H · O · P · E

Holistic Oncology. Patient Empathy.

Oncology Care Clinic

Hormone positive breast cancer: neoadjuvant treatment

Dr. Amish Vora
Director n co-founder

Main aim of debate today is:

- Should we offer neoadjuvant treatment to all/some HR positive breast cancer
- Or
- Existing adjuvant strategies are good enough

A case scenario:

- 62 year old female patient presents in AIIMS opd with:
- 10 cm left breast mass, ER PR +ve, HER2Neu: -ve IDC. Mass touches chest wall. PET CT: no distant mets
- Surgeon says: technically unresectable

- What would you do?

This patient, postmenopausal ER +ve, Local disease but unresectable

- Intent of treatment?
- Neoadjuvant chemo?
- Or
- Hormone (AI+CDK 4/6 inhibitor)

With this, let us move back to 1982/83:

Search All

Enter Search Term

This Issue

Article

July 1982

Chemotherapy Before and After Mastectomy in Stage III Breast Cancer

Marjorie Perloff, MD; Gerson J. Lesnick, MD

» Author Affiliations

Arch Surg. 1982;117(7):879-881. doi:10.1001/archsurg.1982.01380310005002

17 patients data: cytotoxic chemo preceding surgery

- 6/17 long term survivors (upto 79 months) compared to 40 months median survival of patients who did not receive preceding cytotoxic drugs

Same year/next year, another small experience

Case Reports > J Surg Oncol. 1983 Apr;22(4):278-82. doi: 10.1002/jso.2930220415.

Preoperative chemotherapy followed by mastectomy for locally advanced breast cancer

P Schick, J Goodstein, J Moor, J Butler, K L Senter

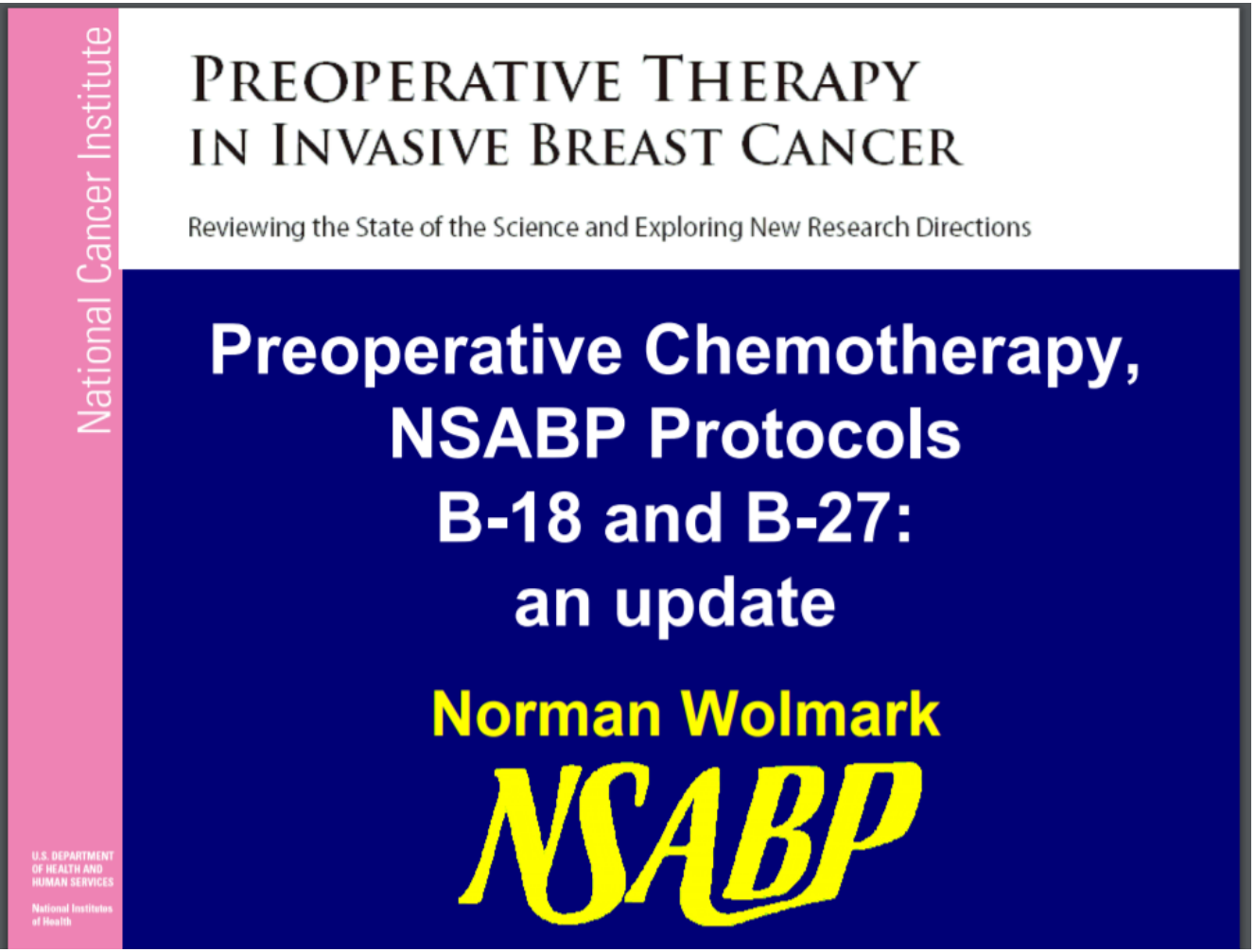
PMID: 6834850 DOI: 10.1002/jso.2930220415

Abstract

Six patients with advanced local-regional breast cancer were reviewed. Five out of the six patients previously had had radiation therapy as part of the initial therapy. All patients had preoperative cycles of combination chemotherapy, either CMF or CAF. The two stage III patients had greater than 75% reduction in measurable tumor mass, which allowed a conventional modified radical or radical mastectomy to be performed. Both of these patients are now disease free at 26 and 27 months. The four stage IV patients had lesser operations following the chemotherapy (two simple mastectomies, one simple mastectomy plus axillary resection, and one axillary debulking). Reconstruction utilized advancement flaps in three patients and split-thickness skin grafts in the other. None of the patients had postoperative wound problems, and none of the patients had further problems with local cancer control. All patients had combination chemotherapy starting two to six weeks following surgery. Preoperative chemotherapy followed by surgery plays an important role in management of locally advanced stage III and stage IV breast cancer.

From these small patients data, let us move to large trials/meta-analysis

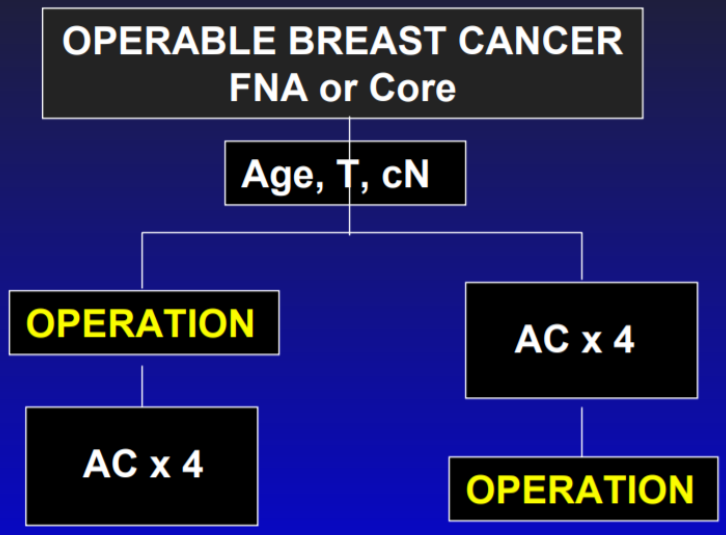
- Famous NSABP series
- B 18 and then B 27
- Publications spanning from 1998 to 2008



Preoperative Chemotherapy, NSABP Protocols B-18 and B-27: an update

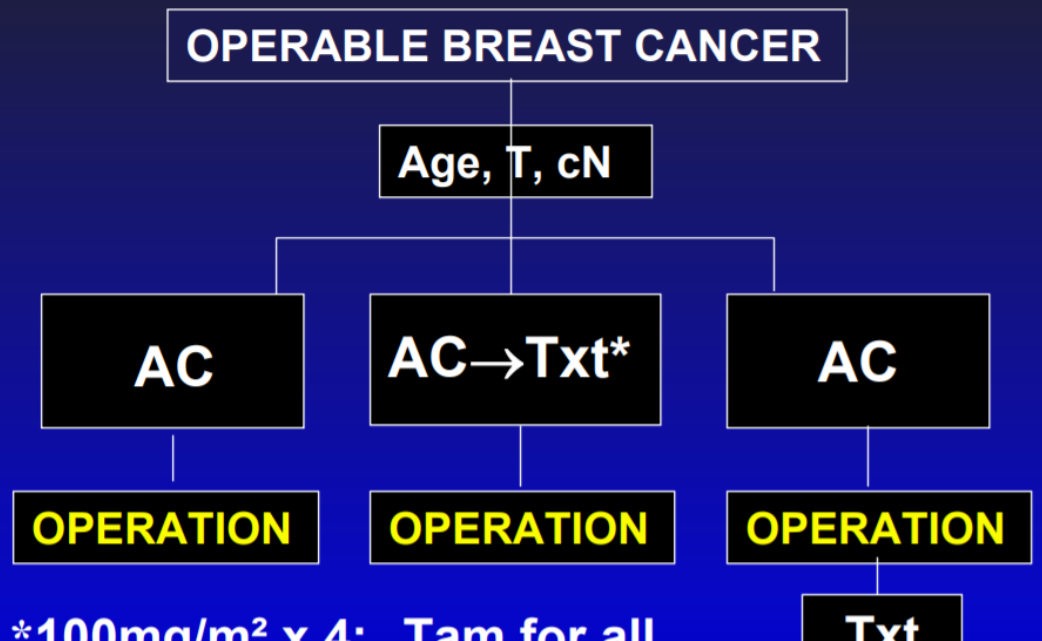
Norman Wolmark
NSABP

B-18

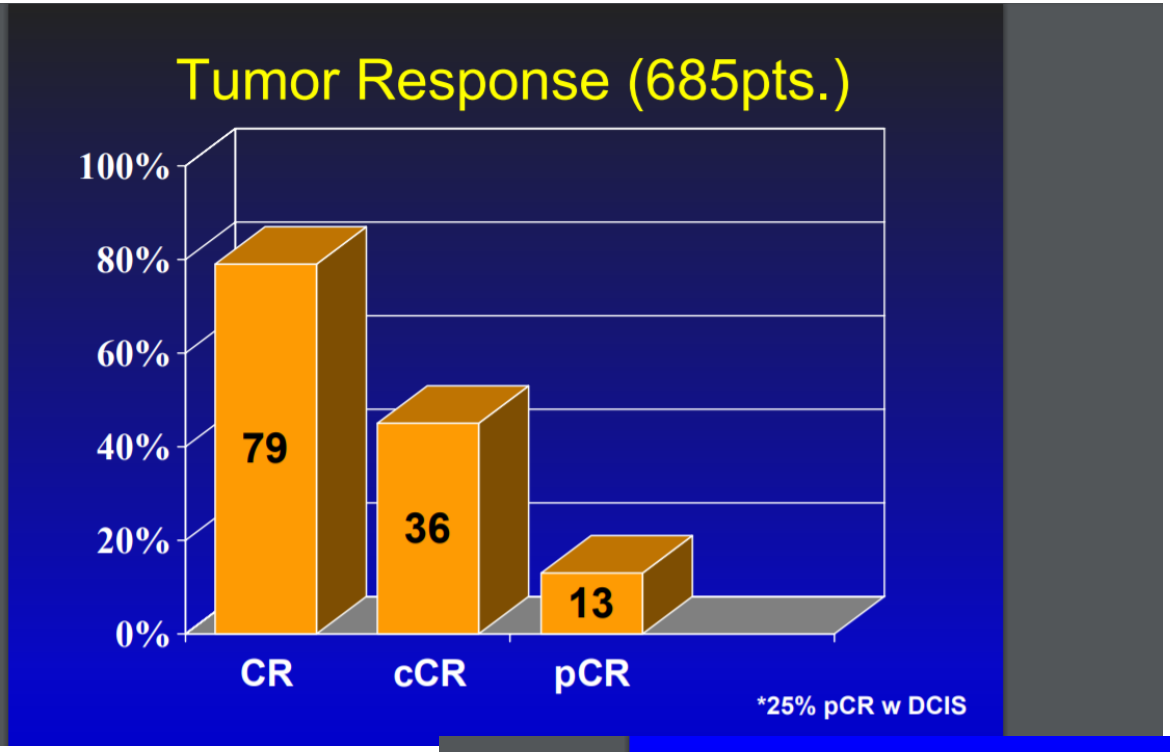


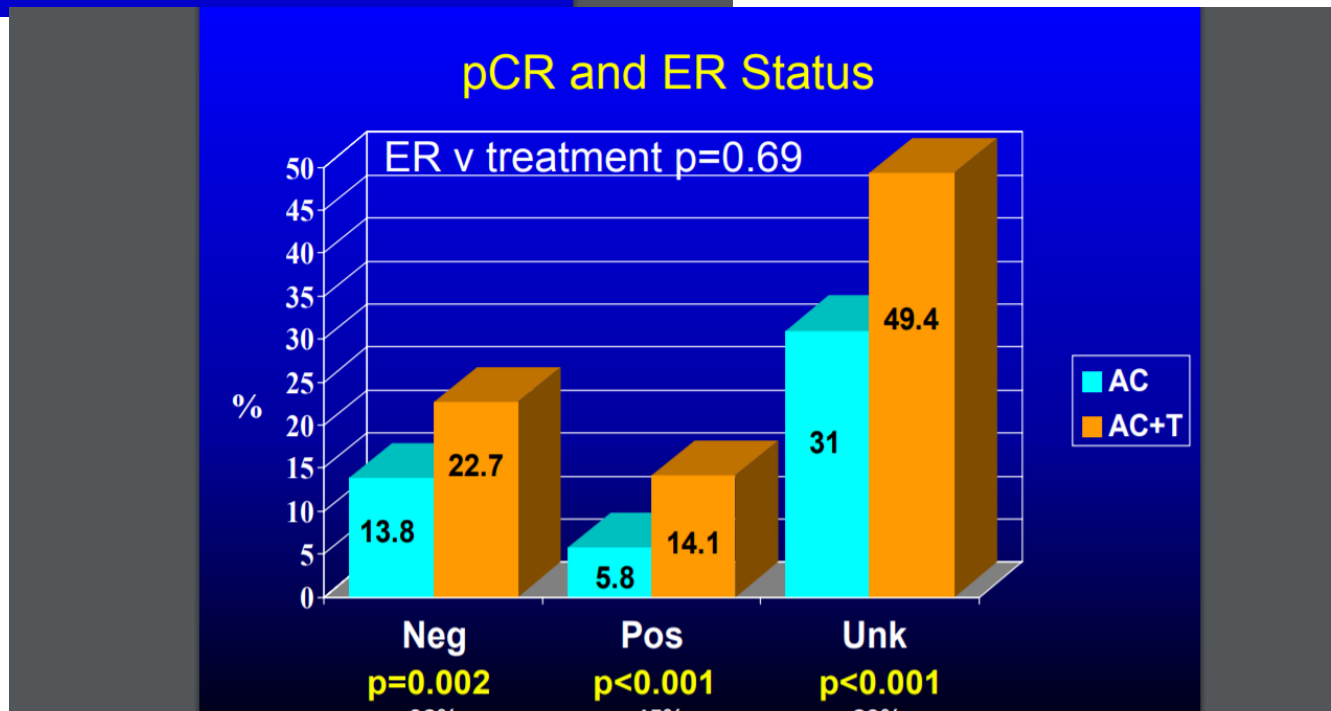
Ta

B-27

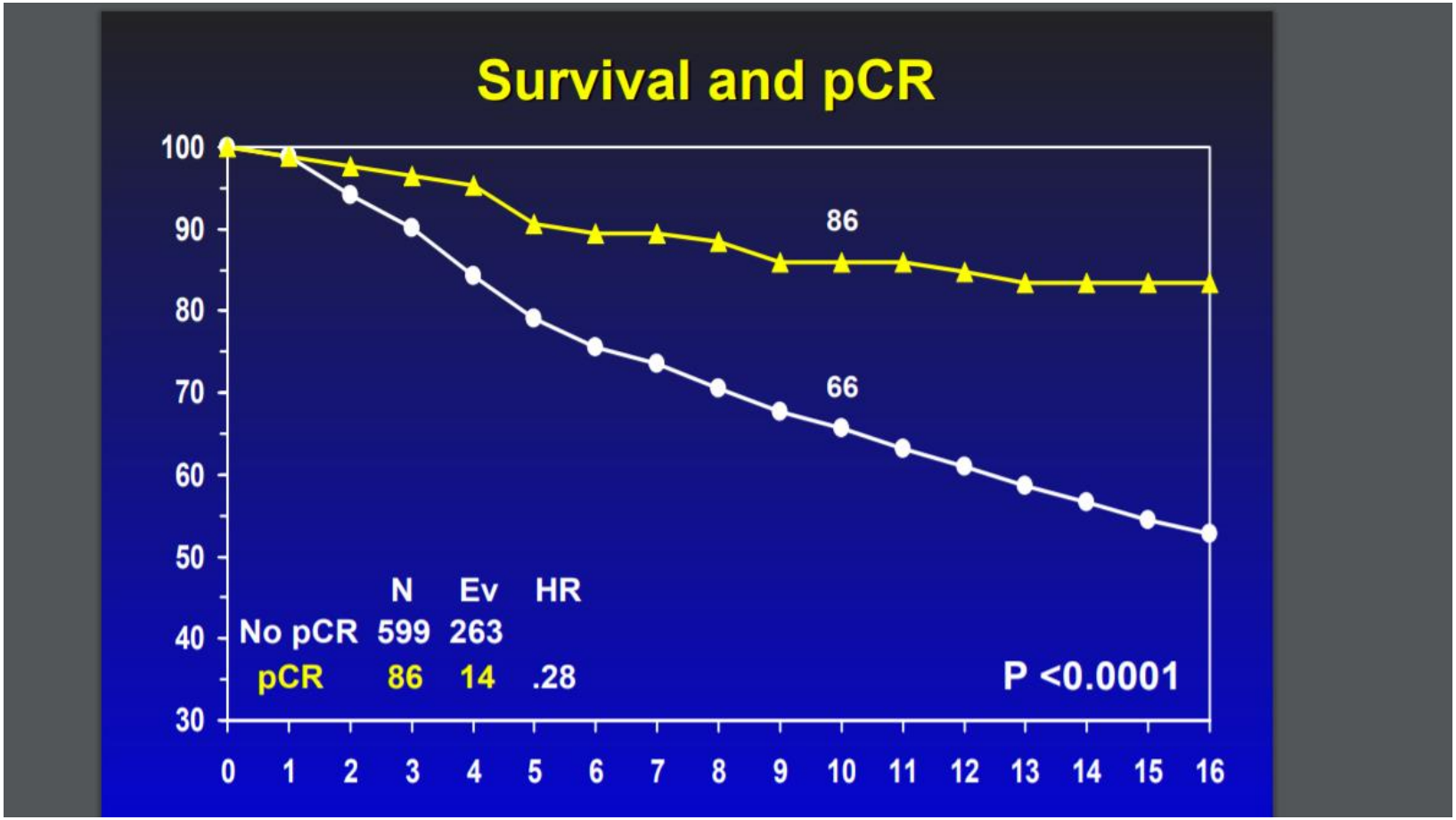


*100mg/m² x 4; Tam for all


Tumor Response (685pts.)
100%
80%
60%
40%
20%
0%
79
36
13
CR
cCR
pCR
*25% pCR w DCIS


pCR and ER Status
ER v treatment p=0.69
50
45
40
35
30
25
20
15
10
5
0
%
13.8
22.7
5.8
14.1
31
49.4
AC
AC+T
Neg
p=0.002
Pos
p<0.001
Unk
p<0.001

From here, the story of path CR and NACT started…



What we learnt so far?

- Neo-adjuvant chemotherapy can make UNRESECTABLE breast cancer to RESECTABLE
- 12% more patients can undergo breast conservation with NACT
- 14% patients with HR +ve achieve PathCR and LIVE LONGER
- Women less than 50 years have a trend towards improved OS with NACT
- Overall, there was similar overall survival between Neo-adjuvant and adjuvant chemotherapy

Most important learning was…

- Same Chemotherapy which is given either before or after surgery gave similar survival

From here…

- HER 2 Neu positive breast cancer moved towards trastuzumab, pertuzumab, TDM1
- TNBC moved towards platinum, immunotherapy
- BUT in HR positive tumors, this debate is asking us to move backwards… AMAZING

Obviously, progress in science is not dependent on this debate (outcome)

- In HR +ve breast cancer, neo-adjuvant space has moved towards:
- Neo-adjuvant hormone treatment
- Neo-adjuvant immunotherapy
- Biomarker based neo-adjuvant treatment
- Genomic assay based neo-adjuvant treatment

Neo-adjuvant chemotherapy plus immunotherapy: Increase in CR

ASCO 2017: I-SPY 2 Trial: Combination of Pembrolizumab Plus Standard Neoadjuvant Therapy in High-Risk Breast Cancer

By The ASCO Post
Posted: 6/9/2017 11:11:18 AM
Last Updated: 6/9/2017 11:11:18 AM

Key Points

- In patients with triple-negative breast cancer, an absolute increase in the estimated pathologic complete response rate of 40% was observed in the pembrolizumab arm.
- In patients with HER2-negative breast cancer, an absolute increase in the estimated pathologic complete response rate of 30% was observed in the pembrolizumab arm.
- In patients with hormone receptor–positive/HER2-negative breast cancer, an absolute increase in the estimated pathologic complete response rate of 21% was observed in the pembrolizumab arm.

At the 2017 ASCO Annual Meeting, results were presented from the phase II I-SPY 2 trial investigating pembrolizumab (Keytruda) in combination with standard therapy (paclitaxel followed by doxorubicin and cyclophosphamide) as a neoadjuvant treatment for patients with locally advanced triple-negative breast cancer or hormone receptor–positive/HER2-negative breast cancer (Abstract 506).

Findings showed that the addition of pembrolizumab increased the estimated pathologic complete response rate nearly threefold in patients with triple-negative breast cancer (60% vs 20%) and in patients with hormone receptor–positive/HER2-negative breast cancer (34% vs 13%) compared to standard therapy. Overall, based on Bayesian predictive probability of success in a confirmatory phase III trial, pembrolizumab has graduated from the I-SPY 2 TRIAL for all signatures in which it was tested (triple-negative breast cancer, all HER2-negative, and hormone

Neo-adjuvant hormone therapy

- Hormone therapy alone
- Hormone therapy+CDK4/6 inhibitor

Hormone therapy alone

Published in final edited form as:

JAMA Oncol. 2016 November 01; 2(11): 1477–1486. doi:10.1001/jamaoncol.2016.1897.

Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer:

A Systematic Review and Meta-analysis

Laura M. Spring, MD,

Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

Arjun Gupta, MD,

Department of Medicine, University of Texas Southwestern Medical Center, Dallas

Kerry L. Reynolds, MD,

Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

Michele A. Gadd, MD,

Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

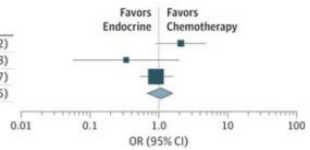
Leif W. Ellisen, MD, PhD

Results of meta-analysis

A Clinical response

Source	OR (95% CI)
Alba et al,[30] 2012	2.11 (0.92-4.82)
Palmieri et al,[31] 2014	0.34 (0.06-1.98)
Semiglazov et al,[32] 2007	0.93 (0.55-1.57)
Total	1.08 (0.50-2.35)

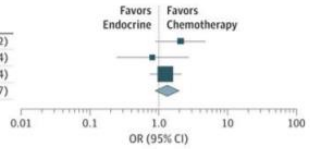
Heterogeneity: $\chi^2_3 = 4.47$ ($P = .11$), $I^2 = 55\%$
Test for overall effect: $z = 0.19$ ($P = .85$)



B Radiological response

Source	OR (95% CI)
Alba et al,[30] 2012	2.11 (0.92-4.82)
Palmieri et al,[31] 2014	0.83 (0.25-2.74)
Semiglazov et al,[32] 2007	1.28 (0.77-2.14)
Total	1.38 (0.92-2.07)

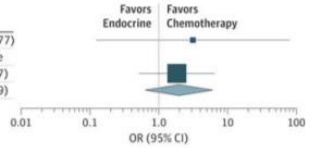
Heterogeneity: $\chi^2_3 = 1.77$ ($P = .41$), $I^2 = 0\%$
Test for overall effect: $z = 1.54$ ($P = .12$)



C Pathologic complete response

Source	OR (95% CI)
Alba et al,[30] 2012	3.13 (0.12-78.77)
Palmieri et al,[31] 2014	Not estimable
Semiglazov et al,[32] 2007	1.84 (0.53-6.47)
Total	1.99 (0.62-6.39)

Heterogeneity: $\chi^2_2 = 0.09$ ($P = .76$), $I^2 = 0\%$
Test for overall effect: $z = 1.16$ ($P = .25$)



D Breast conservation surgery

Source	OR (95% CI)
Alba et al,[30] 2012	0.68 (0.30-1.54)
Semiglazov et al,[32] 2007	0.63 (0.36-1.11)
Total	0.65 (0.41-1.03)

Heterogeneity: $\chi^2_1 = 0.03$ ($P = .87$), $I^2 = 0\%$
Test for overall effect: $z = 1.83$ ($P = .07$)

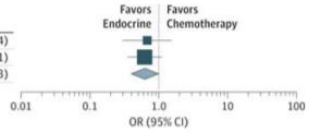


Figure 1. Neoadjuvant Hormone Therapy vs Neoadjuvant Cytotoxic Chemotherapy
Fixed-effects odds ratios (ORs) are calculated using the Mantel-Haenszel test with nonevent as the reference. Error bars represent 95% CI. Different marker sizes indicate the weight given to the specific study.

Randomized trial: neo-adjuvant chemo vs AI+CDK4/6

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 2334–2340, 2018
doi:10.1093/annonc/mdy448
Published online 11 October 2018

ORIGINAL ARTICLE

Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer

P. Cottu[1,2*], V. D'Hondt[3], S. Dureau[4], F. Lerebours[5], I. Desmoulins[6], P.-E. Heudel[7], F. P. Duhoux[8], C. Levy[9], M.-A. Mouret-Reynier[10], F. Dalenc[11], J.-S. Frenel[12], C. Jouannaud[13], L. Venat-Bouvet[14], S. Nguyen[15], J.-M. Ferrero[16], J.-L. Canon[17], J. Grenier[18], C. Callens[2,19], D. Gentien[2,20], J. Lemonnier[21], A. Vincent-Salomon[2,22†] & S. Delaloge[23†]

[1]Department of Medical Oncology, Institut Curie, Paris; [2]Paris Sciences et Lettres University, Paris; [3]Department of Medical Oncology, Institut Régional du Cancer de Montpellier, Montpellier; [4]Departments of Biometry; [5]Medical Oncology, Institut Curie, Saint-Cloud; [6]Department of Medical Oncology, Centre Georges-François Leclerc, Dijon; [7]Department of Medical Oncology, Centre Léon Bérard, Lyon, France; [8]Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [9]Department of Medical Oncology, Centre François Baclesse, Caen; [10]Department of Medical Oncology, Centre Jean Perrin, Clermont-Ferrand; [11]Department of Medical Oncology, Institut Claudius Regaud, IUCT-Oncopole Toulouse, Toulouse; [12]Department of Medical Oncology, ICO Institut de Cancérologie

Cell cycle arrest in almost 90% of patients

Table. Subgroup Analyses of Ki67-Evaluable Population: Percent Change in Ki67 from Baseline to Week 2

Population	Abemaciclib + ANZ	ANZ Alone		
	Mean % change	Mean % change	Mean ratio	*P* value
Disease stage I/II	−92.56	−65.84	0.22	<.001
Disease stage III	−95.28	−54.91	0.10	<.001
Baseline LN-neg	−93.18	−62.21	0.18	<.001
Baseline LN-pos	−92.75	−69.02	0.23	<.001
Tumor grade 1/2	−92.88	−69.61	0.23	<.001
Tumor grade 3	−92.79	−59.68	0.18	.011
Tumor size <2 cm	−93.25	−65.46	0.20	.004
Tumor size 2-5 cm	−91.22	−62.16	0.23	<.001
Tumor size ≥5 cm	−92.94	−59.73	0.14	<.001

References

1. Dickler MN, et al. *Clin Cancer Res*. 2017;23:5218-5224.
2. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884.
3. NeoMONARCH Study Group. *Cancer Discov*. 2017;7:119-120.

Important learning: early HR positive breast cancer, chemo and hormone give same results

by Figures (1) Extras (9) 1 / 7

Results: Overall, 106 patients were randomised [median Prosigna® ROR Score 71 (22–93)]. RCB 0–I was observed in four and eight patients in LETPAL [7.7% (95% CI 0.4–14.9)] and chemotherapy [15.7% (95% CI 5.7–25.7)] arms, respectively. Pathological complete response rates were 3.8% and 5.9%. Clinical response (75%) and breast-conserving surgery rates (69%) were similar in both arms. Preoperative Endocrine Prognostic Index 0 scores (breast cancer-specific survival) were observed in 17.6% and 8.0% of patients in LETPAL and chemotherapy arms, respectively. Safety profile was as expected, with 2 versus 17 serious adverse events (including 11 grade 4 serious AEs in the chemotherapy arm).

Conclusion: LETPAL combination was associated with poor pathological response but encouraging clinical and biomarker responses in Prosigna®-defined high-risk LBC. Contemporary chemotherapy regimen was associated with poor pathological and biomarker responses, with a much less favourable safety profile. LETPAL combination might represent an alternative to chemotherapy in early high-risk LBC.

Clinical Trial Number: NCT02400567.

Key words: luminal breast cancer, palbociclib, neoadjuvant, PAM50

Annals of Oncology

Original a

What more did we learn so far?

- Neo-adjuvant chemo plus immunotherapy increases pathCR rate in HR+ve BC
- Neo-adjuvant hormone therapy is an alternative in patients not eligible for chemotherapy
- Neo-adjuvant Hormone +CDK 4/6 inhibitor may turn out to be practice changing regimen in NACT

Last but never least… NCCN clinical practice guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

Known Benefits of Preoperative Systemic Therapy
- Facilitates breast conservation
- Can render inoperable tumors operable
- Provides important prognostic information at an individual patient level based on response to therapy, particularly in patients with triple-negative (TNBC) and HER2-positive breast cancer
- Allows the modification or addition of adjuvant regimens among patients with HER2-positive and TNBC with residual disease
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy

Opportunities
- May allow SLNB alone if a positive axilla is cleared with therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for smaller radiotherapy ports or less radiotherapy if axillary nodal disease cleared
- Excellent research platform to test novel therapies and predictive biomarkers

Cautions
- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for Preoperative Systemic Therapy
- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted N2 axillary nodes
  - N3 nodal disease
  - T4 tumors
- In patients with operable breast cancer, preoperative systemic therapy is preferred for those with:
  - HER2-positive disease and TNBC, if T ≥2 or N ≥1
  - Large primary tumor relative to breast size in a patient who desires breast conservation
  - With node-positive disease likely to become node-negative with preoperative systemic therapy
  - If time needed to decide surgical options

Non-candidates for Preoperative Systemic Therapy
- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable

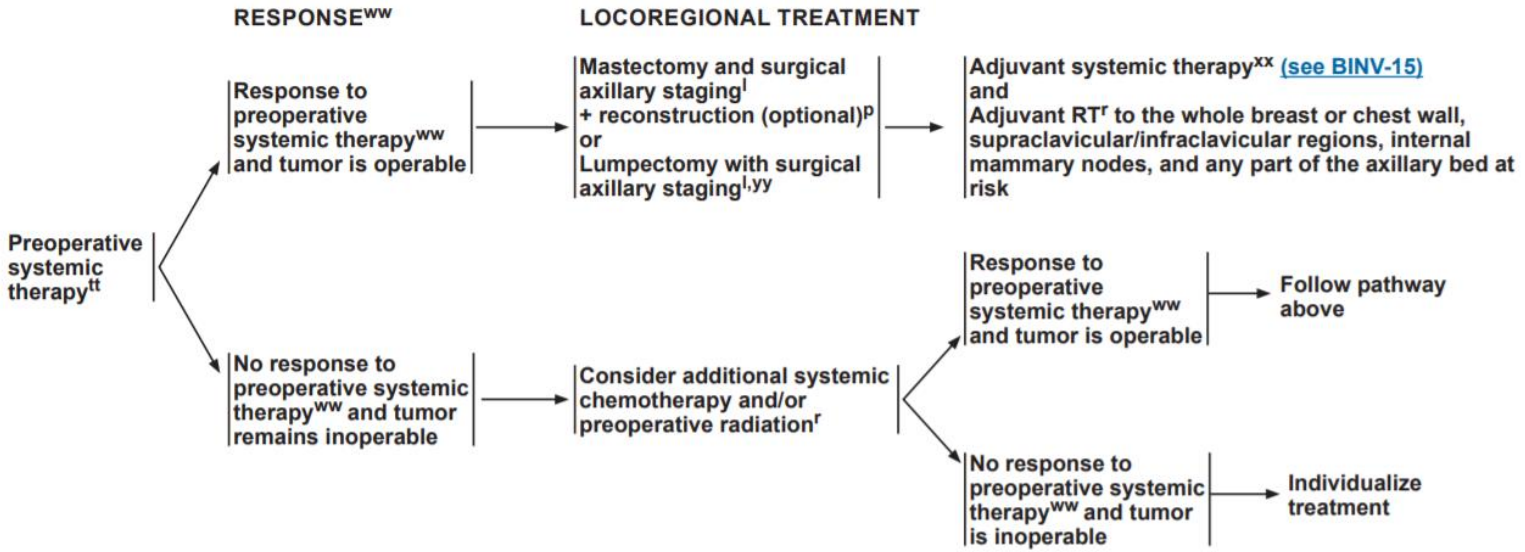
Latest guidelines for unresectable localized breast cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

INOPERABLE OR LOCALLY ADVANCED DISEASE (NON-INFLAMMATORY): PREOPERATIVE SYSTEMIC THERAPY AND SUBSEQUENT TREATMENT



[l] See Surgical Axillary Staging (BINV-D).
[p] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[r] See Principles of Radiation Therapy (BINV-I).

[xx] Complete planned chemotherapy regimen course if not completed preoperatively.

How do we conclude my points: Role of neoadjuvant treatment in Hormone Positive breast cancer

- NACT mandatory in localized unresectable breast cancer

- NACT mandatory for breast conservation in large tumors

Further conclusions:

- NACT plus immunotherapy increases pathCR, waiting for phase 3 data
- NET is an alternative to NACT in select group of patients not eligible for chemotherapy
- NET + CDK4/6 works in 90% of patients in arresting cell cycle

MOST IMPORTANT…

- Once surgery is done, relapse is the only way to know response to particular drug. In addition, whether surgery, chemotherapy, radiation or hormone: which one has failed, there is no way to know

- In NAT, we can pinpoint the action and move forward

- AND, we are certain that we are doing no additional harm by offering NAT

So…

- I conclude very strongly that

- ALMOST every patient of HR+ve Breast cancer (beyond cT1) should be offered Neo-adjuvant treatment either:

- 1) in the form of clinical trial
- 2) Neo-adjuvant chemotherapy
- 3) Neo-adjuvant hormone therapy

THANK YOU

Genomic based

Panel topic today…

- How do we treat breast cancer in elderly?
- Why do we need to discuss this topic?

Panelists… 4 Medical Oncologists, 2 Surgical Oncologist and 2 Radiation Oncologists

What are we worried about when we treat elderly patients with breast cancer?

- They should not die because of treatment
- They should not become permanently disabled because of treatment

In terms of breast cancer… what age group is defined as elderly?

- More than 65
- More than 70
- More than 75 (a cut off where we don’t want to treat!!!)

- Dr. Shakuntala Shah
- Dr. Jigna Bhattacharya
- Dr. Sameer Khatri

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology

Supriya G. Mohile, William Dale, Mark R. Somerfield, Mara A. Schonberg, Cynthia M. Boyd, Peggy S. Burhenn, Beverly Canin, Harvey Jay Cohen, Holly M. Holmes, Judith O. Hopkins, Michelle C. Janelsins, Alok A. Khorana, Heidi D. Klepin, Stuart M. Lichtman, Karen M. Mustian, William P. Tew, and Arti Hurria

J Clin Oncol 36.

Recommendations

In patients ≥ 65 years receiving chemotherapy, geriatric assessment (GA) should be used to identify vulnerabilities that are not routinely captured in oncology assessments. Evidence supports, at a minimum, assessment of function, comorbidity, falls, depression, cognition, and nutrition. The

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY
Strengthening the health care workforce for older people living with cancer

Contact MySIOG SEARCH

HOME ABOUT US OUR APPROACH MEMBERSHIP EVENTS PUBLICATIONS & RESOURCES

Home » Defining the elderly

Defining the elderly

Chapter 01 – Introduction

There is no universally accepted age cut-off defining "elderly." This reflects the fact that chronological age itself is less important than biological events in driving the ageing process within an individual. However, chronological age is a simple and practical way of defining a target population, and 70 years is currently the most commonly used cut-off for defining patients as elderly within the field of geriatric oncology.

Next Page »

JJCO Japanese Journal of Clinical Oncology

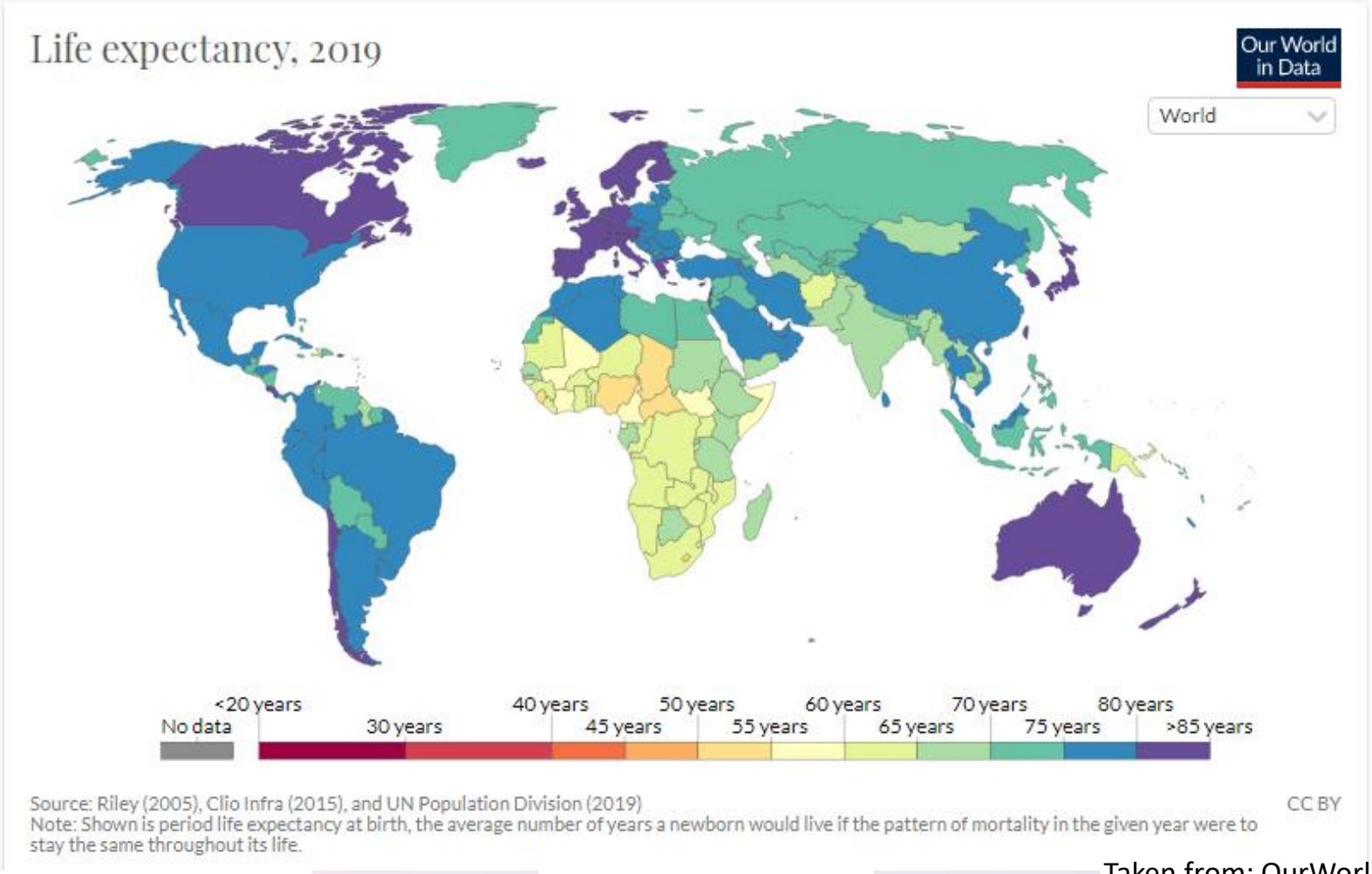
Japanese Journal of Clinical Oncology, 2019, 49(10) 901–909
doi: 10.1093/jjco/hyz093
Advance Access Publication Date: 30 September 2019
JCOG Policy

OXFORD

JCOG Policy

Geriatric Research Policy: Japan Clinical Oncology Group (JCOG) policy

The World Health Organization (WHO) defines the elderly as individuals aged 65 years or older (36). In Japan, the Act on Assurance of Medical Care for Elderly People (Act No. 80 of 1982) and related ordinances define individuals aged 65 to 74 years as young-old and those aged 75 years or older as old-old. Some guidelines define the elderly as ≥70 years and ≥75 years, but such guidelines are not widely accepted. One proposal is to define the elderly as a population for whom there is no reliable evidence to support therapeutic decision making, but this is not acceptable because such a criterion may vary considerably depending on the type of cancer, leading to differing age boundaries depending on the malignancy being addressed. In the current policy, therefore, an individual is defined as geriatric if they are aged 65 years or older, in line with the stipulations of the WHO and Japanese law. Similarly, those aged below 65 years are defined as nongeriatric.



Taken from: OurWorldinData.org

My Take…

- Whatever cut off we take, we should be able to:
- Create a separate OPD
- Create guidelines
- Should be able to do CGA in all of them
- A separate MDT should be made
- Practically, to begin with we can start with 70 years and above

SIOG task force: 2007 first and then updated in 2010:

NO CUT OFF OF AGE DEFINED

THE LANCET
Oncology

REVIEW | VOLUME 13, ISSUE 4, E148-E160, APRIL 01, 2012

Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA)

Dr Laura Biganzoli, MD • Hans Wildiers, MD • Catherine Oakman, MD • Lorenza Marotti, BSc • Sibylle Loibl, MD • Ian Kunkler, FRCR • et al. Show all authors

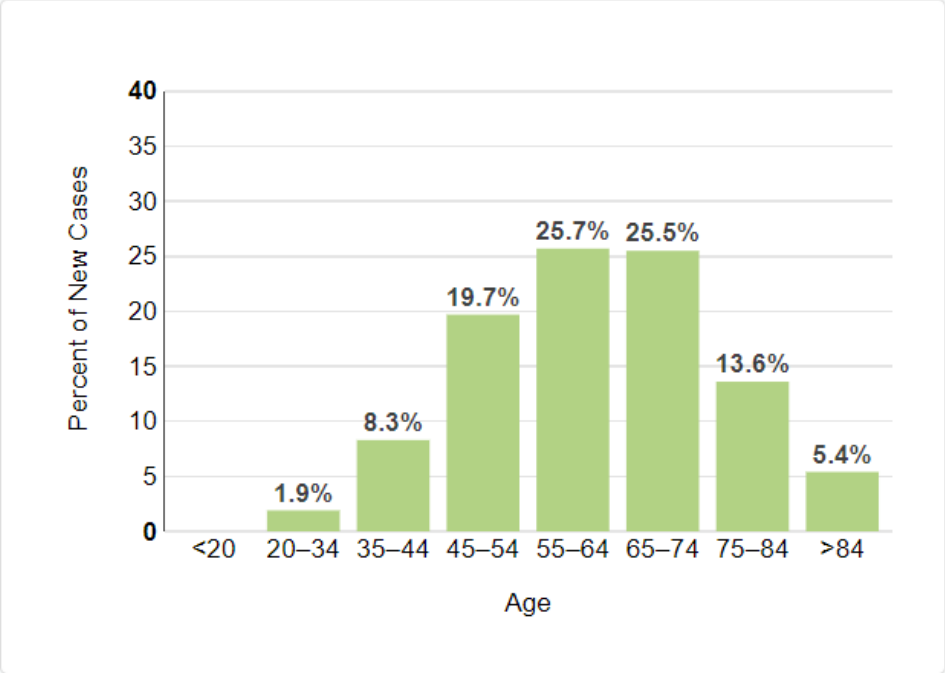
Published: April, 2012 • DOI: https://doi.org/10.1016/S1470-2045(11)70383-7

After definition of cut off, we come to next topic…

- What is the burden of elderly breast cancer patients?
- What % of breast cancer patients in your practice are more than 60, 65 and 70 years and above?
- Dr. Rushabh Kothari
- Dr. Priyanka Chiripal
- Dr. Hemendra Mod

Median age is 62 years means at least 40% of patients will be above 65 years of age, 25% will be above 70 years of age and 12 % will be above 80 years of age

Percent of New Cases by Age Group: Female Breast Cancer



Female breast cancer is most frequently diagnosed among women aged 55–64.

Median Age At Diagnosis
62

SEER 21 2013–2017, All Races, Females

What is the oldest patient of breast cancer you have treated with standard of care without compromising any treatment or dose?

- Dr. Sameer Khatri
- Dr. Shivani Bhatt
- Dr. Shakuntala Shah (at GCRI and in private)
- Dr. Mansi Khanderia (at MSKCC and at Bangalore)