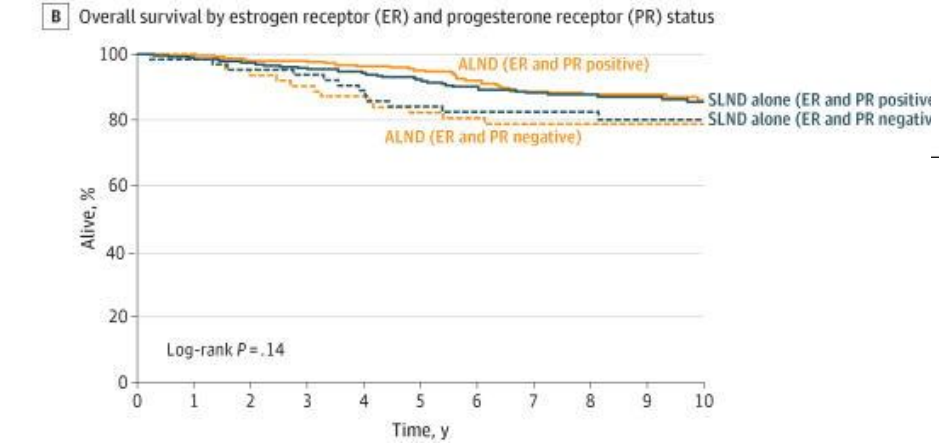


ACOSOG Z0011



No. at risk

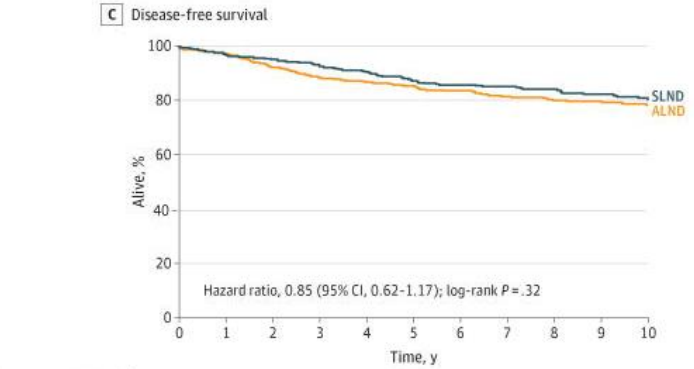
SLND alone	436	411	391	317	246	146
ALND	420	398	381	317	248	134



Time, y

No. at risk

SLND alone						
ER and PR Negative	64	60	56	45	37	19
ER and PR Positive	270	254	240	196	147	92
ALND						
ER and PR Negative	63	58	54	45	31	19
ER and PR Positive	256	243	238	201	163	85



No. at risk

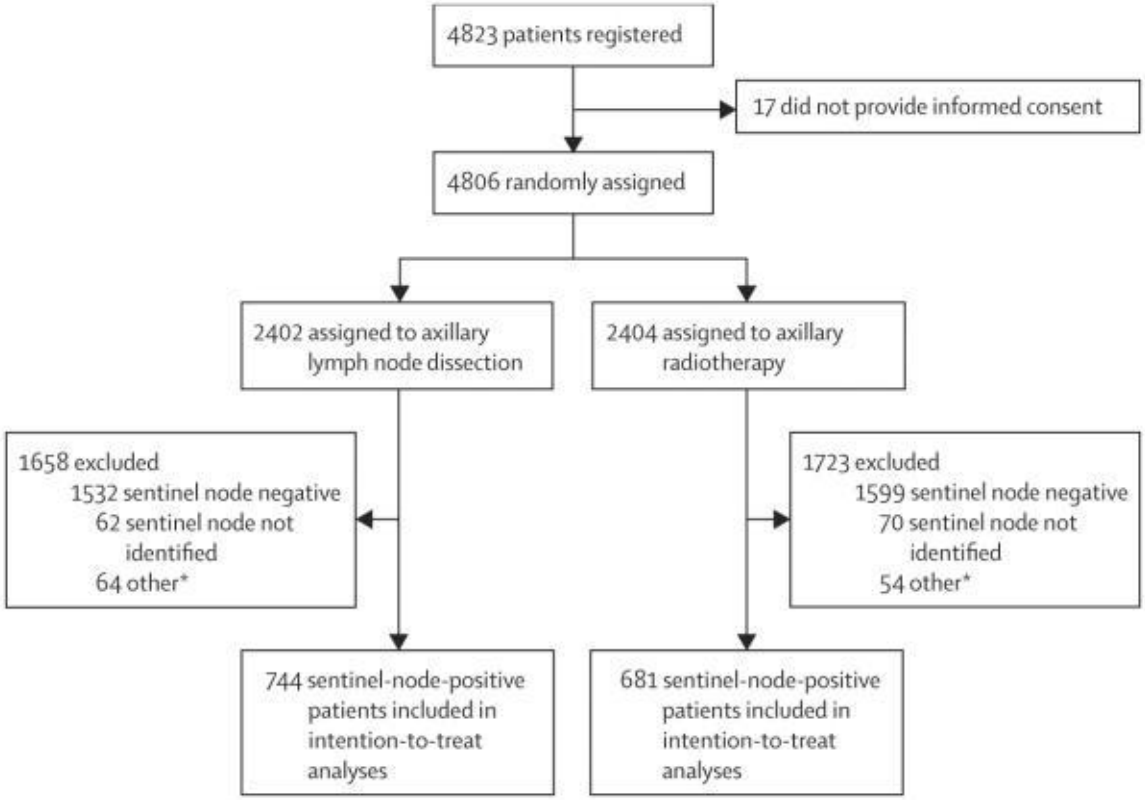
SLND alone	435	399	374	303	237	137
ALND	418	376	352	295	233	126

No difference in OS or DFS

But what about lymph edema?

AMAROS

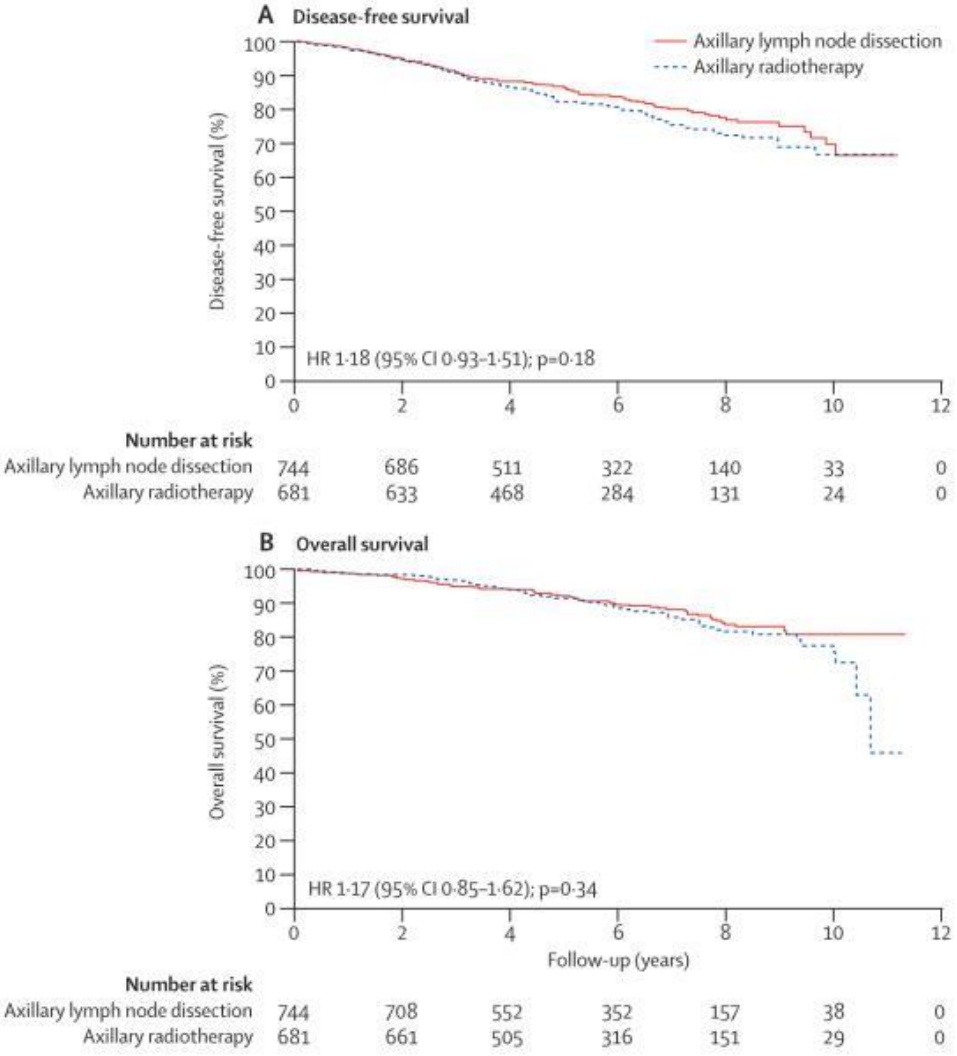
- Patients with T1–2 primary breast cancer and no palpable lymphadenopathy were enrolled in the randomized, multicenter, open-label, phase 3 non-inferiority trial.
- Patients were randomly assigned (1:1) to receive either axillary lymph node dissection or axillary radiotherapy in case of a positive sentinel node.
- The primary endpoint was non-inferiority of 5-year axillary recurrence



AMAROS

Number of positive sentinel nodes		
1	581 (78%)	512 (75%)
2	127 (17%)	134 (20%)
3	29 (4%)	27 (4%)
≥4	7 (1%)	8 (1%)
Size of the largest sentinel node metastasis		
Macrometastasis	442 (59%)	419 (62%)
Micrometastasis	215 (29%)	195 (29%)
Isolated tumour cells	87 (12%)	67 (10%)
Number of positive additional nodes (besides sentinel node)		
0	451/672 (67%)*	26/69 (38%)†
1–3	168/672 (25%)*	24/69 (35%)†
≥4	52/672 (8%)*	17/69 (25%)†
Missing	1/672 (<1%)*	2/69 (3%)†

AMAROS


A Disease-free survival
Axillary lymph node dissection
Axillary radiotherapy
Disease-free survival (%)
HR 1·18 (95% CI 0·93–1·51); p=0·18
Number at risk
Axillary lymph node dissection 744 686 511 322 140 33 0
Axillary radiotherapy 681 633 468 284 131 24 0
B Overall survival
Overall survival (%)
HR 1·17 (95% CI 0·85–1·62); p=0·34
Follow-up (years)
Number at risk
Axillary lymph node dissection 744 708 552 352 157 38 0
Axillary radiotherapy 681 661 505 316 151 29 0

AMAROS

Lymphoedema

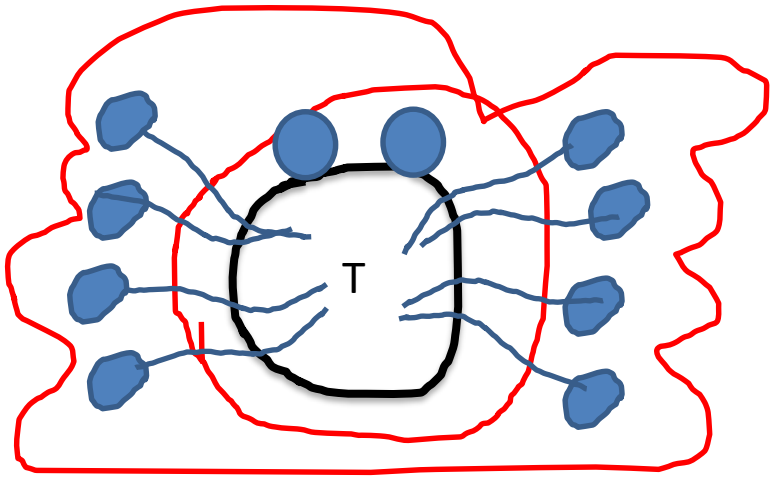
	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0.25
1 year	114/410 (28%)	62/410 (15%)	<0.0001
3 years	84/373 (23%)	47/341 (14%)	0.003
5 years	76/328 (23%)	31/286 (11%)	<0.0001
Arm circumference increase >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

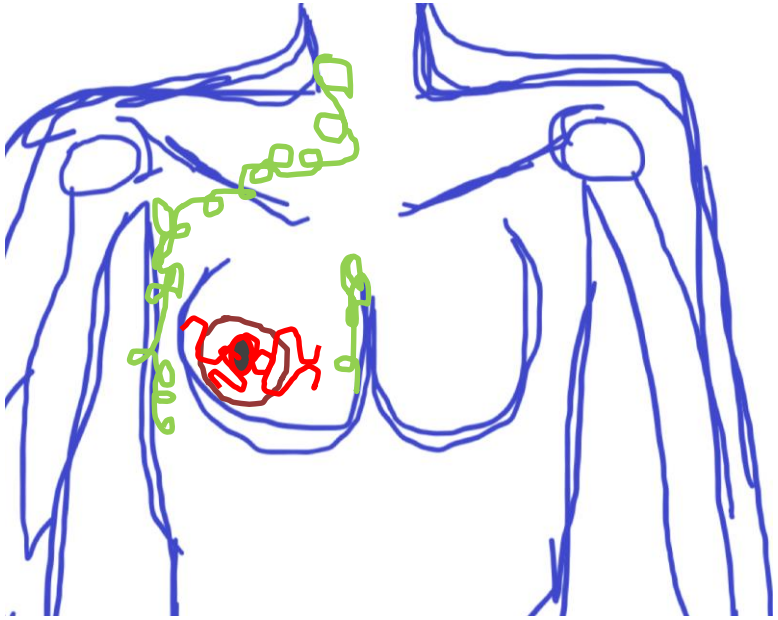
A Patient's Perspective

45 yo female G2p2, menarche 12- LMP 9/25/19, no hormone use, maternal GM with BC age 70, non smoker, no ETOH, noted right sided breast mass; cT2 cN0 MX Grade 3 IDC of the right upper outer breast, ER+, PR-, HER2 non amplified

Lumpectomy and SLNB

Lumpectomy and SLNB





Stage

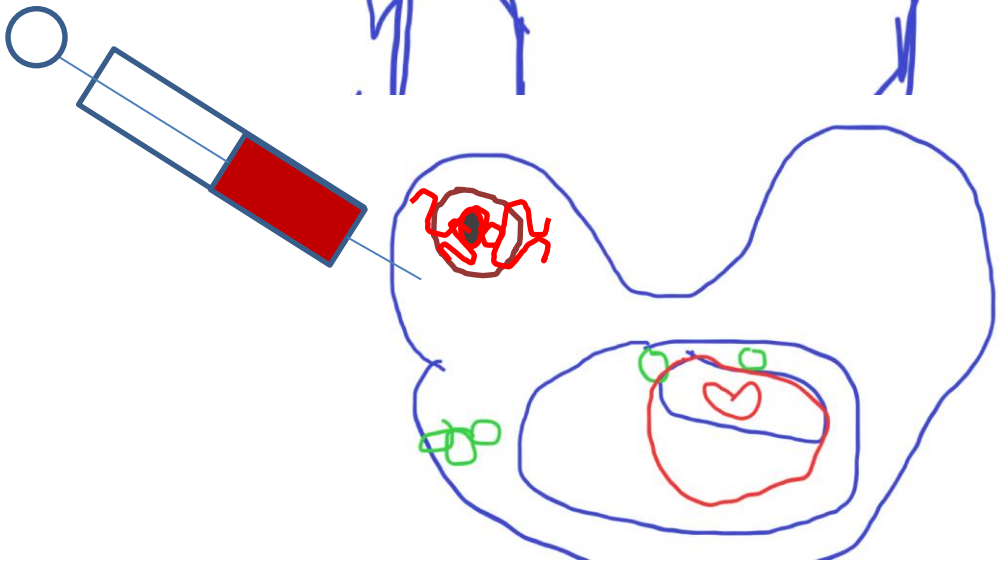
0

1

2

3

4



A Patient's Perspective

45 yo female G2p2, menarche 12- LMP 9/25/19, no hormone use, maternal GM with BC age 70, non smoker, no ETOH, noted right sided breast mass; cT2 cN0 MX Grade 1 IDC of the right upper outer breast, ER+, PR-, HER2 non amplified

SP Lumpectomy and SLNB demonstrating 35 mm IDC, 1 mm margin, no LVSI, no dermal lymphatic invasion, 1/3 nodes with 5 mm of cancer, no ECE, **pT2 pN1a stage IIb**. **Recurrence Score of 45**

A Patient's Perspective

High Risk Feature:

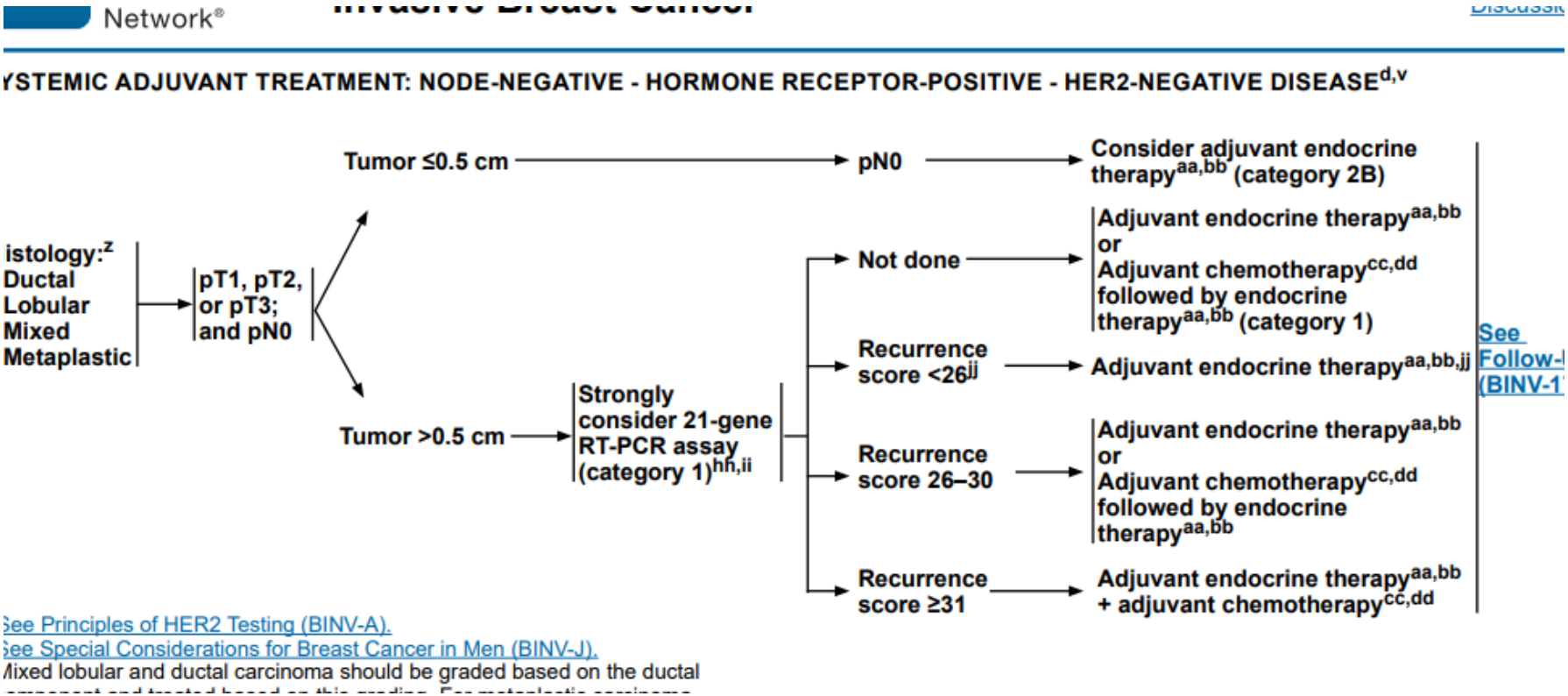
- Triple negative
- HER2 positive
- Grade 3
- Age under 50
- Pre-menopausal
- Lymphovascular invasion
- Dermal lymphovascular invasion
- Dermal involvement
- Tumor size
- Extra capsular extension
- Positive margins
- **High recurrence score**

SP Lumpectomy and SLNB demonstrating 35 mm IDC, 1 mm margin, no LVSI, no dermal lymphatic invasion, 1/3 nodes with 5 mm of cancer, no ECE, **pT2 pN1a stage IIb**. **Recurrence Score of 45**

Recurrence Score

Multigene assays for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy.

Recurrence Score



Multigene assays for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy.

Recurrence Score

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NCCN Guidelines Version 3.2019
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

MULTIGENE ASSAYS FOR CONSIDERATION OF ADDITION OF ADJUVANT SYSTEMIC CHEMOTHERAPY TO ADJUVANT ENDOCRINE THERAPY[a,b]

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk	Treatment Implications (references on next page)
21-gene (Oncotype Dx) (for pN0 or node negative)	Yes	Yes	Preferred	1	<26	Patients with T1b/c and T2, hormone receptor-positive, HER2-negative and lymph node-negative tumors, with risk scores (RS) between 0-10 have a risk of distant recurrence of less than 4% and those with RS 11-25, derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1] In women 50 years of age or younger, with RS 16-25 addition of chemotherapy to endocrine therapy was associated with a lower rate of distance recurrence compared with endocrine monotherapy. Consideration should be given for the addition of chemotherapy to endocrine therapy in this group.[1]
					26-30	In patients with T1 and T2, hormone receptor-positive, HER2-negative and lymph node-negative tumors and an RS of 26-30, the omission of chemotherapy has not been studied prospectively. Clinicians should consider additional clinical and pathologic factors with regard to the addition of chemotherapy to endocrine therapy in decision-making.[2]
					≥31	For patients with T1b/c and T2, hormone receptor-positive, HER2-negative, and lymph node-negative tumor RS ≥31, the addition of chemotherapy to endocrine therapy is recommended.[2]
21-gene (Oncotype Dx) (for pN+ or node positive)	N/A* *awaiting results of RxPONDER study	Yes	Other	2A	Low (<18)	The RS is prognostic in women with hormone receptor-positive, lymph node-positive tumors receiving endocrine monotherapy.[3-10] A secondary analysis of a prospective registry of women with hormone receptor-positive, HER2-negative, lymph node-positive tumors demonstrated a 5-year risk of distant recurrence of 2.7% in patients with an RS of <18 treated with endocrine monotherapy.[9] In the West German Plan B study, 110 women with hormone receptor-positive, HER2-negative, lymph node-positive tumors and an RS of <11, showed a 5-year disease-free survival of 94.4% when treated with endocrine monotherapy.[6] For hormone receptor-positive, HER2-negative, lymph node-positive tumors, clinicians should be aware that the optimal RS cut-off (< 11 vs. < 18) is still unknown both for prognosis (risk of recurrence) as well as prediction of chemotherapy benefit.
					Intermediate (18-30) or High (≥31)	In a secondary analysis of the SWOG 8814 trial of women with hormone receptor-positive, lymph node-positive tumors, high RS (≥31) was predictive of chemotherapy benefit. Because of a higher risk of distant recurrence, patients with hormone receptor-positive, 1-3 positive lymph nodes and RS of ≥18 should be considered for adjuvant chemotherapy in addition to endocrine therapy.[3]
70-gene (MammaPrint) (for node negative and 1-3 positive nodes)	Not determined	Yes	Other	1	Low	With a median follow-up of 5 years, among patients at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% CI, 92.5%–96.2%) among those who did not receive adjuvant chemotherapy. Among patients with 1-3 positive nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1–98.1) in those who received adjuvant chemotherapy versus 95.6 (95% CI, 92.7–97.4) in those who did not receive adjuvant chemotherapy.[11] Therefore, the additional benefit of adjuvant chemotherapy may be small in this group.
					High	
50-gene (PAM 50) (for node negative and 1-3 positive nodes)	Not determined	Yes	Other	2A	Node negative: Low (0-40)	For patients with T1 and T2 hormone receptor-positive, HER2- negative, lymph node-negative tumors, a risk of recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0.[12]
					Node negative: Intermediate (41-60)	
					Node negative: High (61-100)	
					Node positive: Low (0-40)	In patients with hormone receptor-positive, HER2-negative, 1-3 positive lymph nodes with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10 years [12] and no distant recurrence was seen at 10 years in TransATAC study in a similar group.[13]
					Node positive: High (41-100)	
12-gene (EndoPredict) (node negative and 1-3 nodes)	Not determined	Yes	Other	2A	Low (<3.3287)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0.[13] In ABCSG 6/8, patients in the low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1-3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years.[13]
					High (>3.3287)	
Breast Cancer Index (BCI)	Not determined	Yes	Other	2A	Low risk of late occurrence (0-5)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. There are limited data as to the role of BCI in hormone receptor-positive, HER2-negative, and lymph node-positive breast cancer.[13]
					High risk of late occurrence (5.1-10)	

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Can be considered in Node positive patients
Note takes 2-3 weeks to get the results
Ideally, start radiation 4-5 weeks after surgery

A Patient's Perspective

Completed chemotherapy, now what?

Adjuvant Radiation

Who needs radiation therapy

- Invasive breast cancer patient who opt for breast conserving therapy, lumpectomy and lymph node sampling (sentinel or axillary).

- Non-invasive breast cancer patient who opt for breast conserving therapy.

- Post mastectomy patient with high risk features.

Who needs radiation therapy

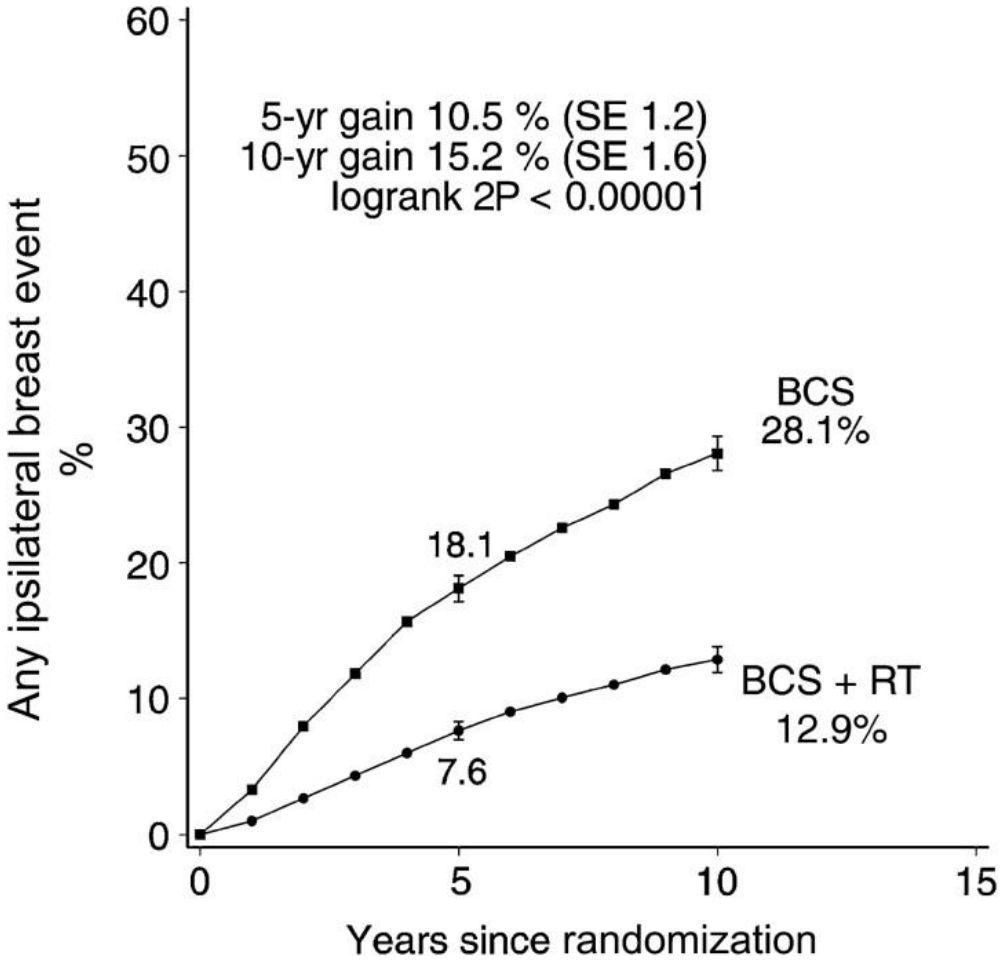
DCIS

4 RCT's comparing Lumpectomy alone to Lumpectomy + RT

	NSABP B17		EORTC 10853		UKCCCR		SWE DCIS	
Date	1985-1990		1986-1996		1990-1998		1987-1999	
Patients randomized	818		1010		1030		1046	
Median f/u	12 yr actuarial		10.2 yr median		4.38 yr median		5.2 yr median	
RT Dose	50 Gy/25 fx's		50 Gy/25 fx's		50 Gy/25 fx's		50-54/25-27 fx	
Mammo Detected	81%		71%		NA		87%	
Margins	"histologically tumor free"		"not present at margin"		"free"		22% unk or microscopically pos.	
Local Recurrence	L	L+RT	L	L+RT	L	L+RT	L	L+RT
Total	31.7%	15.7%	25%	15%	22%	8%	22%	8%
Invasive	16.8%	7.7%	13%	8%	7%	3.7%	13%	4.3%
Non-invasive	14.6%	8%	14%	7%	14%	4.5%	9%	3.9%

RT decreases risk of ipsilat breast recurrence by app 50%; half of recurrences are invasive, half non-invasive

Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast.
J Natl Cancer Inst Monogr. 2010;2010(41):162-77. doi: 10.1093/jncimonographs/lgq039.



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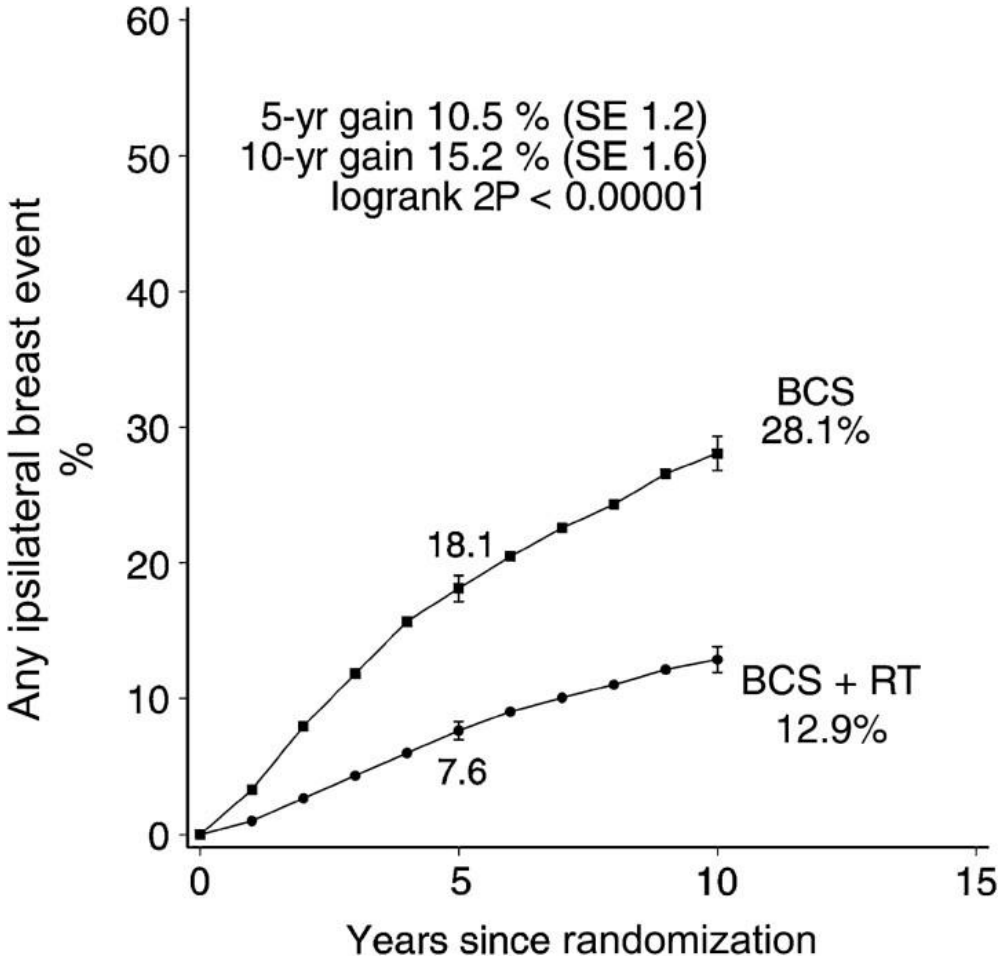

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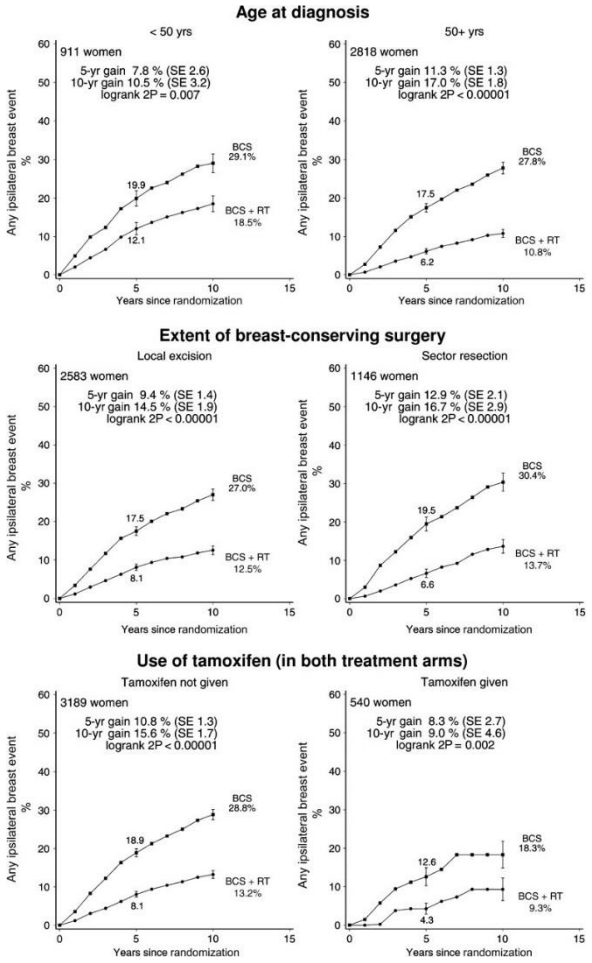

Measurable benefit even across age, margin and anti-estrogen use

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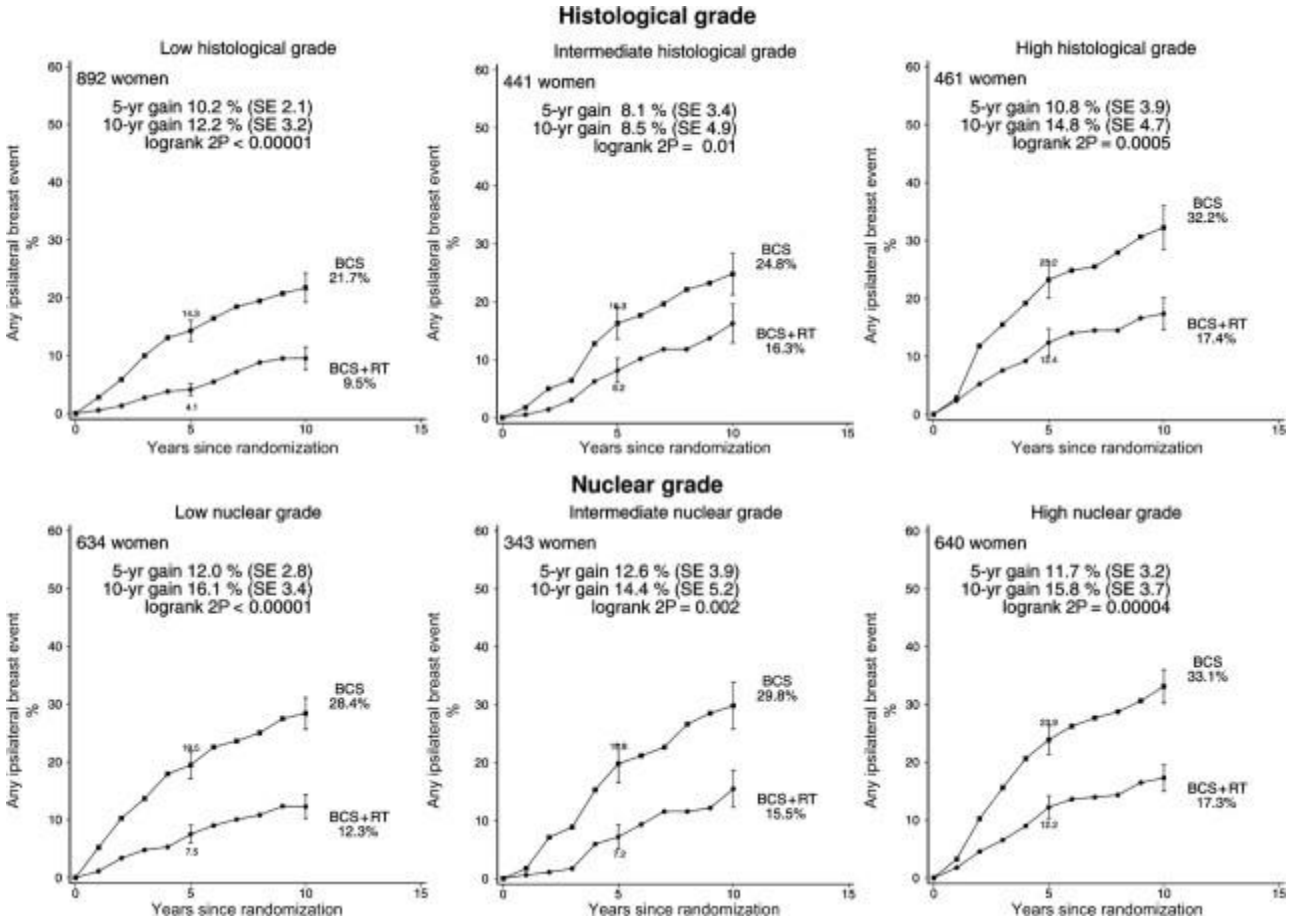

Measurable benefit even across gradeuse

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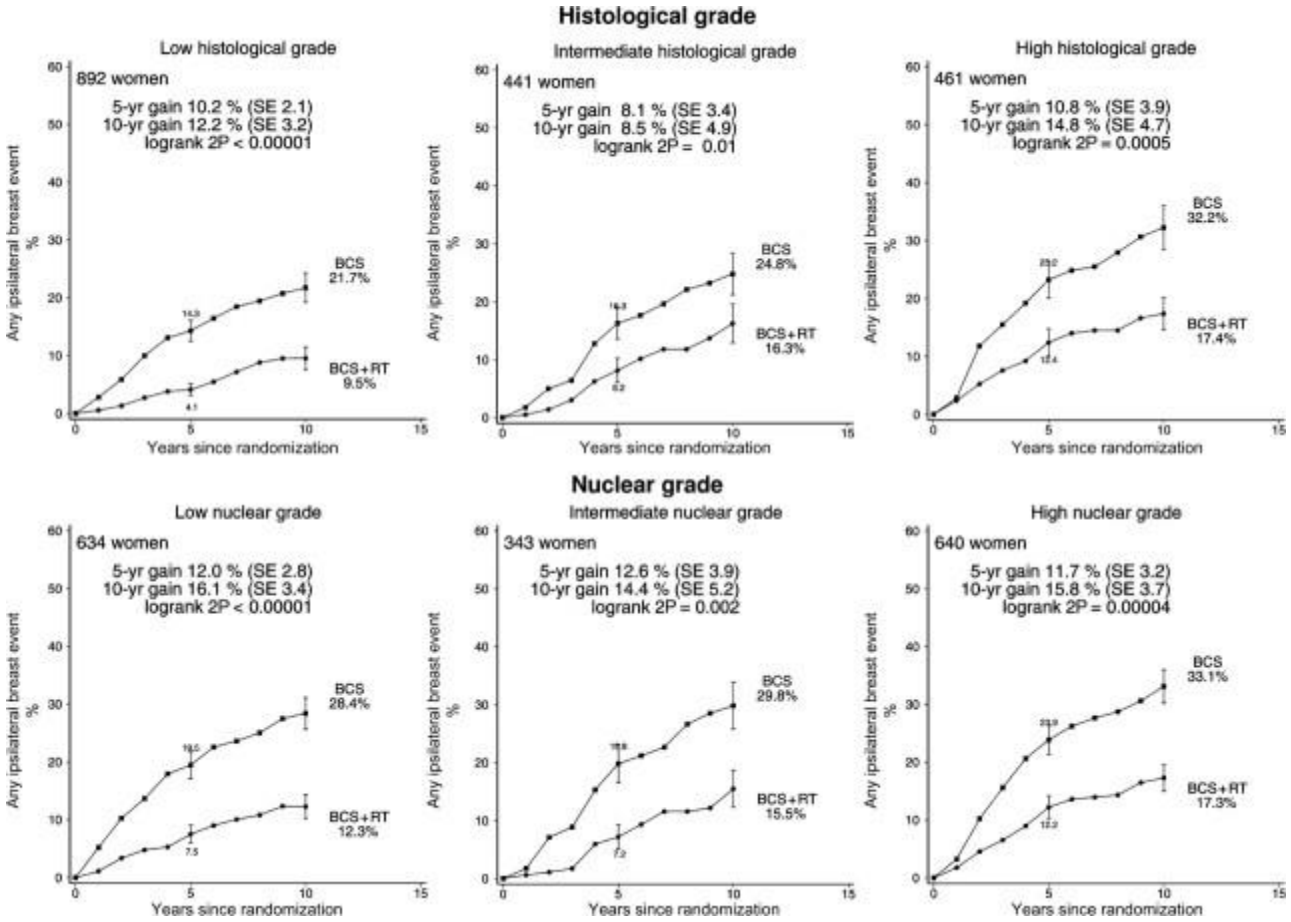

Measurable benefit even across histology grade and nuclear grade

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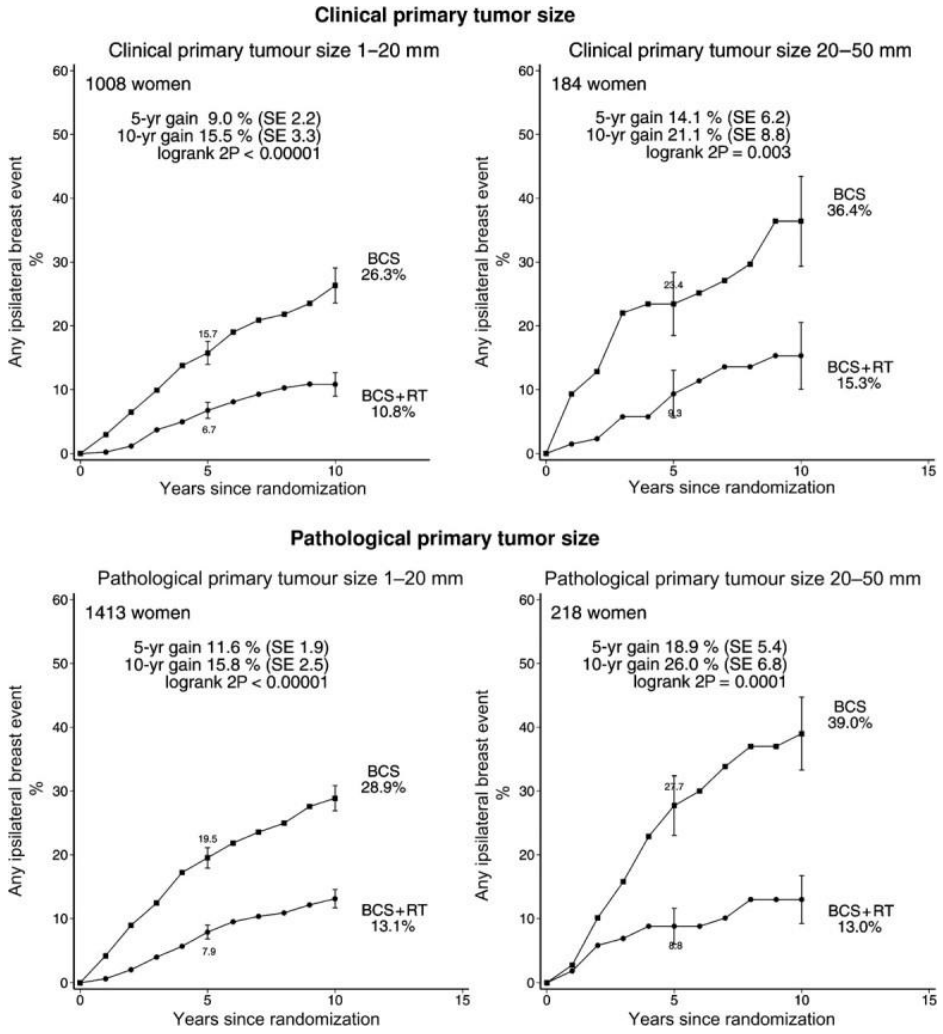


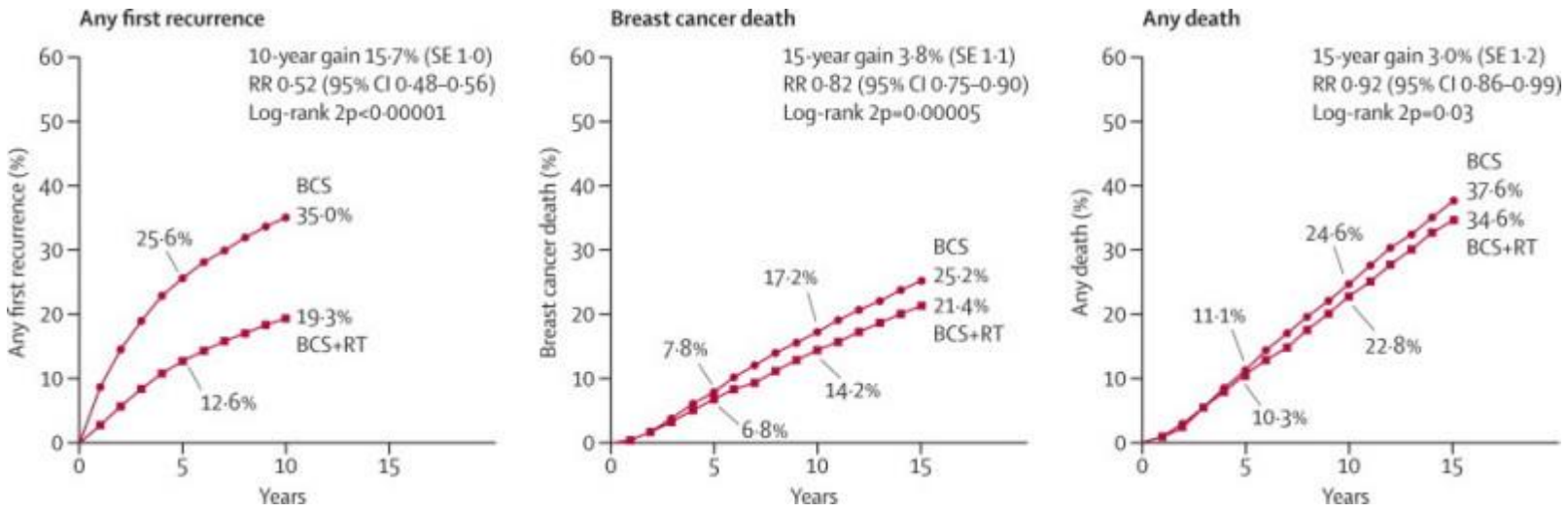
Measurable benefit even across tumor size.

Who needs radiation therapy

Invasive Disease, Breast Conserving Therapy

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomized trials

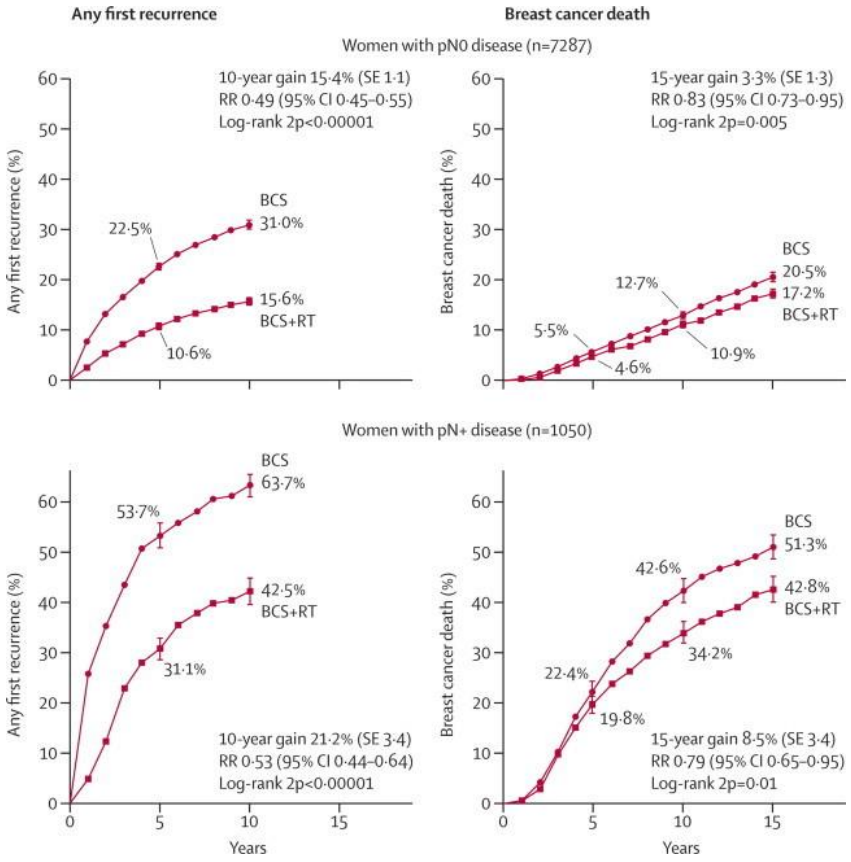
Lancet. 2011 Nov 12; 378(9804): 1707–1716.



Significant benefit for local control for all patients, some benefit to breast cancer specific death.

Who needs radiation therapy

Invasive Disease, Breast Conserving Therapy



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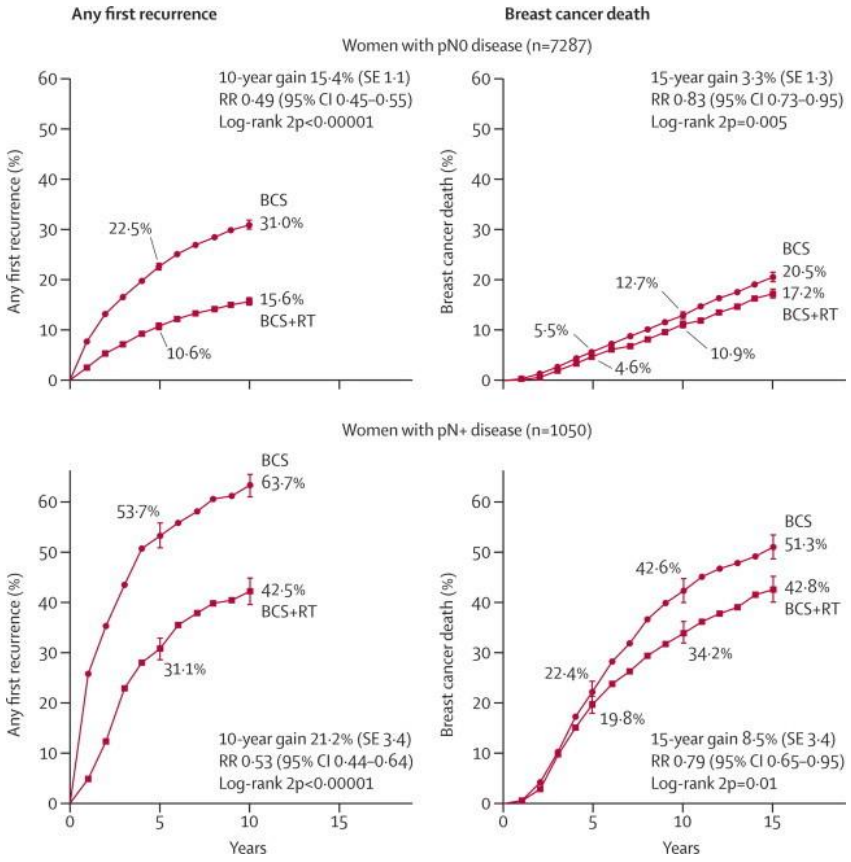


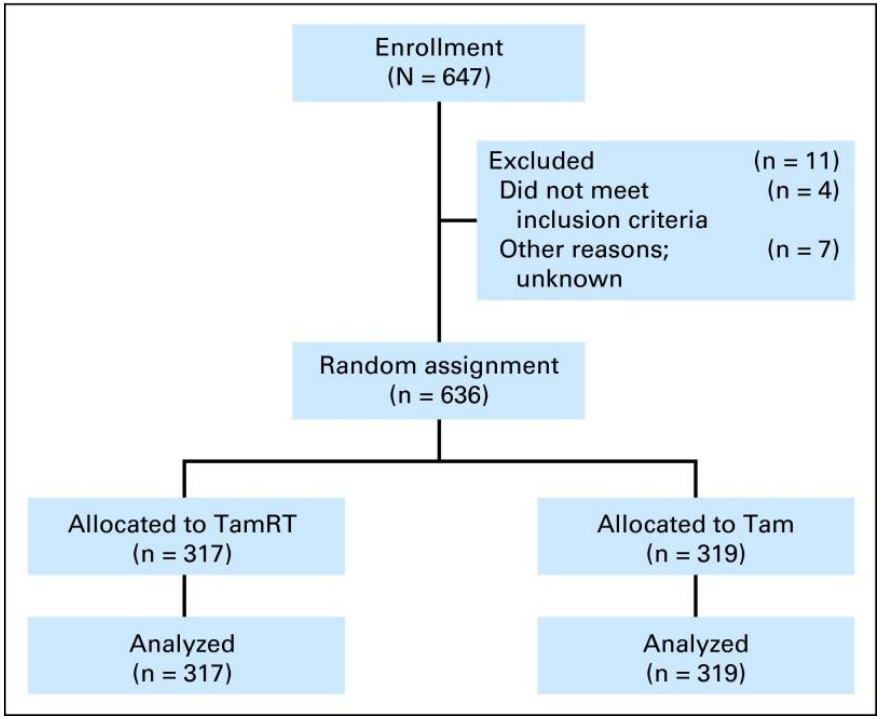
Significant benefit for local control for all patients, some benefit to breast cancer specific death.

Who needs radiation therapy

What about women over 65 with favorable disease

Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343.

J Clin Oncol. 2013 Jul 1;31(19):2382-7. doi: 10.1200/JCO.2012.45.2615. Epub 2013 May 20.



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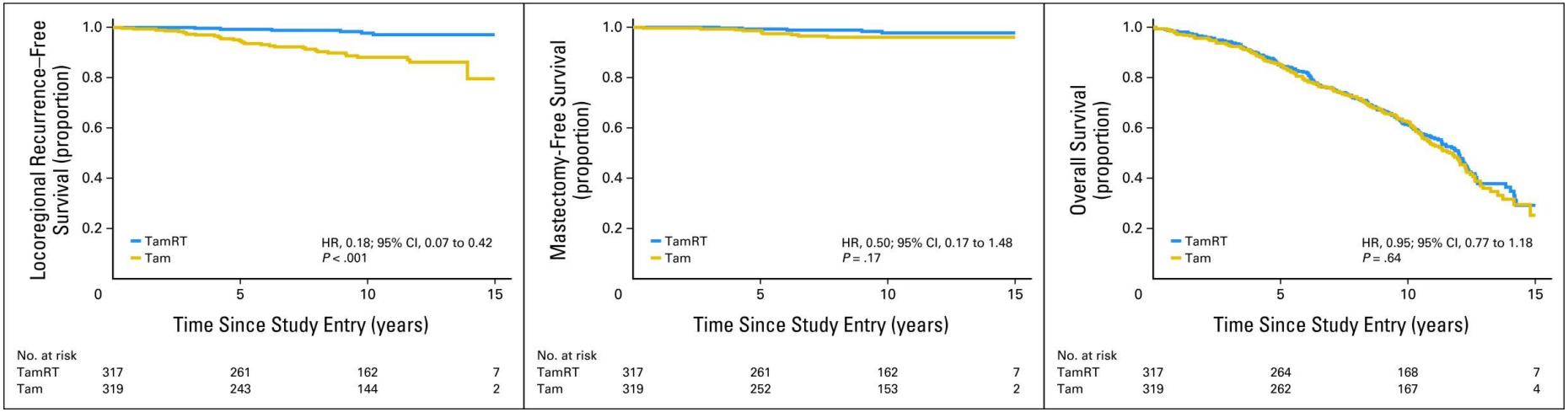


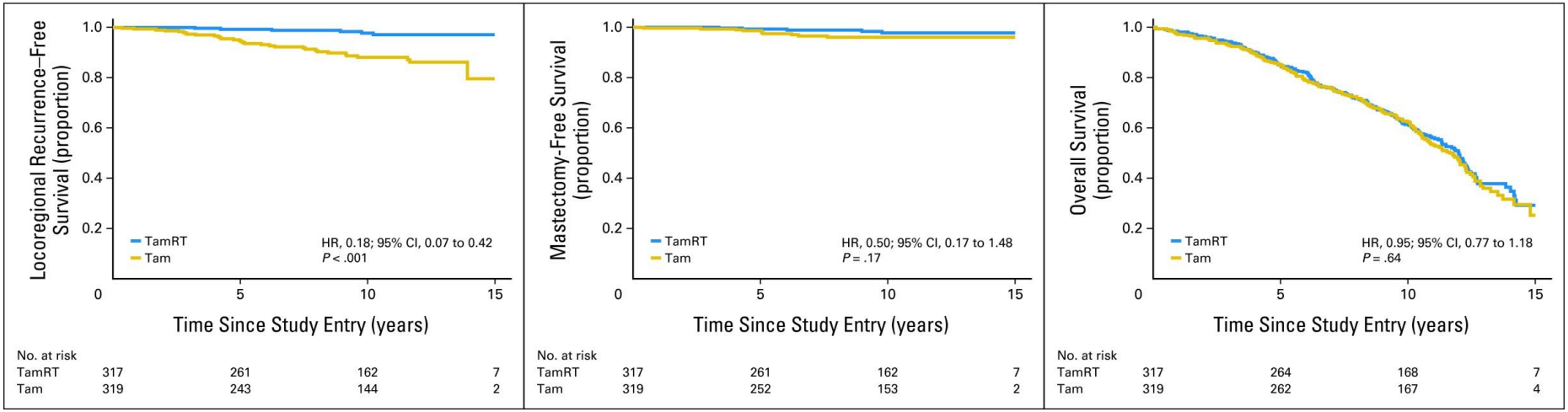
Slightly better local control
Same distal control
Some survival

Who needs radiation therapy

What about women over 65 with favorable disease

Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343.

J Clin Oncol. 2013 Jul 1;31(19):2382-7. doi: 10.1200/JCO.2012.45.2615. Epub 2013 May 20.



Slightly better local control
Same distal control
Some survival

Who needs radiation therapy

What about women over 65 with favorable disease

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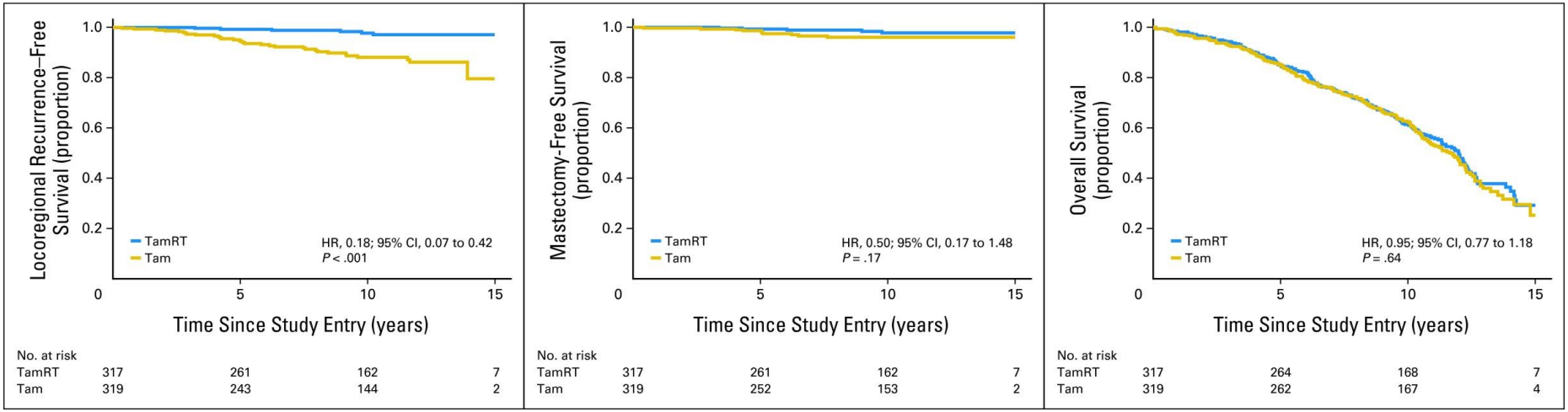


Slightly better local control
Same distal control
Some survival

Who needs radiation therapy

What about women over 65 with favorable disease

Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomized controlled trial.

Lancet Oncol. 2015 Mar;16(3):266-73. doi: 10.1016/S1470-2045(14)71221-5. Epub 2015 Jan 28.

- Similar results, but slightly higher risk patient, age 65, tumors up to 3 cm.
- Bottom line:
  - No quality of life study
  - Have to take a pill for 10 years versus 16 days of RT
  - No RT and lumpectomy arm
  - Disease control rates mirror older studies suggesting still a 20-30% probability of cancer cells.
  - Anti-estrogen does not necessarily kill cancer cells but holds them at bay.
  - Radiation is 16 days and kills cancer cells and is very well tolerated.
  - Thus, this is an area of controversy, and these patient should discuss the pros and cons of radiation in the context of their personal goals

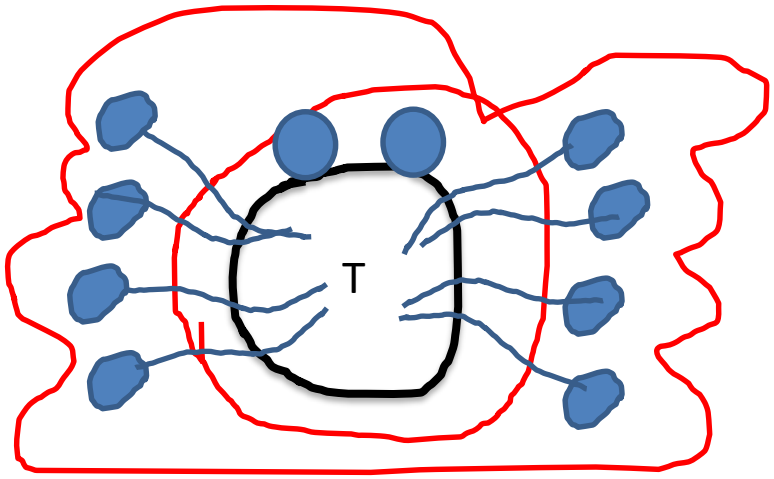
Who needs radiation therapy

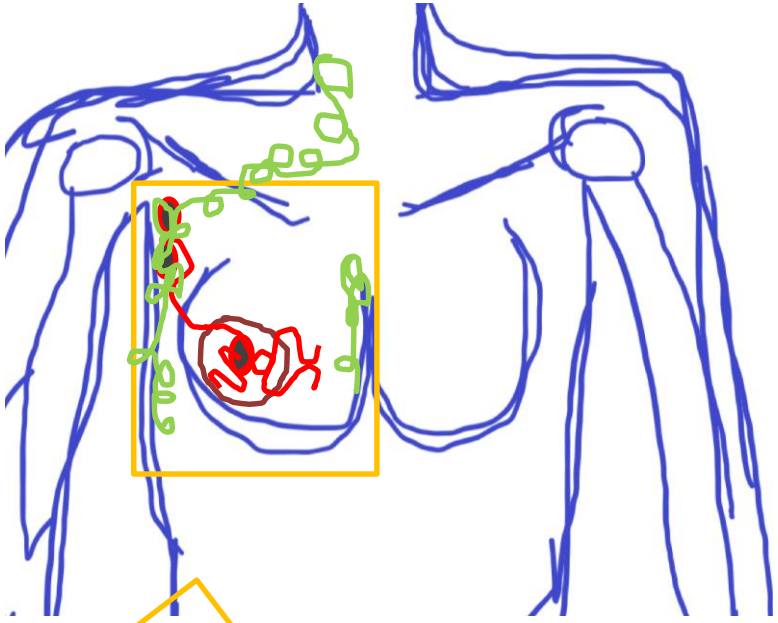
Post Mastectomy

Factors that have been shown to be associated with increased risk of LRR among patients with 1-3 LNs positive

Risk Factor for LRR	Independent prognostic factor for LRR>20%	Prognostic factor in combination with other factors
Younger age	BCCA/Fodor	NSABP/Cheng/ECOG
Tumor size	MDACC/Fodor	NSABP/Cheng/IBCSG
Close/pos margins (<5mm)	MDACC	
ER-	BCCA	Cheng
Medial tumor location	BCCA	
Invasion of skin or cw fascia	MDACC	
ECE ≥2mm	MDACC	
≥20% positive LN (only applies to ALND)	MDACC/BCCA	
<10 LN's dissected	MDACC	ECOG
Grade 3	---	IBCSG
LVSI	---	IBCSG/Cheng
Premenopausal	---	ECOG/IBCSG

Stage 2, high Recurrence Score





Stage

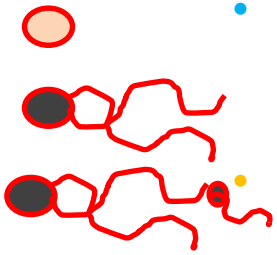
0

1

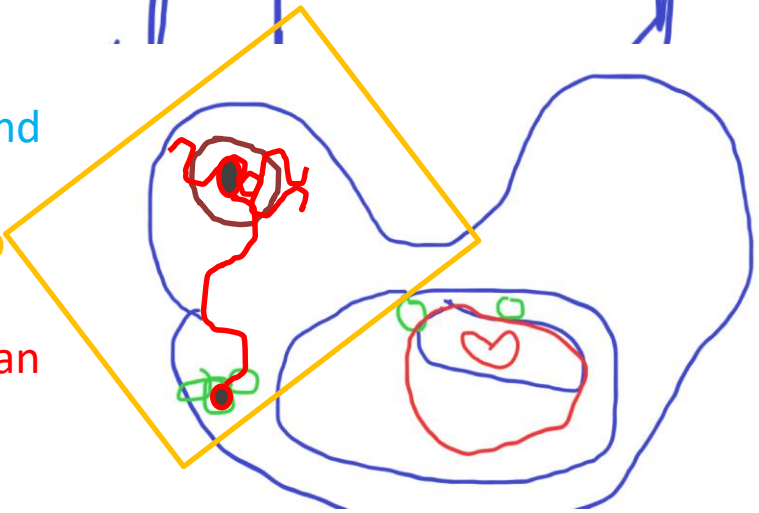
2

3

4



- Lumpectomy to remove the body of the crab
- Chemotherapy for possible spread beyond the breast.
- Radiation for the crab legs
- Hormone therapy as an insurance plan



A Patient's Perspective

Completed chemotherapy, now what?

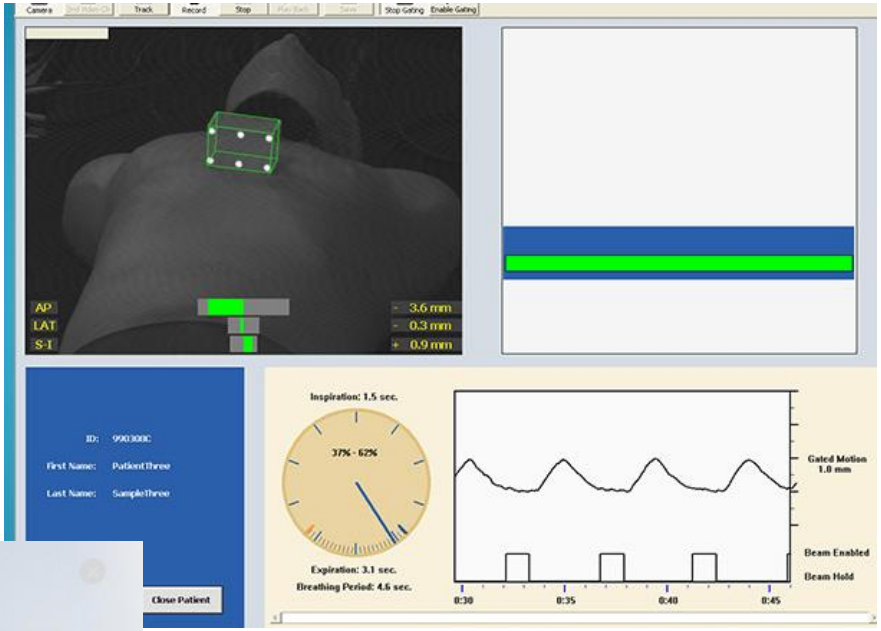
Radiation to the breast and axillary level I and II

CT simulation for planning

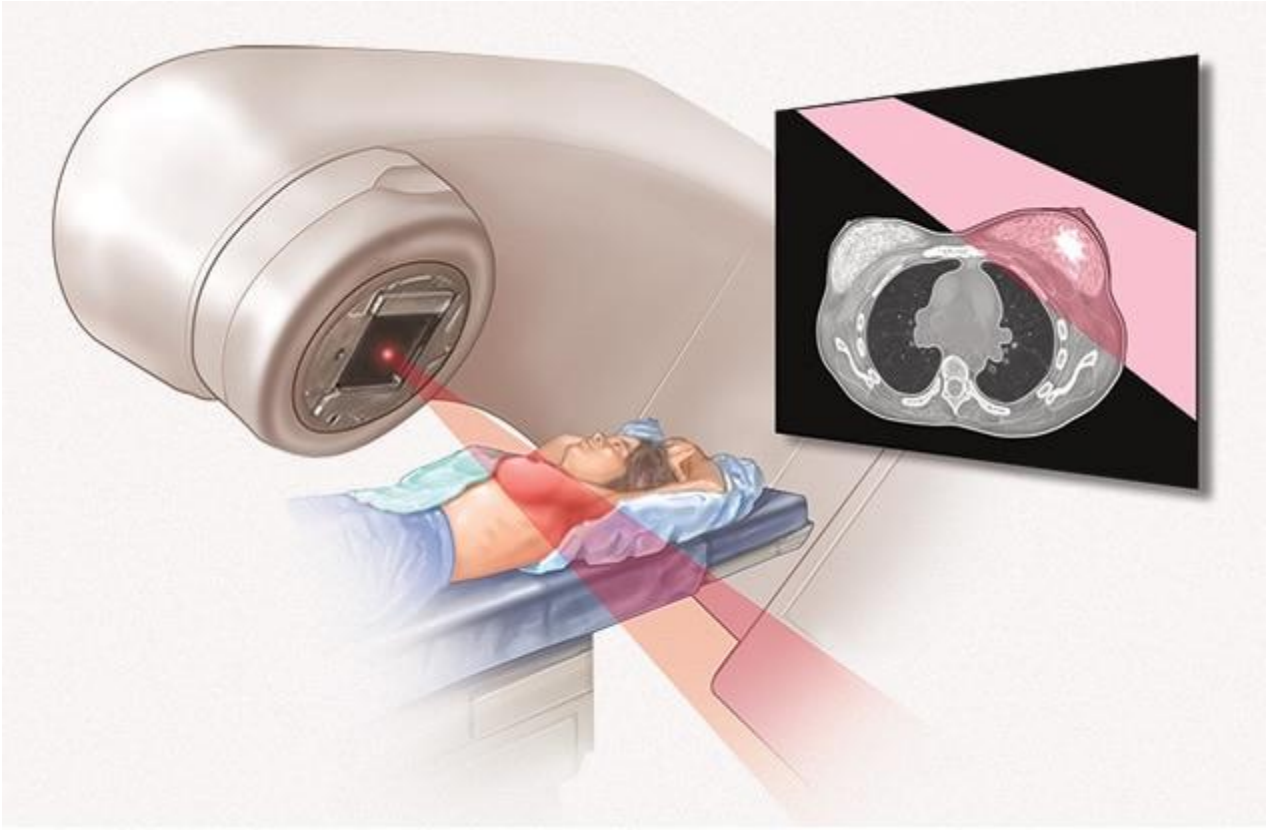
Reparatory Gating

77293

- Deep inspiratory breath hold for breast
- Tumor motion for lung/abdomen



Left Breast RT



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With DIBH and Respiratory Gating

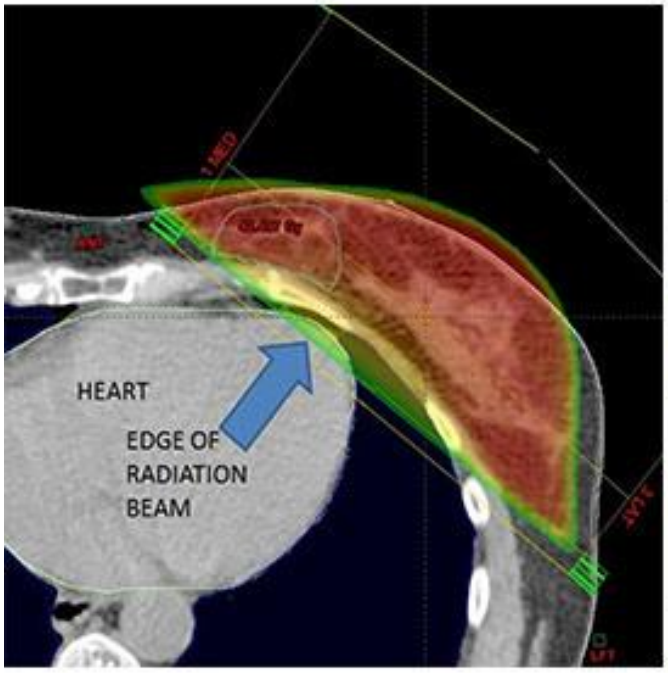


Fig. 1

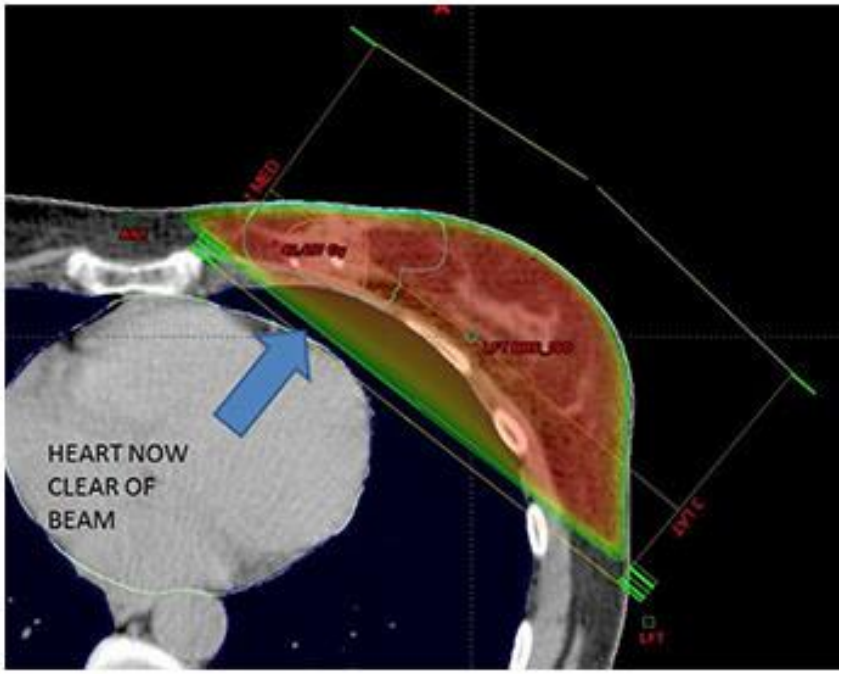
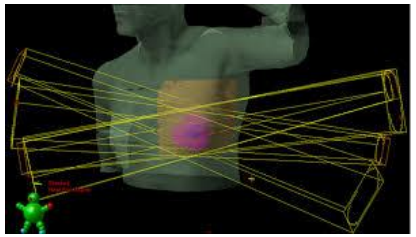


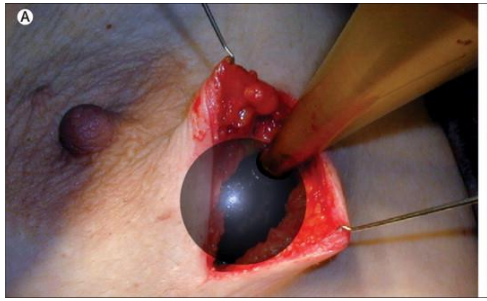
Fig. 2

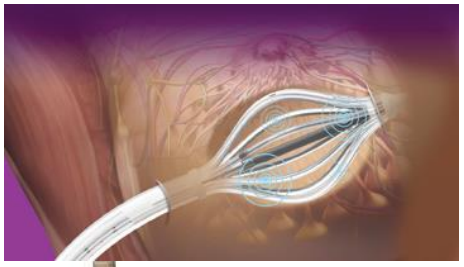
Different types of breast radiation

Whole Breast RT

Partial Breast RT







A Patient's Perspective

Toxicities

Toxicity

Acute toxicity: happens during treatment, and starts resolving once treatment is over. Mediated by normal tissue response to RT, often from cell cycle arrest during repair hindering the normal day to day function of the cells. This can also cause cell death and damage leading to inflammation.

Erythema
Dermatitis
Edema
Epilation
Folliculitis
Hyperpigmentation

Late toxicity: tender to occur 6 months after treatment indefinitely. Usually caused by tissue fibrosis and is dependent on dose.

Fibrosis
Edema
Hyperpigmentation

Acute radiation dermatitis scoring systems

(**A**) Follicular reaction with pruritus.
(**B**) Skin erythema and edema.
(**C**) Dry desquamation in axillary fold.
(**D**) Moist desquamation in inflammatory fold.

- Patient are instructed to use hypoallergenic water based moisturizers 2-3 times a day
- In a 16 day course, no significant side effects for the first 2-3 weeks, peak at weak 5-6 and resolve during the following 2 weeks.
- Time is the most effective remedy, but we will support the patient with barrier ointments as needed, topical steroids, Silvadene for moist desquamation, Mepilex dressing to guard against chafing.
- Patient are instructed to avoid anything that would further irritate the skin such as spas, chorine, sun etc.

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Breast

Late

- Fibrosis, breast shrinkage
- Decreased range of motion
- Lymphedema
- Hyperpigmentation
  - Mostly treated with PT
- Subscapular contracture
  - Surgery
- Necrosis
- Poor wound healing.
- Shoulder stiffness

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Thanks!