BREAST CANCER IN THE ELDERLY

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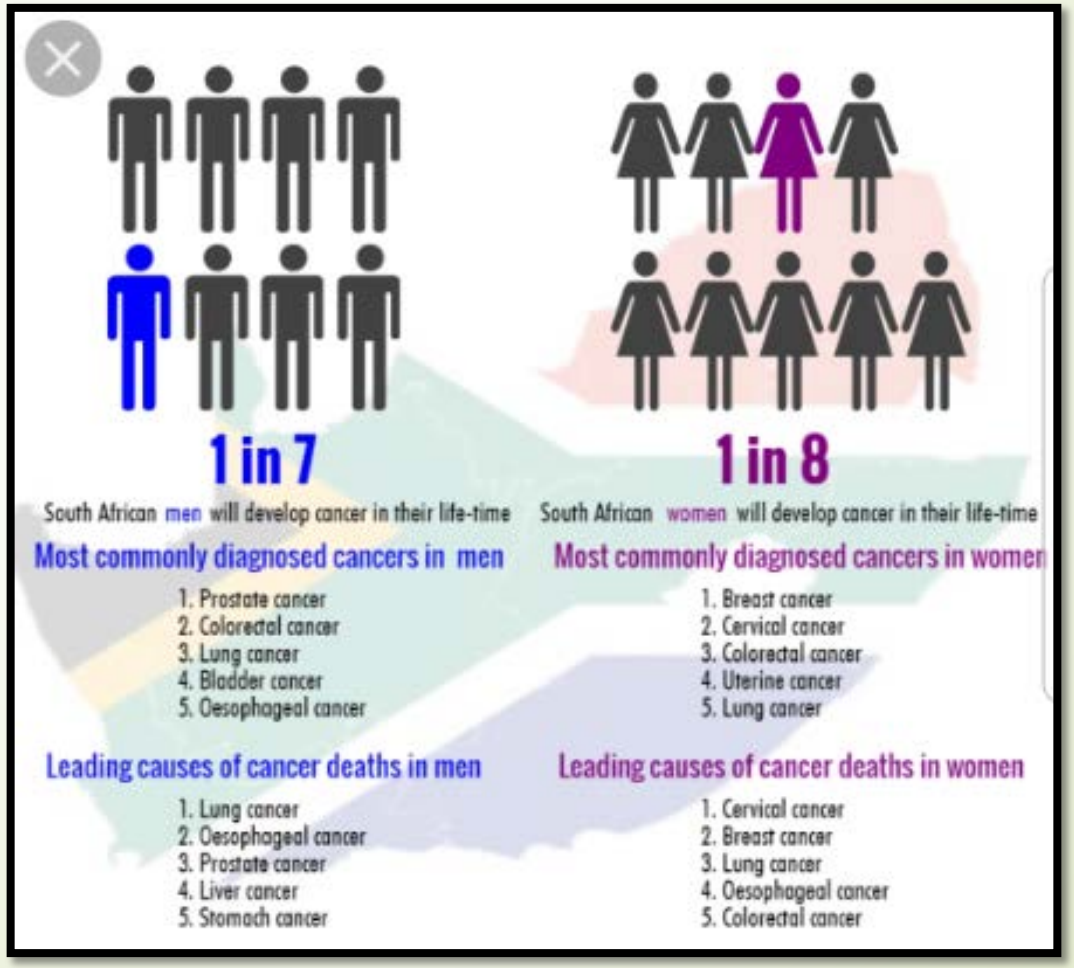
INTRODUCTION

- Breast cancer[BC], most common cancer in women world-wide, including South Africa[SA]



Cancerresearch.org.za

- 2nd to basal cell ca and cervical ca among White and Black SA women respectively according to National Cancer Registry[NCR] 2014 report.
- Average age at diagnosis 61yrs[63yrs Whites, 59 yrs young Black women in the US]
- Majority of deaths after age of 65yrs

Table 1. Estimated New Female Breast Cancer Cases and Deaths by Age, US, 2017

	In Situ Cases		Invasive Cases		Deaths	
Age	**Number**	**%**	**Number**	**%**	**Number**	**%**
<40	1,610	3%	11,160	4%	990	2%
40-49	12,440	20%	36,920	15%	3,480	9%
50-59	17,680	28%	58,620	23%	7,590	19%
60-69	17,550	28%	68,070	27%	9,420	23%
70-79	10,370	16%	47,860	19%	8,220	20%
80+	3,760	6%	30,080	12%	10,910	27%
All ages	**63,410**		**252,710**		**40,610**	

Estimates are rounded to the nearest 10. Percentages may not sum to 100 due to rounding.

DEFINITION OF THE "ELDERLY"

- ≥ 65yrs or ≥70yrs[no consensus]
- "elderly", "older" or "geriatric" patient: which one is more appropriate???[controversy]
- Is "elderly" ageist, does it promote prejudice and discrimination against this age- group?
- Does it promote less optimal treatment and care , and thus impacting negatively on survival

- Heterogeneity: co-morbidity
  life expectancy
  functional status
  cognitive function
  frailty
- Move towards: biological + physiological factors
  not chronological age
- ASCO, NCCN, International Society for geriatric Oncology [SIOG] recommend routine use of comprehensive geriatric assessment tools in the management of these patients.

FACTS TO CONSIDER

1. BC is a disease associated with aging[incidence increases with age]
2. Almost 50% of new cases are diagnosed annually in women 65 yrs in the USA
3. Improvement in health care- dramatic increases in life expectancy[developed countries]
   Population ≥65yrs increasing rapidly

4. Life expectancy: USA 2017

81.1yrs females, 76.1 males[78.6]

Life expectancy in Africa: 2018

64yrs females, 61yrs males

Life expectancy globally:2018

74yrs females, 70 males

5. BC in older women: more favorable biological characteristics[receptor positive, HER 2 negative compared to young patients.
6. Outcomes of BC in younger patients- substantial improvements [advances in treatment and screening], but not in the elderly
   Breast cancer-specific mortality[BCSM], decreased by 13%[2000-2004],17% for ages 25-64 yrs and 6% for >65yrs

7 BC patients >70yrs:exclusion from screening programs in most countries

~ late diagnoses and advanced disease

8 Elderly less likely to be treated according to guide-lines vs younger patients. Why?

9 Due to lack of evidence : under-representation in randomized controlled trials[RCT], testing efficacy and safety of drugs and drug safety vs tolerance[co-morbidity]

BIOLOGICAL CHANGES ASSOCIATED WITH AGEING

1. Changes in tumorigenesis and host defences

   Increased risk of ca attributed to:

   a. Slow accruing damage to DNA

      carcinogenic chemicals

      radiation exposure

      viruses

      reactive O2 species

   b. Progressive decline in host defenses against tumor growth

      carcinogenesis : time consuming process, hence incidence of many types of ca increasing with age.

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2. Specific age related pharmacokinetics

a. Volume of distribution shrinkage due to:

- Decrease in total body water
- Anaemia [chronic disease], affect drugs that bind to erythrocytes eg anthracyclines
- Hypoproteinemia: inadequate synthesis
  excessive loss of albumin
  and other carrier proteins

b. Decrese in glomerular filtration rate due to loss of nephrons/methotrexate, carboplatin

c. Decrease in hepatic excretion

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3. Changes in pharmacodynamics
   Changes resulting in increase in anti-tumor activity- express a multidrug resistance gene
   loss of apoptosis[drugs less effective]
   - Low blood circulation- tumor anoxia
   Tumoricidal effects of both chemo and RT are best in well oxygenated and rapidly proliferating cells.

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4 Changes in cancer activity

- Ageing: decline in tumor aggressiveness and thus decline in chemo effectiveness
- Tumor indolence due to natural selection thus tumor aggressiveness at younger age

5 Disease factors

Cancer diagnosed at more advanced stage due to:

Reluctance in seeking treatment or

Bias against aggressive treatment by physician

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6 Patient factors:

- Clinical work-up and CGA should document potential risk factors that could affect outcome
- Decline in physiological function: CVS, renal, hepatic, hematopoetic reserve

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SCREENING FOR BC IN THE ELDERLY

- Long-term beneficial effect
- 20% reduction in BC associated mortality
- A meta-analysis of mammogram screening trials showed a BC mortality benefit for all age-groups, yet screening programs from many countries exclude women > 70yrs

Table 1. Recommendations for Breast Cancer Screening in Average-Risk Women ⇦

	American College of Obstetricians and Gynecologists	U.S. Preventive Services Task Force	American Cancer Society	National Comprehensive Cancer Network
Clinical breast examination	May be offered* every 1–3 years for women aged 25–39 years and annually for women 40 years and older.	Insufficient evidence to recommend for or against.†	Does not recommend‡	Recommend every 1–3 years for women aged 25–39 years. Recommend annually for women 40 years and older.
Mammography initiation age	Offer starting at age 40 years.§ Initiate at ages 40–49 years after counseling, if patient desires. Recommend by no later than age 50 years if patient has not already initiated.	Recommend at age 50 years.‖ Age 40–49 years: The decision to start screening mammography in women before age 50 years should be an individual one.¶	Offer at ages 40–45 years.¶ Recommend at age 45 years.#	Recommend at age 40 years.
Mammography screening interval	Annual or biennial§	Biennial‖	Annual for women aged 40–54 years‡ Biennial with the option to continue annual screening for women 55 years or older‡	Annual
Mammography stop age	Continue until age 75 years. Beyond age 75 years, the decision to discontinue should be based on a shared decision-making process that includes a discussion of the woman's health status and longevity.	The current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women 75 years and older.†	When life expectancy is less than 10 years‡	When severe comorbidities limit life expectancy to 10 years or less

http/www.acog.org/women-health/breast-cancer-screening.

BC SCREENING IN SA

- Only for high risk patients[lack of resources and Infra structure in public health care]
- ≥40 yrs attending Primary Health Care Clinic undergoes Provider Initiated Screening Clinical Breast Examination[PI-SCBE] biannually+ risk assessment

  Referral for mammogram if: symptomatic

  increased risk[screening]

- Moderate to high risk:

  40-50yrs ,yearly mammogram

  > 50yrs, biannual mammogram ? Cut-off age
- < 40yrs with moderate to high risk: annual

  [PI-BCE] FROM 10yrs younger than the age of onset for the youngest family member

  Annual MRI where available

Guide-lines according to National Department Health June 2017

CLINICAL ASSESSMENT AND WORK-UP

- Triple assessment[same as in young patients]
- Comprehensive geriatric assessment
  in preparation for surgery, chemotherapy,
  hormonal therapy and or radiotherapy

Table TABLE 1. Basic Components of the Geriatric Assessment Recommended for All Breast Cancer Patients Over the Age of 70

Parameter	Key Elements of Assessment
Function	Independent performance of Activities of Daily Living (ADLs)
	Instrumental Activities of Daily Living (IADLs), including transportation, money management, medication management, meal preparation
	Performance status
Comorbidity	Number and severity of comorbid conditions
Socioeconomic	Social support, including caregivers
	Access to transportation
Geriatric syndromes	Screen for dementia/depression
	Vision, gait, balance, and hearing assessment
	Neglect and abuse
Polypharmacy	Number of medications and potential drug-drug interactions
Nutrition	Weight, nutritional assessment, weight loss

Table 1 Relevant domains and evaluation tools in the assessment of older women with breast cancer

Domain	Tool	References
Screening for frailty	G-8	(39-41)
	VES-13	
Comorbidity	CIRS-G	(23,24)
Physical activity and performance	Physical Activity Scale for the Elderly (PASE)	(42-45)
	Short Physical Performance Battery (SPPB)	
	Timed Up and Go Test (TUG)	
	Hang-grip strength	
Functional Status	ADLs (Katz index)	(46-48)
	IADL (Lawton scale)	
	Lawton-Brody IADL Scale	
	ECOG PS	
	Karnofsky health reported performance scale	
Cognition	Mini Mental State Examination	(21)
Depression	Geriatric Depression Scale	(22,49)
	Distress thermometer	
Nutritional status/body composition	Body-mass Index	(25,30,32)
	Mini Nutritional Assessment	
	DEXA scan (for muscle mass and bone mass)	
Pain	Numeric Rating Scale	
	Visual Analogue Scale	
Fatigue, Nausea, Dyspnea and other symptoms	Edmonton Symptom Assessment Scale	(50,51)
	modified Medical Research Council dyspnea scale (mMRC)	
	NYHA Class (for dyspnea)	
Falls	History of self-reported falls (one or more in last 90 days)	
Quality of Life	FACT-B	(52,53)
	EQ-5D	

THE ROLE OF SURGERY

- Gold standard of treatment for early BC in all age-groups[except limited life-expectancy or patients refusal]
- Concerns/issues in the elderly
  - Fitness for anesthesia and surgery
  - Role of BCT vs mastectomy
  - Role of SLNB and or axillary dissection
  - Recurrence and mortality rates

- Surgical mortality in older women with BC is negligible[0.5%-1%]

- Body image and cosmesis important in the elderly therefore- BCT+SLNB+ adjuvant radiation in EBC according to guidelines

EVIDENCE FOR OMISSION OF SLNB IN THE ELDERLY

- Low risk patients, ideal for omission of SLNB.
- Had G1 cT1mi-T1c[<2cm] or G2 CT1mi-T1b tumor

  Welsh et al

- “Choose wisely” guidelines 2016 by the Society for Surgical oncology[SSO] recommended: not to do routine SLNB in clinically node-negative women ≥70yrs, with EBC, HR positive/HER2 negative invasive BC.
- Does not result in increased loco-regional recurrence and does not impact on BC survival

- Tamarisa et al suggested a selective approach to axillary staging in patients ≥70yrs
- National Cancer Data Base [NCDB] review[2004-2014], of T1-3,N0 ca patients, post BCT with or without lymph node evaluation

THE ROLE OF RECONSTRUCTIVE SURGERY IN THE ELDERLY

- Very few studies
- Rate decreases with age, income and race

  53% <50yrs to 8.3% ≥65yrs

NCCN Task Force 2008: Consultation with a reconstructive surgeon for women of all age-groups

- Further investigations: ? Unique risks for elder women
- Less complicated alternatives like contralateral breast reduction+ implant instead of full breast reconstruction

PROPHYLACTIC MASTECTOMY

- Studies on contralateral prophylactic mastectomy [CPM] in the US, concentrated in younger patients
- Marmor et al, in a SEER PBS, reported increase in rate of CPM from 1% to 3% from 2004-2014 post surgery among 261 281 patients ≥65yrs
- NB: Role of patients choice and life-expectancy

THE ROLE OF RADIOTHERAPY[RT]

- Adjuvant RT recommended for women of all age-groups[according to guidelines]
- Role in reducing rates of loco-regional recurrence: NSABPB-04, B-06 39.2% for lumpectomy only vs 14.3% for lumpectomy + RT, after 25 and 20yrs follow-up respectively. No survival benefit.
- Early Breast Cancer Trialist Collaborative Group[EBCTCG], women post BCT, randomized to RT or no RT,10yr risk of loco-regional recurrence was reduced by 15% and risk of BC death by 3.8%

- SEER analysis of 11594 women >70yrs[1992-1997], - post mastectomy radiotherapy[PMRT] was associated with improved survival for high risk BC[T3/4 N2/3], 5yr survival was 50%
- Cao et al, 111 patients[2007-2013],>65yrs,1-3 positive LNs. There was significantly improved DDFS, RFS but marginal OS only in tumors >5cm therefore recommended that PMRT should not be compromised in all elderly patients with tumors >5cm.

RT AFTER BCT IN THE ELDERLY

- CALGB 9343 Trial[Dec 1996- Feb 1999], in co-operation with ECOG and RTOG, 636 women >70yrs,with stage 1,ER positive tumors , post BCT, randomized to RT+ tamoxifen vs Tamoxifen only.

  After 5yrs,only significant difference was in loco-regional recurrence. 1%[RT+ tam]vs 4%[tam onl]

- PRIME 2 Trial[Apr 2003- Dec 2009],women >65yrs ,tumors<3cm, G1/2, ER pos, LN neg, clear margins, adjuvant hormonal therapy, randomized to whole breast irradiation[WBI] or no RT. 5YR relapse rate of 1.3% vs 4.1% 10yr relapse rate of 2% vs 10%. Omission of RT to be considered for some.

ALTERNATIVES TO WBI SUITABLE FOR ELDERLY PATIENTS

A. Hypo-fractionation

- Period shortened from 5-7 weeks to 3 weeks
- 16 F/2.66 Gy for a total of 42.56 Gy, no boost
- Recommended by ASTRO

B. Accelerated partial breast irradiation[ABPI]

- Twice daily 6 hrs apart for 5 consecutive days
- Elderly most suitable, ASTRO >60yrs,T1NpN0
- Higher rate of side effects than WBI[RAPID] study

C. Intra operative radiotherapy[IOR]

- TARGIT Trial
- ELLIOT Trial >1300 patients,<75yrs, 2.5cm tumor 21Gy IORT
- Tumor recurrence rate 4.4% IORT vs 0.4% WBI

D. Gamma Pod Stereotactic Breast Radiotherapy and other ablative therapy

SUMMARY

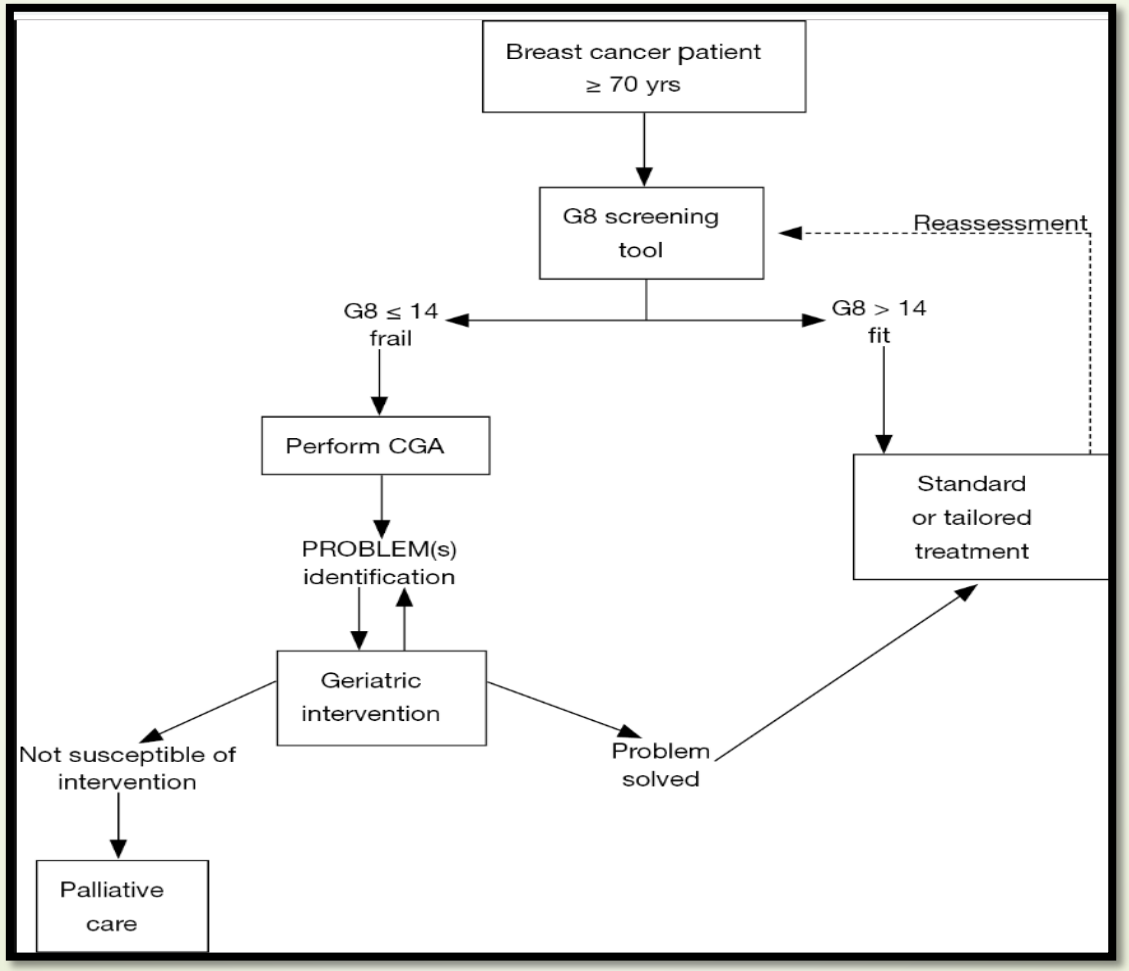
RT should be offered to elderly patients, according to tumor biology and stage, after considering/weighing risks[co-morbidities, toxicity, functional status, life expectancy] and benefits and also patients choice.

CHEMOTHERAPY IN THE ELDERLY

- The benefit of adjuvant chemotherapy on DFS and OS vs Surgery alone, was established in land-mark trials by the Milan group and the NSABP[eg NSABP B13]
- Adjuvant chemotherapy of choice should be anthracycline and or texane based poly-chemotherapy or combination regimen
- These have demonstrated survival benefit in a number of studies

- Little data exist about the benefit of chemotherapy in patients >70yrs due to under-representation in clinical trials
- A CALGB 49907 Trial, randomized 633 women >65yrs to CMF, TC[docetaxel and cyclophosphamide] and capecitabine
- Conclusion: adjuvant chemotherapy improves survival among elderly patients, though with greater toxicity

ASSESSMENT AND DECISION MAKING FOR CHEMOTHERAPY



http://tcr.amegroups.com/issue/view/296

SUMMARY

- No upper limit for utilization of chemotherapy
- No chemotherapy drug is contra-indicated for the elderly including cardio-toxic drugs like anthracyclines, texanes, and Herceptin, provided cardiac function is optimal
- Chemotherapy should not be withheld on the basis of chronological age only.
- Prevention and management of chemo-induced toxicity: ECHO/MUGA scan, FBC+ differential count, U&E+C, LFT
- Role of tools like: CGA, Adjuvant! Online [www.adjuvantonline.com], PREDICT, OS for herceptin [www.predict.nhs.uk/predict.html], Charlson comorbidity score

- Chemotherapy Risk Assessment Scale for High-Age patients[CRASH] score
- Cancer and Aging Research Group[CARG] score
- Both for toxicity
- Role of MDT, including a geriatric oncologist
- Compliance, treatment tolerability, survival, quality of life
- No treatment at all may be the best option for some

Role of genomic essays in management of BC ??? The future!!!

- Role of genomic essays like Oncotype Dx[21 gene essay and MammaPrint [70 gene signature test] in predicting recurrence rate, benefit of chemotherapy, survival in EBC.
- TAILORx trial[Oncotype Dx] concluded that in 70% of women with ER pos, HER2 neg, node neg EBC, chemotherapy may be avoided.
- MINDACT Trial[MammaPrint] concluded that 46% of high clinical risk, low genomic risk, might not require chemotherapy
- Problem: elderly women under represented in both trials

ROLE OF ENDOCRINE THERAPY

- Clear benefits ER positive EBC
- Most widely used form of adjuvant treatment for BC in the older women
- Majority of cases ER positive, also:
- Favorable toxicity profile[vs chemo] and effectiveness in improving DFS[adjuvant]

SIDE EFFECTS

- Endometrial ca and thromboembolic phenomena[tamoxifen]
- Musculo-skeletal pain, accelerated bone loss[osteoporosis, osteopenia, osteonecrosis, risk of fractures], aromatase inhibitors
- Bone density studies to be done
- Role of bisphosphonates

DCIS AND MALE BC

Not discussed

THANK YOU!

REALEBOGA!

RIALIVHUWA!

ADUPE!

NDIYABULELA!