Therapeutic choices and medical decision-making: Geriatric Oncology Perspective

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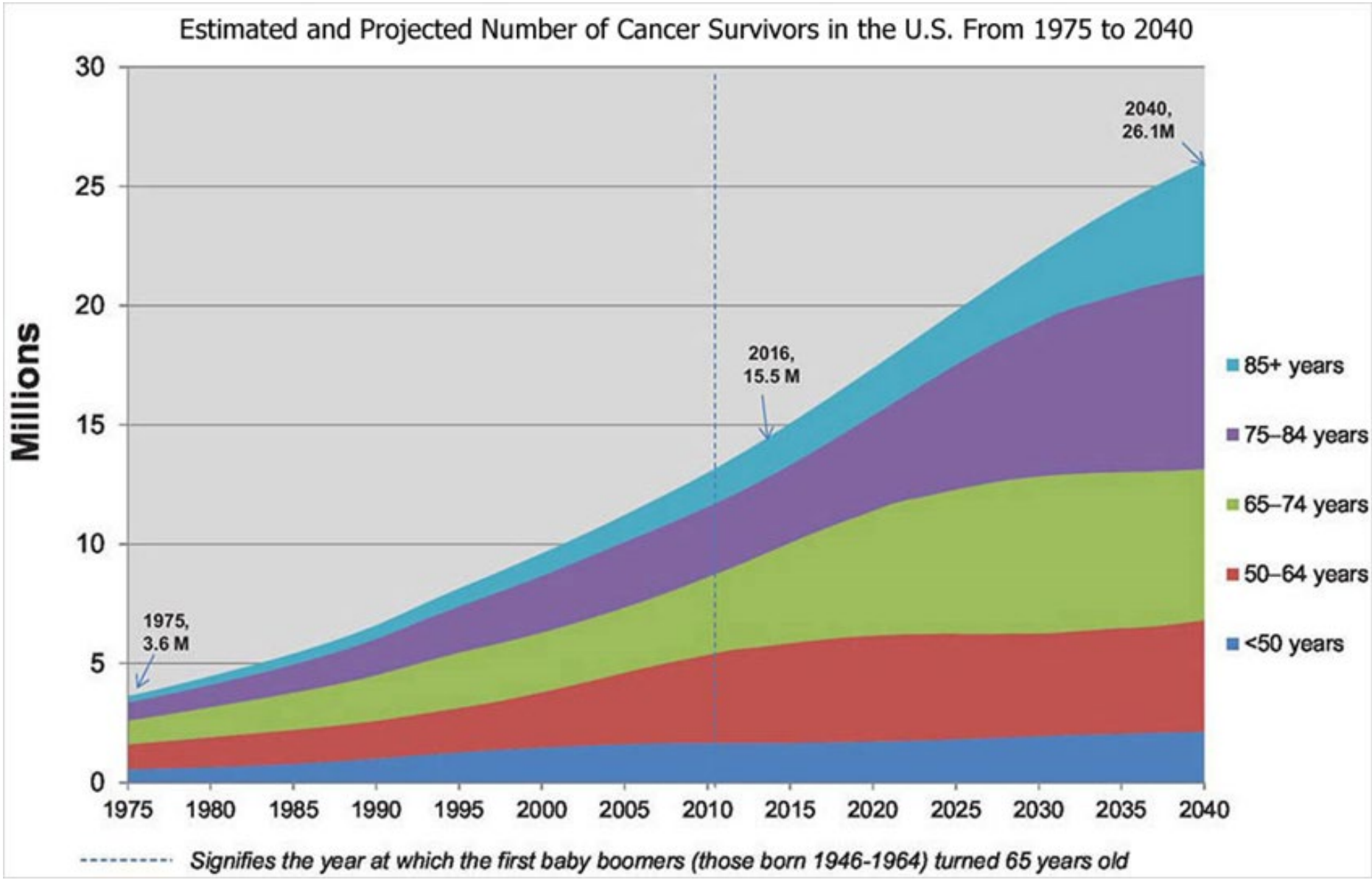
Session Objectives

- 1. Recognize the cardiac toxicities of cancer therapies specific to the geriatric population
- 2. Identify cancer treatment-specific considerations in the geriatric population
- 3. Recognize the need for a multidisciplinary approach to older cancer patients both during treatment and in surveillance


Estimated and Projected Number of Cancer Survivors in the U.S. From 1975 to 2040
Millions
30
25
20
15
10
5
0
1975
1980
1985
1990
1995
2000
2005
2010
2015
2020
2025
2030
2035
2040
1975, 3.6 M
2016, 15.5 M
2040, 26.1M
85+ years
75–84 years
65–74 years
50–64 years
<50 years
Signifies the year at which the first baby boomers (those born 1946-1964) turned 65 years old

Assessing the geriatric oncology patient

- Oncologists face uncertainty when making management decision for older adults
- Gap in literature:
  - Clinical trials primarily enroll healthy individuals with few comorbidities
  - Frail older adults are typically treated in community oncology practices

Framework around the care of older patients with cancer

- ASCO, NCCN, ISGO, American Geriatrics Society
- Framework:
  - 1. Determining age related vulnerabilities
  - 2. Consider the benefits and harms of cancer treatments in light of this vulnerability
  - 3. Consider patient values, preferences and trade-offs
    - (prolonging survival while minimizing treatment burden and toxicity)

Chronological age *vs.* functional age

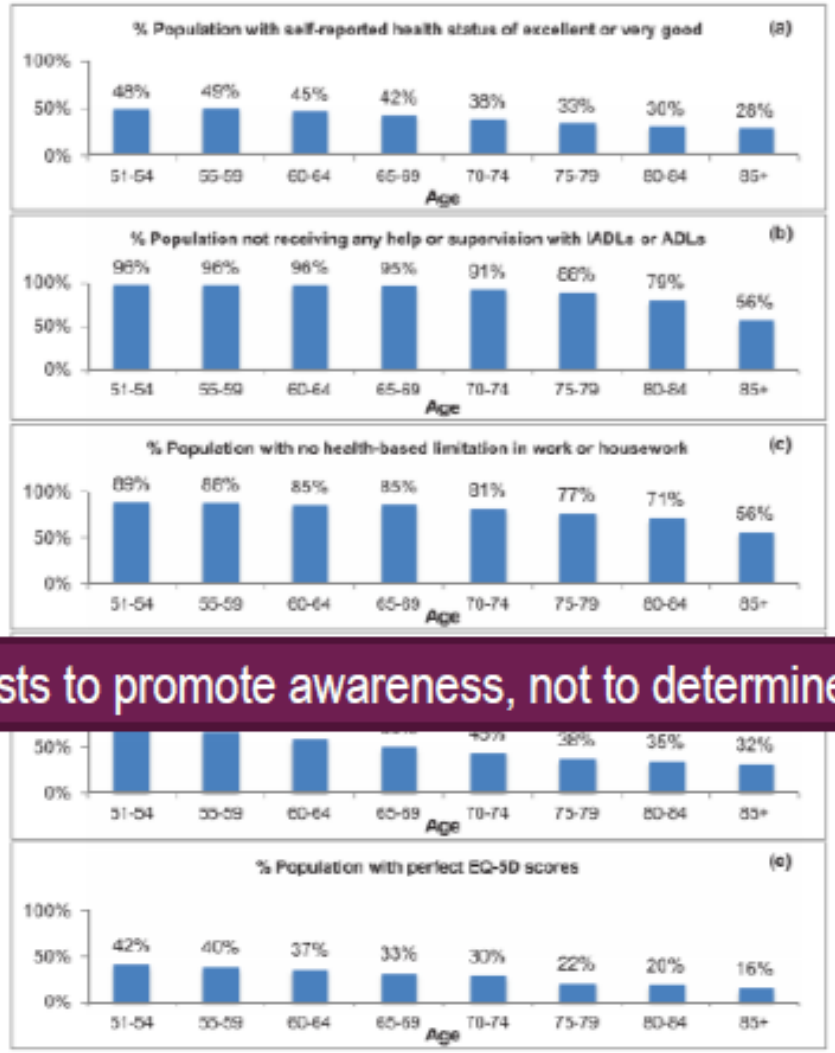
What does being elderly mean?

- Elderly is a subjective cultural concept that varies from culture to culture, depending on a mixture of health-related, social and economic factors
- In industrialised societies, 70 years old is a standard cut-off point used to define elderly; however, in other, poorer or more traditional societies, a lower age may be more appropriate (such as 65, 60 or even 55)
- Chronological age and functional age can differ greatly from person to person

In geriatric oncology, it is functional age that determines management – and therefore a great deal of effort is dedicated to accurately evaluating and maintaining functionality during treatment

Aging is a heterogeneous process

Not all "young persons" are healthy and functional



Not all "elderly persons" are sick and dependent

Age cut-off exists to promote awareness, not to determine management!

Lowsky J, *et al.*, Gerontol A Biol Sci Med Sci (2014) 69 (6):640-649, by permission of Oxford University Press

The aging process – Impact on organs and systems

Heart: Decreased heart rate, decreased responsiveness to adrenergic stimuli, increased afterload

Brain: Neuronal loss, changes in synaptic function, hyperactivation of microglial cells

Immune system: Reduced immune response to aggressors

Lungs: Decreasing lung volumes and maximal rates of airflow; decreasing forced vital capacity; decreased diffusing capacity

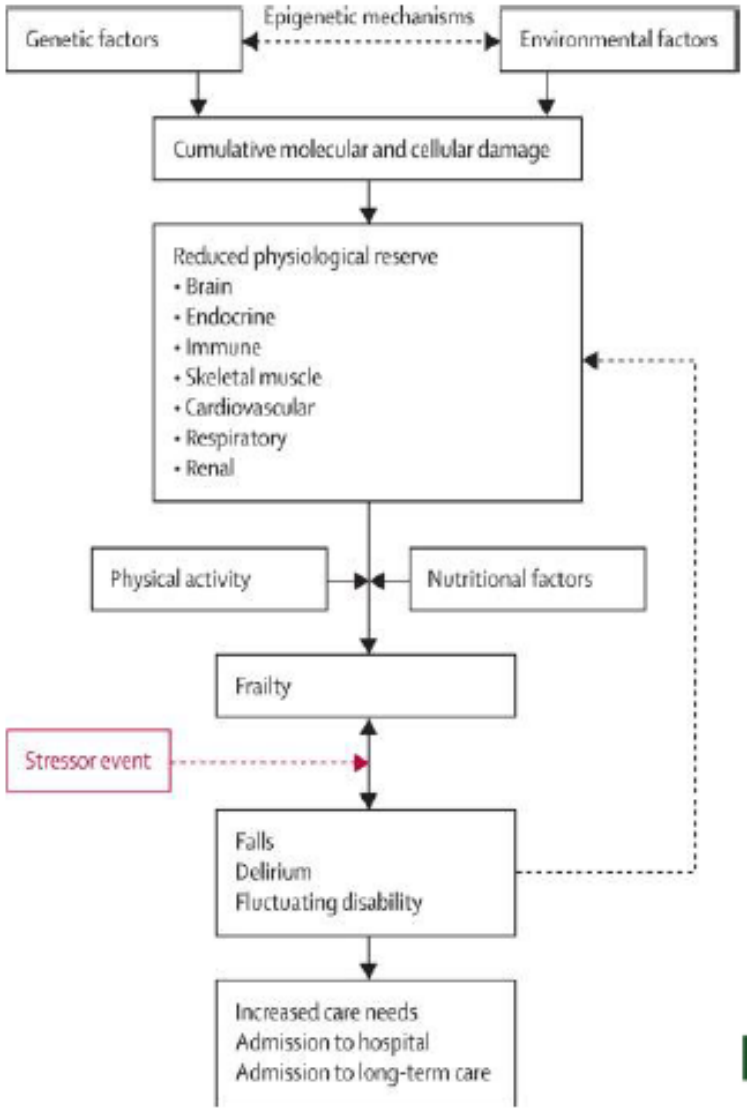
Kidney: Increasing renal cortical loss; progressive decrease in glomerular filtration rate and renal blood flow

The end result = Increased risk of acute illness and of complications during cancer treatment

The aging process – Frailty

Frailty is a state of increased vulnerability to stress, which increases the risk of adverse outcomes during cancer treatment

It is very important to note that risk factors for frailty include psychological and social issues, such as being in a minority ethnic group, being unmarried or being depressed



Comprehensive Geriatric Assessment – Principles

Comprehensive Geriatric Assessment (CGA) should be the standard form of evaluation and follow-up for elderly patients before and during cancer treatment

CGA can be defined as "multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up"

It identifies problems that are not identified by routine patient history and physical examination

Comprehensive Geriatric Assessment

Domains	Scales
Functional status	Eastern Cooperative Oncology Group performance status, Katz basic Activities of Daily Living Scale, Simplified Lawton's Instrumental Activities of Daily Living Scale
Comorbidities	Charlson comorbidity index
Medications	Number, type, indication
Cognitive function	Folstein Mini-Mental State Examination, Schultz-Larsen Mini-Mental State Examination
Geriatric syndrome	Repeated falls, fecal and/or urinary incontinence
Depression/mood	Geriatric Depression Scale 5, Emotional questionnaire
Nutrition	Body mass index
Mobility	Timed Up and Go test
Situational assessment	Accessibility of services, mobility, social environment, accessibility of home rooms

Comparison of 4 tools for evaluation of frailty

All tools predict 1-year mortality

Classification	No. (%) of Patients	No. (%) of Events	*P**	HR (95% CI)†
Balducci			< .001, < .001	
Fit	97 (12.9)	11 (11.3)		1.00 (reference)
Vulnerable	113 (14.9)	31 (27.4)		1.91 (0.95 to 3.85)
Frail	544 (72.2)	278 (51.1)		2.94 (1.59 to 5.43)
SIOG1			< .001, < .001	
Fit	147 (19.5)	19 (12.9)		1.00 (reference)
Vulnerable	234 (31.1)	66 (28.2)		1.75 (1.03 to 2.97)
Frail	286 (37.9)	167 (58.4)		3.31 (2.00 to 5.50)
Too sick	87 (11.5)	68 (78.2)		6.12 (3.45 to 10.85)
SIOG2			< .001, < .001	
Fit	134 (17.8)	11 (8.2)		1.00 (reference)
Vulnerable	112 (14.8)	28 (25.0)		2.08 (1.02 to 4.22)
Frail	508 (67.4)	281 (55.3)		3.69 (1.97 to 6.89)
LC typology			< .001, < .001	
Relatively healthy	227 (30.1)	27 (11.9)		1.00 (reference)
Malnourished	252 (33.4)	110 (43.6)		2.15 (1.34 to 3.47)
Cognitively and/or mood impaired	103 (13.7)	44 (42.7)		2.66 (1.54 to 4.61)
Globally impaired	172 (22.8)	139 (80.8)		4.84 (2.82 to 8.31)

Ferrat E, *et al.*, Performance of Four Frailty Classifications in Older Patients With Cancer: Prospective Elderly Cancer Patients Cohort StudyJ Clin Oncol. 2017;35(7):766–777. Reprinted with permission. © 2017 American Society of Clinical Oncology

Consideration for the Geriatric Oncology patient

Box 2: Summary of a Minimum Data Set for Practical Assessment of Vulnerabilities in Older Patients With Cancer

See Table 1 for more details and rationale.

1. Predict chemotherapy toxicity (if clinically applicable): Cancer and Aging Research Group or Chemotherapy Risk Assessment Scale for High-Age Patients tools
2. Estimate (noncancer) life expectancy (if clinically applicable): ePrognosis
3. Functional assessment: instrumental activities of daily living
4. Comorbidity assessment: medical record review or validated tool
5. Screening for falls, one question: how many falls or falls with an injury have you had in the previous 6 months (or since your last visit)?
6. Screening for depression: Geriatric Depression Scale or other validated tool
7. Screening for cognitive impairment: Mini-Cog or Blessed Orientation-Memory-Concentration test
8. Screening for malnutrition: weight loss/body mass index

Mohile et al, ASCO Guideline for Geriatric Oncology 2018

Consider benefits of cancer treatment

- 1. Evaluate whether the patient's cancer will cause symptoms in their remaining lifetime
  - Aggressiveness of the cancer vs noncancer life expectancy
- 2. If cancer is likely to affect a patient during their remaining lifetime, what evidence is there regarding beneficial treatments?

Consider harms of cancer treatment in older adults

- Variation in harms of cancer therapies
  - i.e. local surgery, large abdominal surgery, intensity of chemotherapy, stereotactic radiation
- Other considerations:
  - Time in infusion center away from home and family
  - Financial implications

- From this information, oncologists decide 1. adjust treatment decisions? 2. prescribe appropriate interventions for GA deficits

Toxicities of chemotherapy

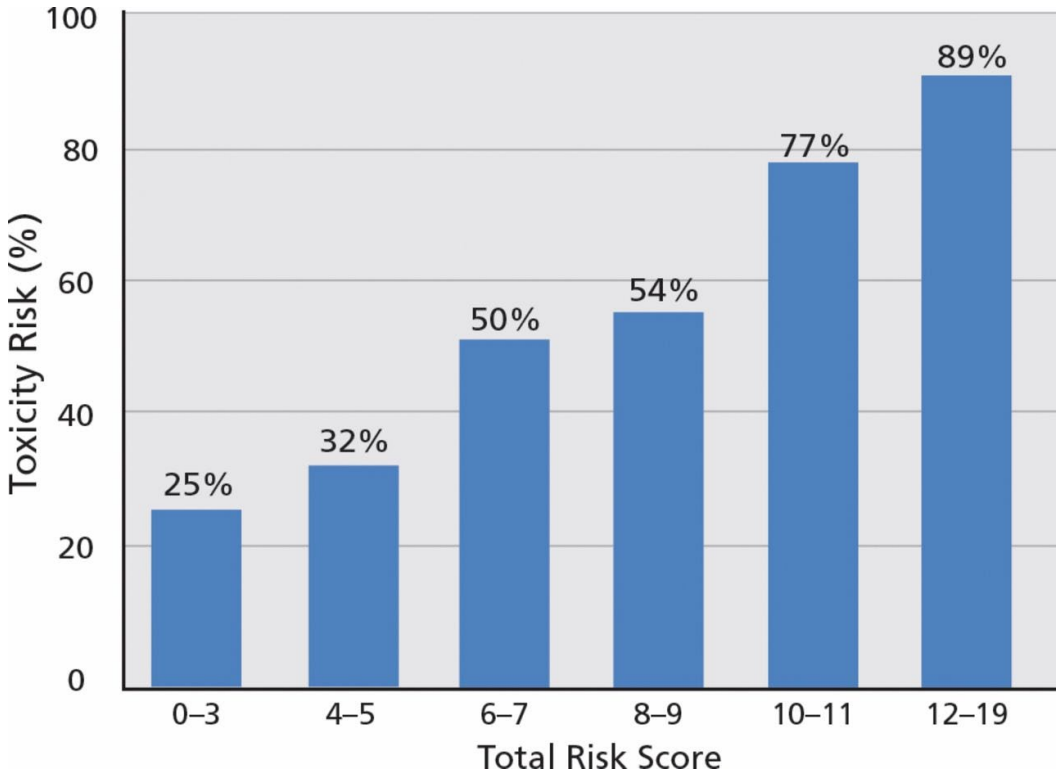
The Cancer and Aging Research Group (CARG) Chemotoxicity Risk Score

Risk Factors for Grade 3-5 Toxicity	Score
GI/genitourinary cancer	3
Standard dose chemotherapy	3
Low hemoglobin level:	
<11 g/dL for men and <10 g/dL for women	3
Low creatinine clearance (based on Jelliffe equation): <34 mL/min per 1.73 m^2	3
1 or more falls in last 6 months	3
Age >/=73 years	2
Polychemotherapy	2
Fair or worse hearing	2
Limited ability to walk one block	2
Assistance needed with medications	1
Decrease in social activity	1

Notes: Possible score range: 0-25. Risk: 0-5 = low risk, 6-11 = intermediate risk, 12+ = high risk.

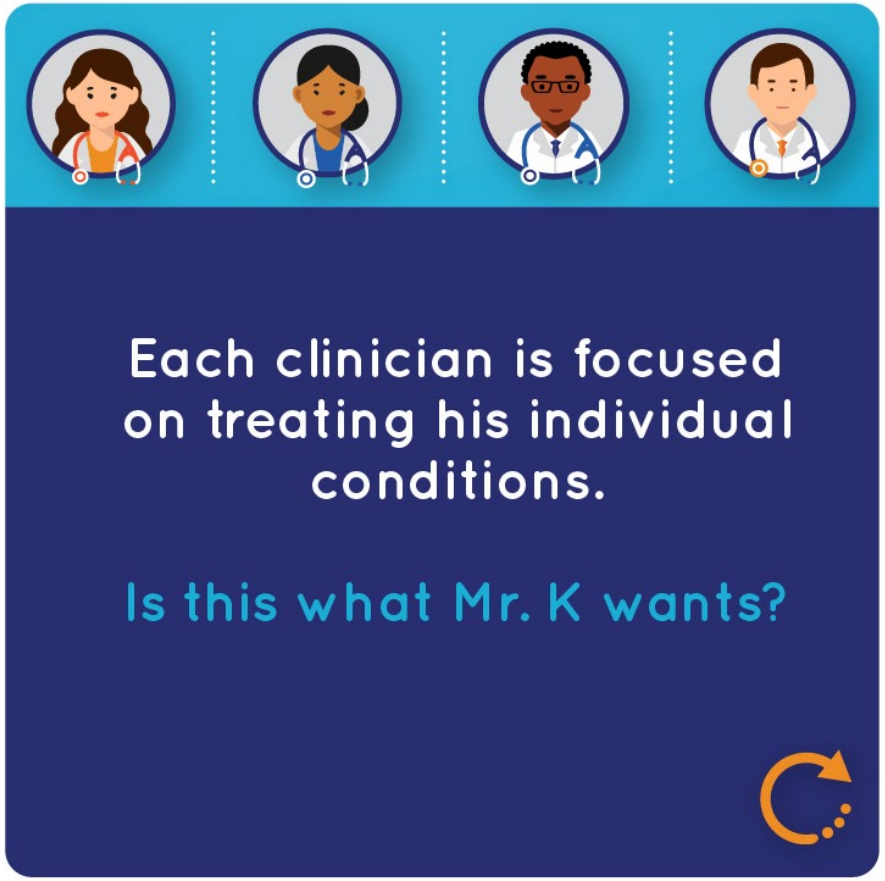
Source: Hurria, A. et al. Predicting Chemotherapy Toxicity in Older Adults with Cancer: A Prospective 500 Patient Multicenter Study. American Society of Clinical Oncology 2010. Abstract 9001.

Elsevier Global Medical News



Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 2002;20:494-502

Considering values, preferences and trade-offs

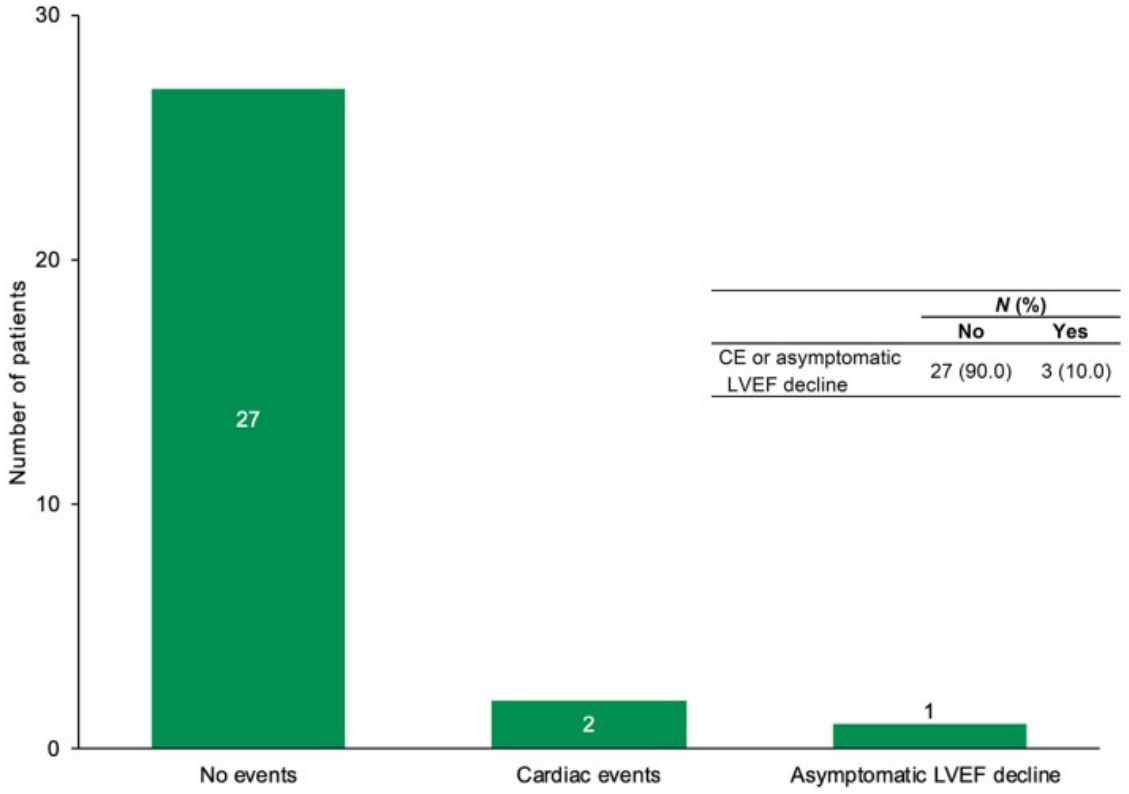


Minimizing undertreatment vs overtreatment

- What are your treatment options from an oncology perspective?

SAFE HEaRt trial

- Stage 1-4 her2 positive breast cancer
- Her2 based therapy
- LVEF 40-49%, no symptoms of HF
- All patients underwent:
  - Cardiology visit
  - Serial echo
  - Received BB, ACEI
- Primary endpoint: completion of her2 directed therapy without cardiac event (HF, MI, arrhythmia, or cardiac death or symptomatic worsening LVEF)



Lynce F, Barac A. Breast Cancer Res Treat 2019

Other considerations

- Caregivers and culture
  - Real life decision making is embedded in social context
  - Shared decision making studies rarely have included underrepresented minorities
  - Decision making: predominant leader, single individual, single group

- Psychology, cognitive biases and informed consent

TABLE 2. Selected Biases to Avoid in Decision Making Involving Older Adults With Cancer

Bias Name	Definition	Example
Affect heuristic[96]	A decision overly influenced by emotion and not logic can occur in scenarios with time-sensitive decisions	An older patient anxious over new diagnosis of AML immediately opts for intensive treatment, fearing the effects of the cancer without carefully evaluating treatment benefits and harms
Ageism[84]	Attitudes or stereotypes on the basis of a person's age	Not recommending a beneficial treatment for an older patient on the basis of age alone (a form of undertreatment)
Anchoring[97]	Adhering to an initial choice despite new evidence supporting an alternative	Continuing to recommend intensive chemotherapy in a frail older adult despite minimal response and evidence of toxicity
Availability[97]	Estimating the probability of an event on the basis of a readily available case that may not be representative	Recommending radical prostatectomy in all older adults with prostate cancer because of one case of early metastasis in a patient who chose active surveillance
Framing[98]	Decision is influenced by the way facts are presented, not by the facts themselves	Selectively emphasizing the harms of a treatment and minimizing its benefits

Abbreviation: AML, acute myeloid leukemia.

DuMontier et al, JCO 2021

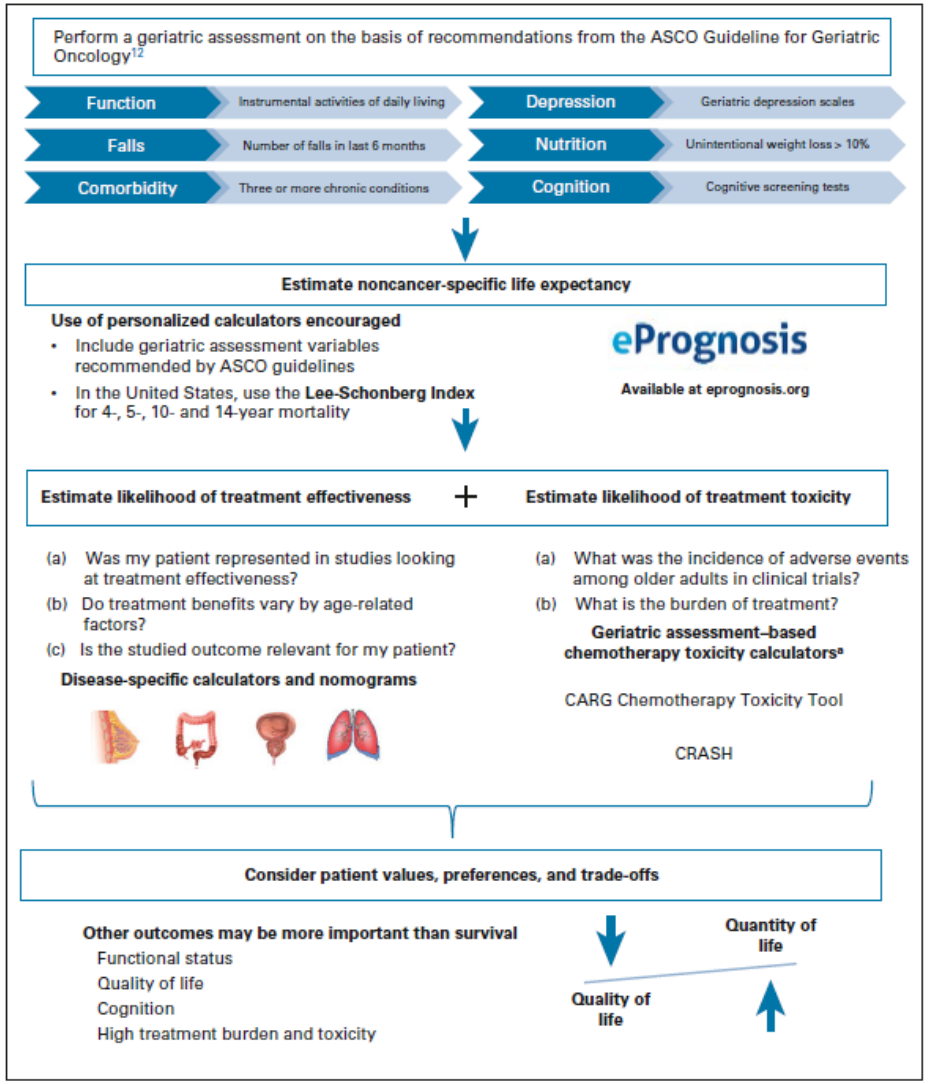


FIG 1. Framework for decision making in older adults with cancer. [a]Current toxicity calculators exist for chemotherapy only. For surgical risks, consider the ACS NSQIP Surgical Risk Calculator, which was recently updated to include outcomes for older adults.[41] ACS, American College of Surgeons; CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; NSQIP, National Surgical Quality Improvement Program.

Case examples

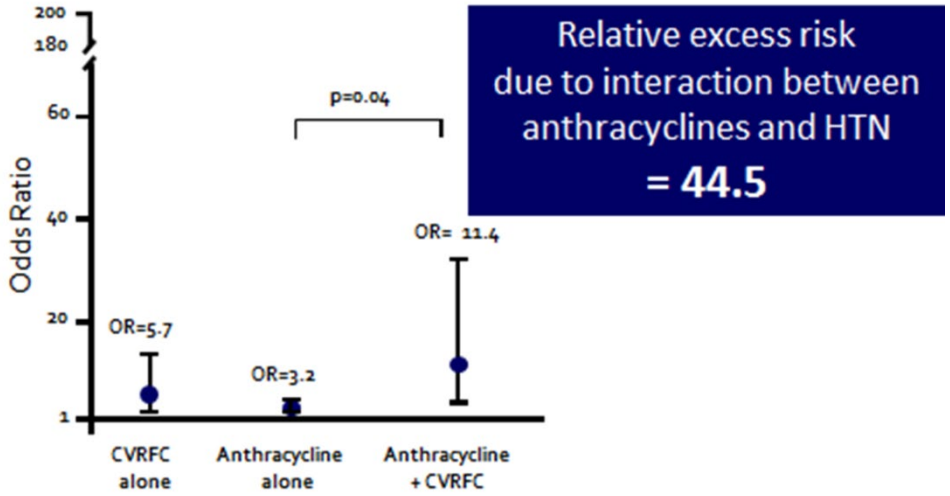
- 72 y/o female with T4N1 colon cancer treated with hemicolectomy
- Age related vulnerabilities:
  - BMI 24, independent ADLs and IADLs, cognitively intact, walks independently with an aid, comorbidities (htn, dm, former smoker)
- Estimated noncancer survival: 70-74% at 5 years, 40-47% 10 years
- Adjuvant chemotherapy options:
  - CAPOX 3 months 5yr DFS 65.4%, FOLFOX 6 months 63.4%, 5FU alone, Capecitabine alone 57.8%, no treatment: 45.8%
- CARG toxicities: neuropathy grade 3-5 44-59%
- Pt is concerned about intensity of treatment impacting QOL but has a fear of recurrence and is willing to accept some toxicity for a goal of complete remission

Second example

Controlling risk factors

Odds of congestive heart failure with cardiovascular risk factor cluster, anthracycline exposure, or both

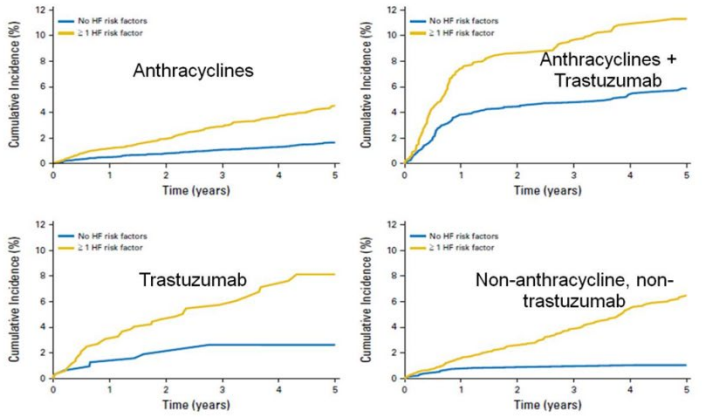
Childhood Cancer Survivor Study



Relative excess risk due to interaction between anthracyclines and HTN = 44.5

Armstrong GT, et al. J Clin Oncol, 2013

Anthracyclines, Trastuzumab



Thavendiranathan et al , JCO May 2018

- Age >60
- Diabetes
- Hypertension
- Atrial Fibrillation
- Coronary Artery Disease

Summary and Future Directions

- Oncologists face uncertainty when making management decision for older adults
- Incorporating geriatric assessments into clinical practice can improve overall care of the older oncology patient
- There is a need to build the underlying evidence base around the care of the older oncology patient
  - Clinical trials primarily enroll healthy individuals with few comorbidities
  - Frail older adults are typically treated in community oncology practices
  - More diverse individuals are needed in cancer clinical trials

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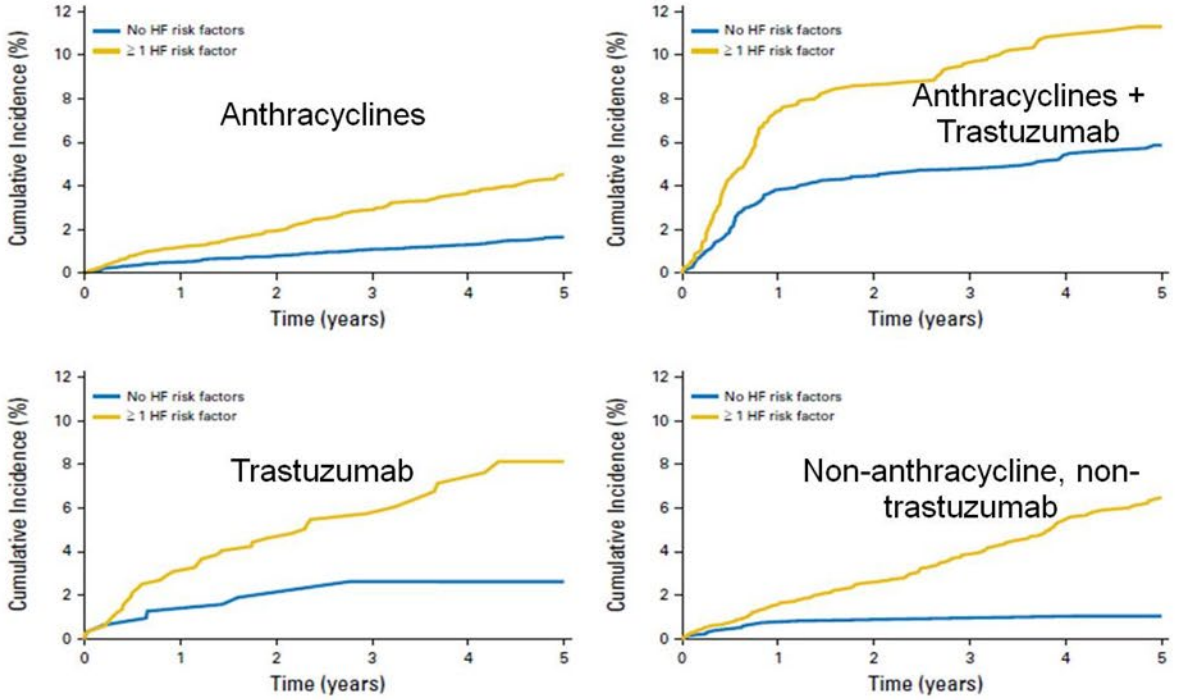
Risk factors for cardiotoxicity

Anthracyclines, Trastuzumab



Thavendiranathan et al , JCO May 2018

Age >60

Diabetes

Hypertension

Atrial Fibrillation

Coronary Artery Disease

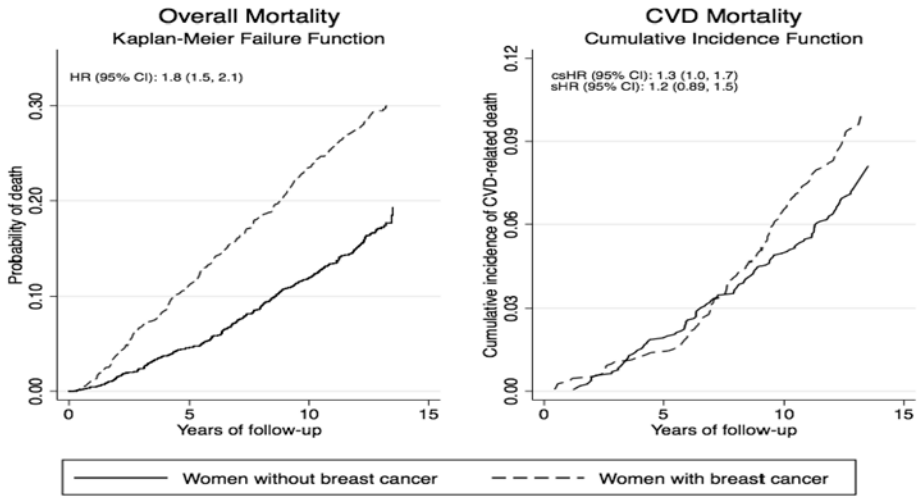
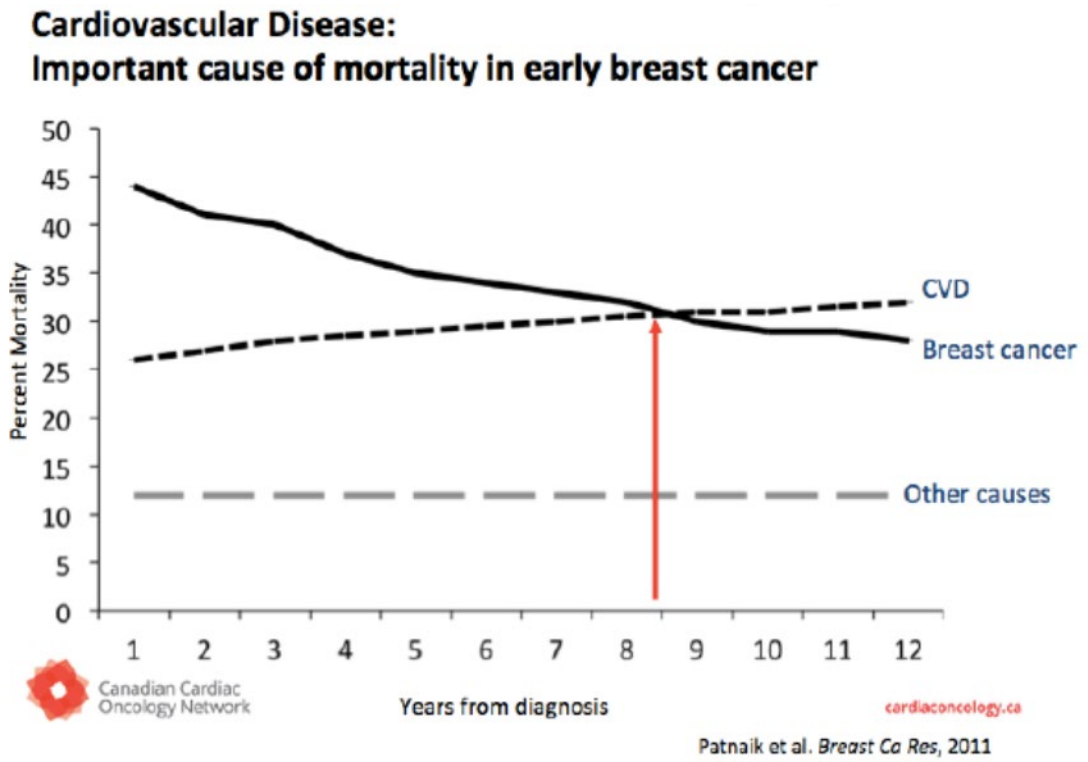
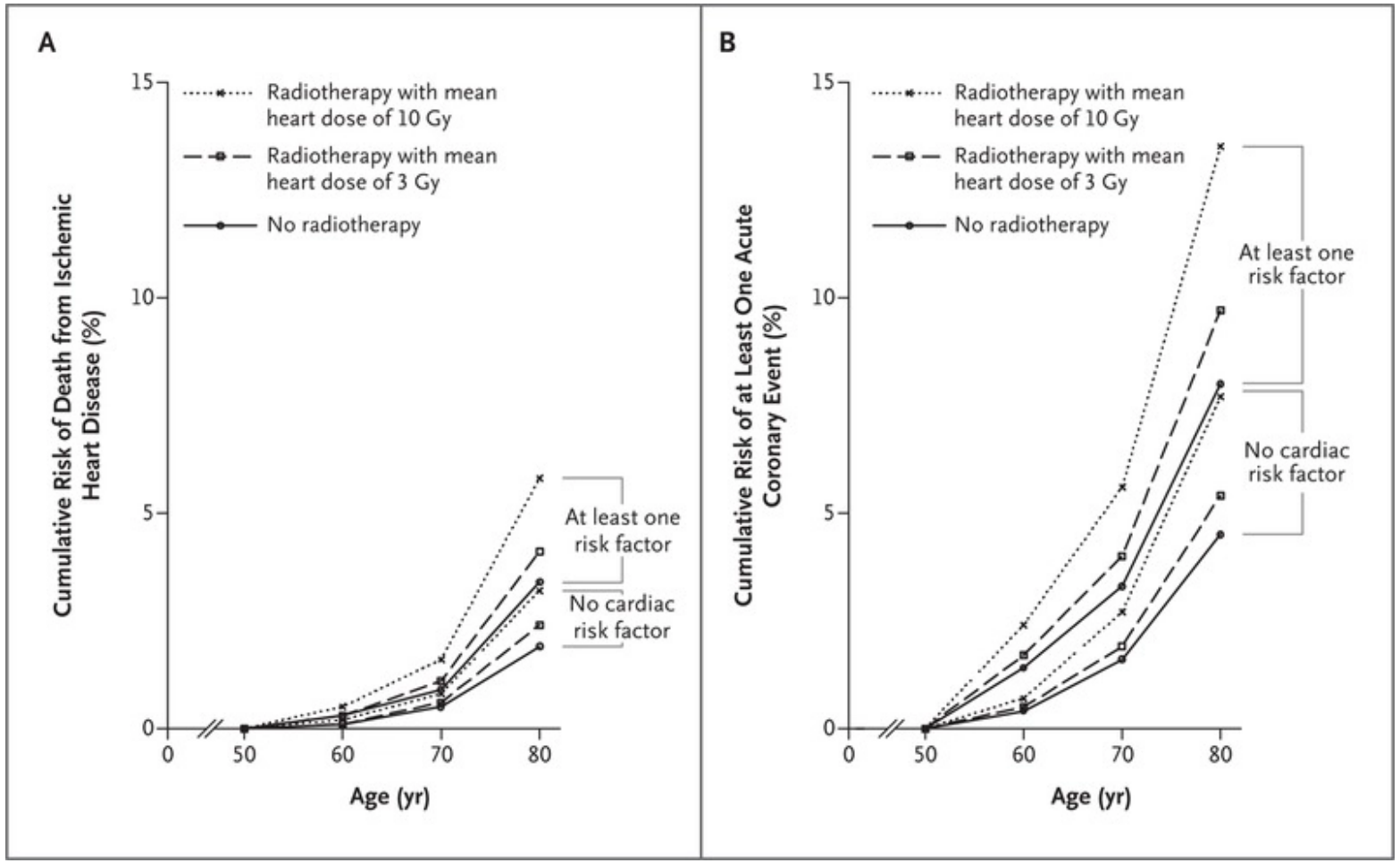


Figure 1.
Unadjusted Kaplan-Meier failure curves and adjusted hazard ratios (HR) for overall mortality (first panel) and cumulative incidence function, cause-specific HR (csHR) and subdistribution HR (sHR) for CVD-related mortality (second panel) among a population-based sample of breast cancer survivors and age-matched women without breast cancer. The Long Island Breast Cancer Study, 1996-2009.



Bradshaw et al, Epidemiology 2016



Darby et al, NEJM 2013

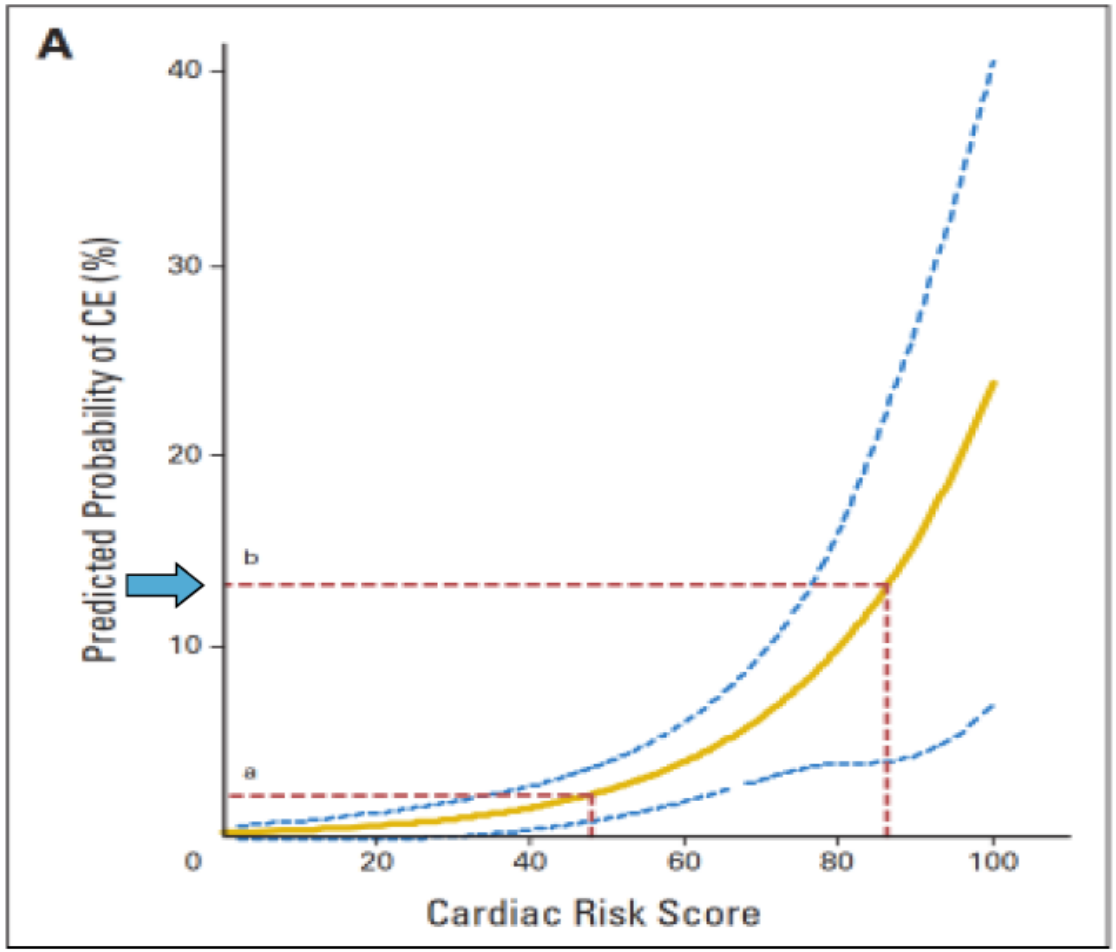
Risk Predication Models for Cardiotoxicity in Breast Cancer

- NSABP – B31 - Phase 3 adjuvant trial of 1830 breast cancer patients, node positive
- Adriamycin and Cytoxan followed by paclitaxel plus/minus trastuzumab
- At 7 year follow-up:
  - Paclitaxel: 1.3% CE
  - Paclitaxel plus trastuzumab: 4%
- Modeled the cardiac event rate up to five years after AC
- In the model, age and baseline LVEF were predictors

Romond EH et al, JCO 2012

#1 – NSABP B-31: Predicted Probability of Cardiac Event (CE) at Year 5 by CRS

age 65 years
LVEF = 55%
CRS = 86.1
Risk of CE = 13%



Romond et al. Journal of Clinical Oncology 2012

Trastuzumab prediction models

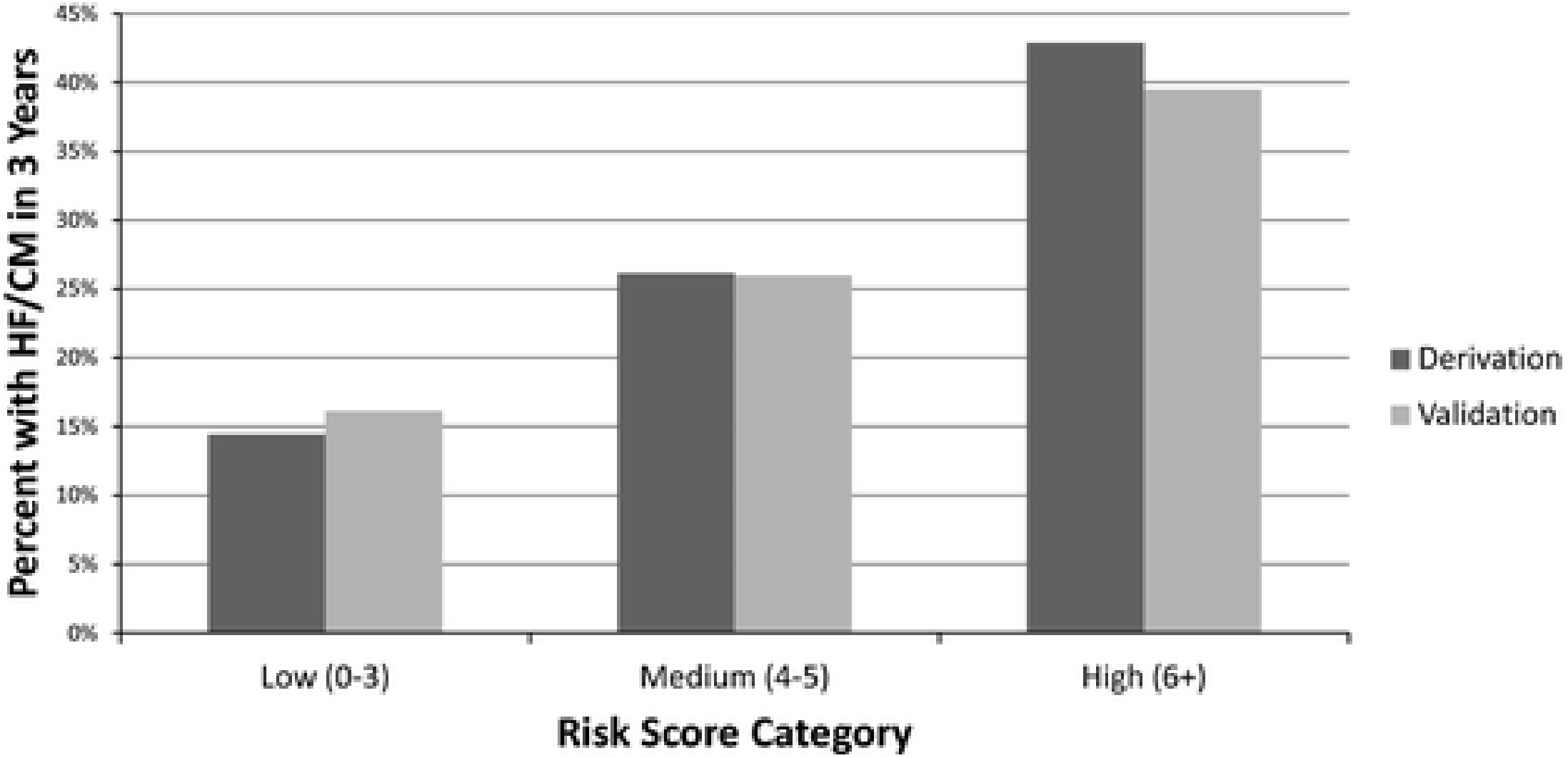
- Risk prediction model of cardiac toxicity using SEER/Medicare
- Using a split-sample design, they used a proportional hazards model to identify candidate predictors of HF/CM in a derivation cohort.
- Overall risk score 0-9 summed
- Grouped into low, middle and high risk strata:
  - Low < 20% incidence (<3 points)
  - Middle 20-39% (4-5 points)
  - High > 40% (>6 points)

Ezaz et al, JAHA 2014

Cox Regression Coefficients and Point Assignment for Each Risk Factor

Risk Factor	Hazard Ratio (95% Confidence Interval)	Regression Coefficient	*P* Value	Points Assigned
Adjuvant therapy				
Anthracycline chemotherapy	1.93 (1.11 to 3.36)	0.66	0.020	2
Non-anthracycline chemotherapy	1.64 (0.99 to 2.73)	0.50	0.055	2
No identified chemotherapy	Reference	Reference		
Age category, y				
67 to 74	Reference	Reference		
75 to 79	1.36 (0.92 to 2.01)	0.31	0.125	1
80 to 94	2.04 (1.29 to 3.24)	0.71	0.003	2
Cardiovascular conditions and risk factors				
Coronary artery disease	2.16 (1.21 to 3.86)	0.77	0.009	2
Atrial fibrillation/flutter	1.69 (0.98 to 2.91)	0.53	0.058	2
Diabetes mellitus	1.50 (1.03 to 2.18)	0.41	0.034	1
Hypertension	1.44 (0.99 to 2.08)	0.36	0.054	1
Renal failure	1.99 (0.96 to 4.14)	0.69	0.065	2

Ezaz et al. Journal of the American Heart Association 2014



Ezaz et al, JAHA 2014

#3 – Ontario Administrative CRS for Early-Stage Breast Cancer

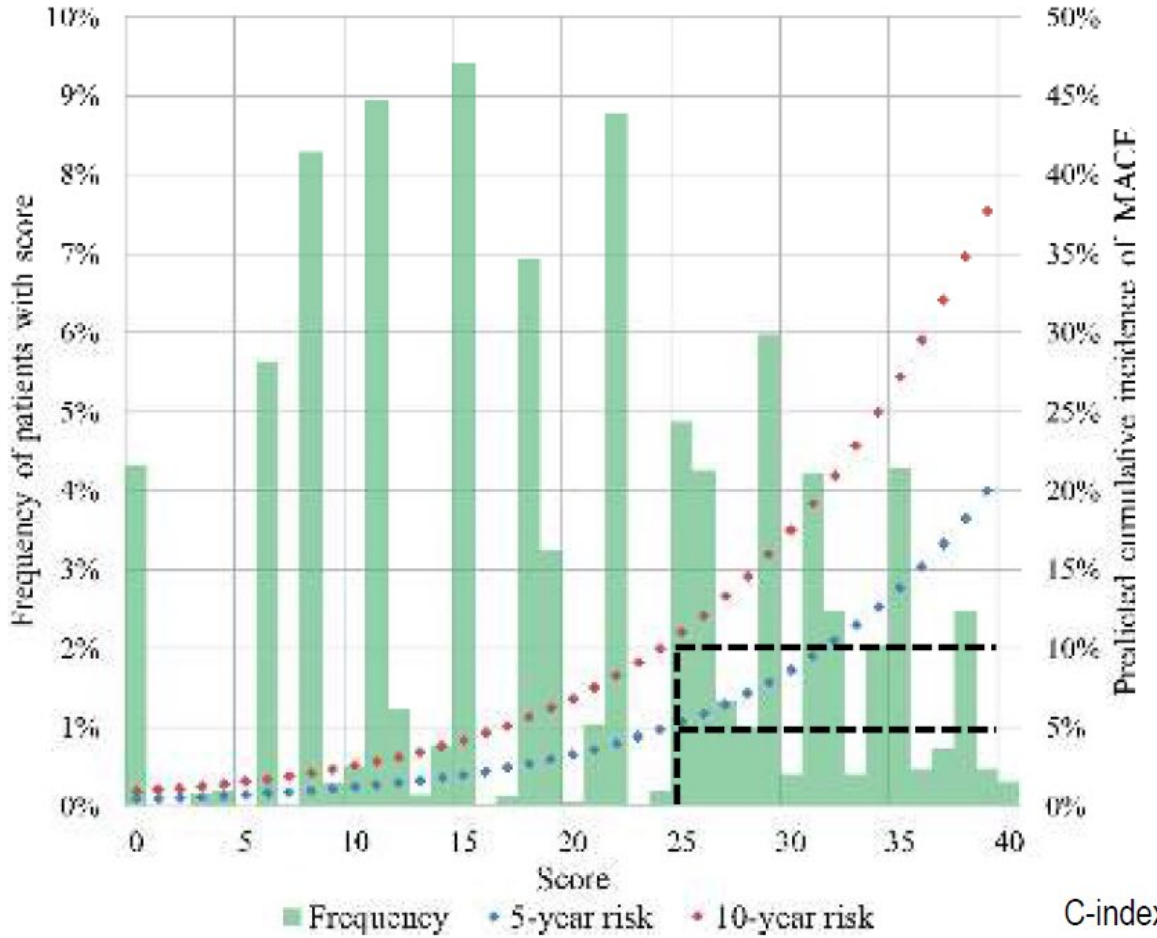
- Women age 18-105 years old diagnosed with early-stage breast cancer (stages I-III) from 1/1/03-12/31/14 (n=90,104)
- Ontario, Canada resident, eligible for Ontario Health Insurance Plan (OHIP) coverage for at least 1 year before breast cancer diagnosis
- Outcome: MACE = composite of hospitalizations for acute MI, unstable angina, TIA, stroke, peripheral vascular disease, and HF, and deaths from circulatory disease

Abdel-Qadir et al. European Heart Journal 2019

Risk Score

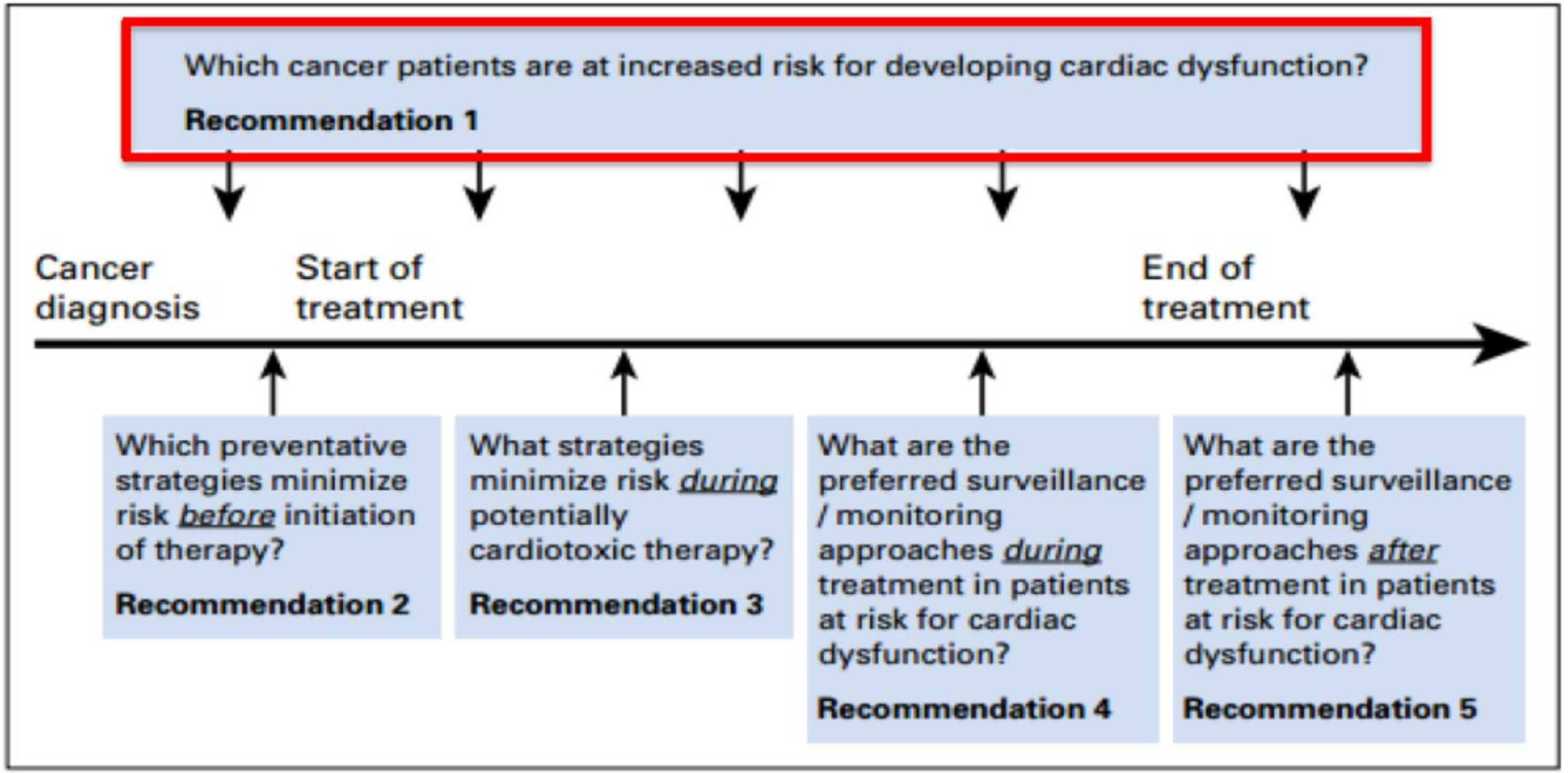
Select age category		Select past medical history	
<40 years	0	Heart failure	7
40–44 years	6	Atrial fibrillation	4
45–49 years	8	Peripheral vascular disease	4
50–54 years	11	Hypertension	4
55–59 years	15	Ischaemic heart disease	3
60–64 years	18	Diabetes	3
65–69 years	22	Chronic kidney disease	3
70–74 years	25	COPD	3
75–79 years	27	Cerebrovascular disease	2
≥80 years	31	Total score	

Ontario Administrative CRS: Proportion of patients at each value of the risk score, and predicted risk of MACE at 5 and 10 years



Score=25:
4.8% risk at 5 y,
10.0% at 10 y

C-index: 81.9% at 5 y
79.8% at 10 y


Which cancer patients are at increased risk for developing cardiac dysfunction?
Recommendation 1
Cancer diagnosis
Start of treatment
End of treatment
Which preventative strategies minimize risk before initiation of therapy?
Recommendation 2
What strategies minimize risk during potentially cardiotoxic therapy?
Recommendation 3
What are the preferred surveillance / monitoring approaches during treatment in patients at risk for cardiac dysfunction?
Recommendation 4
What are the preferred surveillance / monitoring approaches after treatment in patients at risk for cardiac dysfunction?
Recommendation 5

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