Physiological Changes and Comorbidities Associated with Aging:
Relation to Risk of Cancer Therapy Toxicity

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CARG
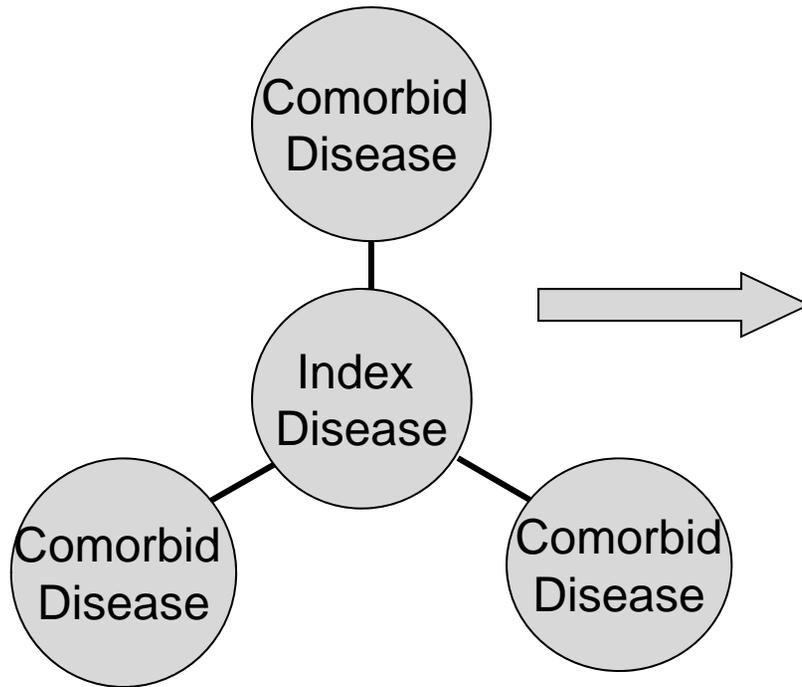CANCER & AGING RESEARCH GROUP

Aging and Cancer

- Comorbidity and Aging
  - What is comorbidity?
  - How do we "measure" it?
  - How do co-existing comorbidities influence overall outcomes in older adults with cancer?
  - How does comorbidity affect cancer treatment and toxicity?
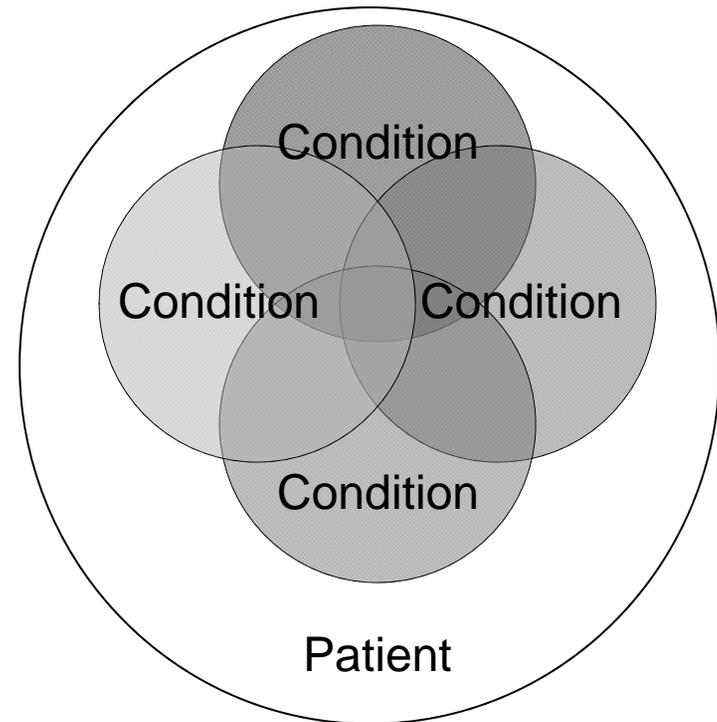
What Is Comorbidity?

- A coexisting medical condition that exists along with an index condition that has implications for an outcome

- No gold standard for measurement

- Particular importance in cancer
  - Confounder or mediator of effect
  - Outcome of interest
  - Distinguish from toxicity

Sorensen HT. Clin Epi 2013:5 (suppl1):1-2.
Ritchie CS. J Oncol Practice 2011;7:371-4.

More than half of people 65 and older have 3+ chronic conditions

Comorbidity

Multimorbidity

Boyd, CM, Fortin M. Public Health Reviews, 2011.

Importance of Multimorbidity

Brendan Smialowski (NY Times)

- *Increased risk of*:
  - Death
  - Institutionalization
  - Increased utilization of healthcare resources
  - Decreased quality of life
  - Higher rates of adverse effects of treatment or interventions

- *Almost all existing "guidelines" have single disease focus*

- *Best approaches to decision-making and clinical management of older adults with multimorbidity **remain unclear***

AGS Expert Panel on the Care of Older Adults with Multimorbidity. J Am Geriatr Soc 2012;60:1957-68

Comorbidity ≠ Disability ≠ Geriatric Syndromes

Colorectal Cancer

Breast Cancer

Koroukian, S. M. et al. *J Clin Oncol*; 24:2304-2310 2006
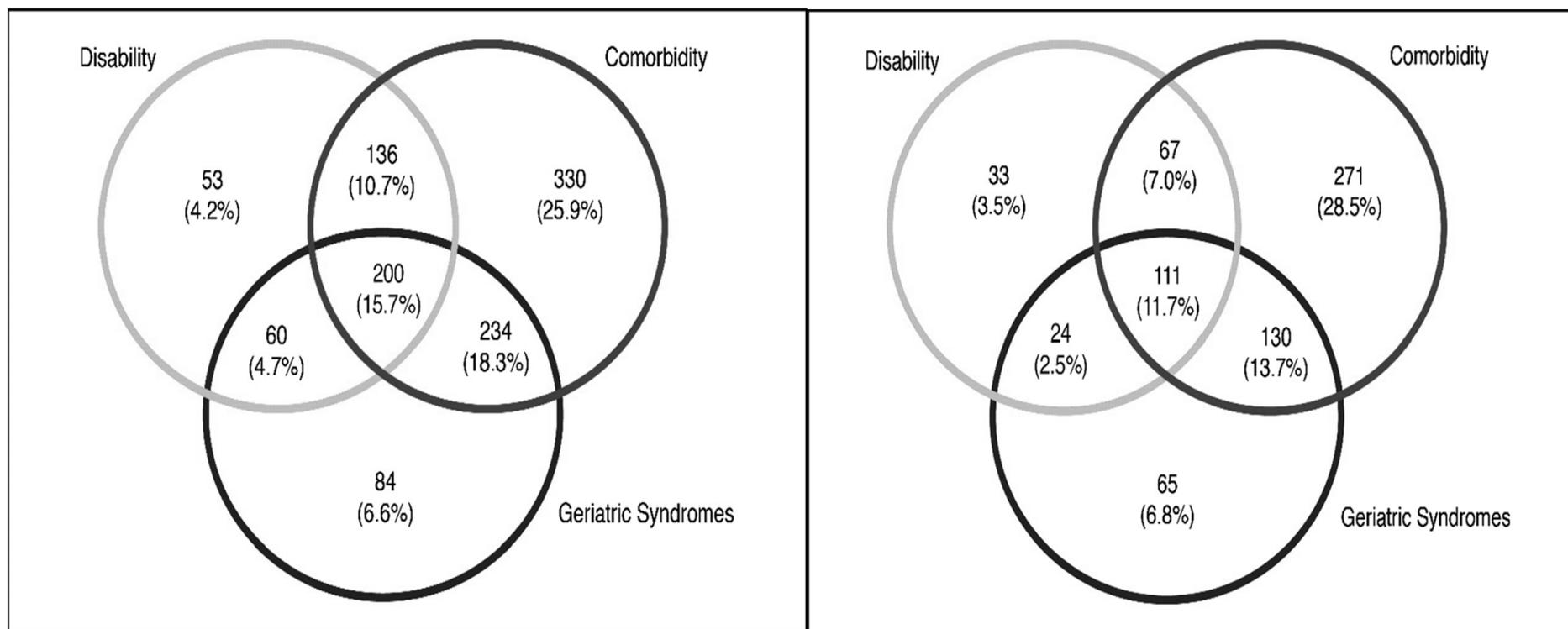
How Do We Measure Comorbidity?

- Charlson Comorbidity Scale; Cumulative Illness Rating Scale-Geriatric (European)
  - Extermann et al. JCO 1998;16(4):1542.
  - Standardized scoring
  - May be self-administered
  - Public Domain
  - Demonstrated predictive value for hospitalization, mortality

Categories of Comorbidities

Terminal

- Dementia, class IV CHF, end-stage COPD

Function-limiting, possible life-limiting

- stroke, severe COPD, PVD, OA, vision impairment, depression, urinary incontinence
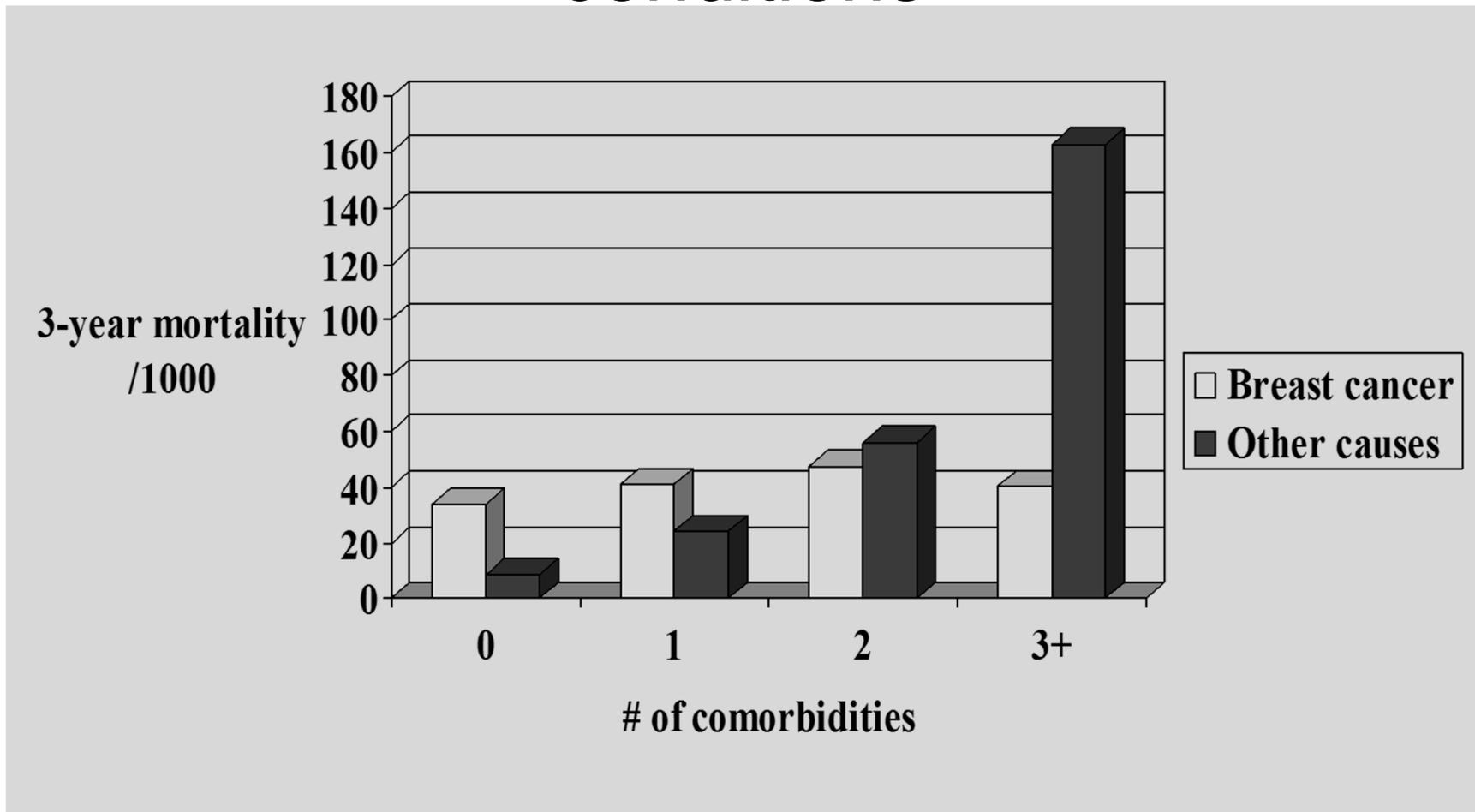
Reserve-limiting

- renal insufficiency, diabetes, COPD, stable angina

Influence on Outcomes

- How does comorbidity affect overall outcomes in cancer patients?
  - Competing cause of death
  - Affects patient's ability to receive standard of care cancer treatment

Comorbidity and prognosis: Simply adding up the number of co-existing conditions

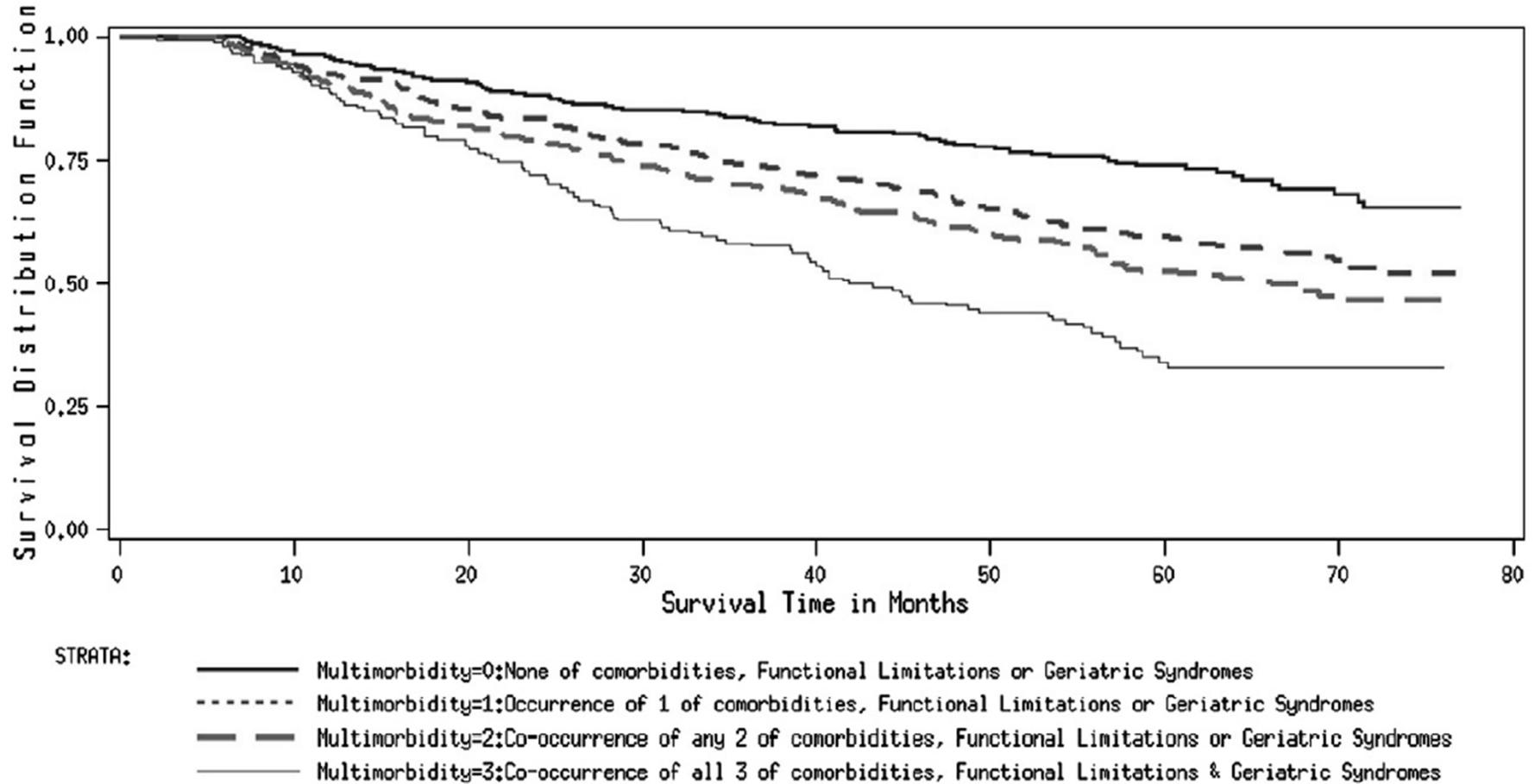SEER Registry. Satariano & Ragland 1994

Multimorbidity

STRATA:
— Multimorbidity=0:None of comorbidities, Functional Limitations or Geriatric Syndromes
----- Multimorbidity=1:Occurrence of 1 of comorbidities, Functional Limitations or Geriatric Syndromes
— — Multimorbidity=2:Co-occurrence of any 2 of comorbidities, Functional Limitations or Geriatric Syndromes
—— Multimorbidity=3:Co-occurrence of all 3 of comorbidities, Functional Limitations & Geriatric Syndromes

Fig. 1 – Overall survival by Multimorbidity. Log-Rank chi-square=58.3 p<0.0001.

Koroukian S, et al. J Geriatr Oncol 2011;2:200-8.

Influence on Outcomes

- How does comorbidity affect the ability of an older adult with cancer to tolerate therapy?
  - Physiologic reserve
  - Treatment-related toxicity

What is Physiologic Reserve?

Aging involves progressive decline in reserve and eventual loss of homeostasis.

- This process is highly individualized.
- It is influenced by multiple genetic, epigenetic and environmental factors.

Physiologic reserve is the capacity of an individual to sustain and recover from insult/injury

- Because the aging process is individualized, persons of similar chronologic age may have very different physiologic reserve.
- Primary goal of treating frail patients with limited physiologic reserve is palliation

Clinical Example #1

- How does decreased physiologic reserve affect older adults with cancer?

Decreased Physiologic Reserve
Considerations in Cancer Treatment

Metabolism

– Metabolic clearance of a drug by the liver may be reduced because aging decreases liver blood flow, size, and mass

• Excretion

– Decreased renal physiologic reserve with aging

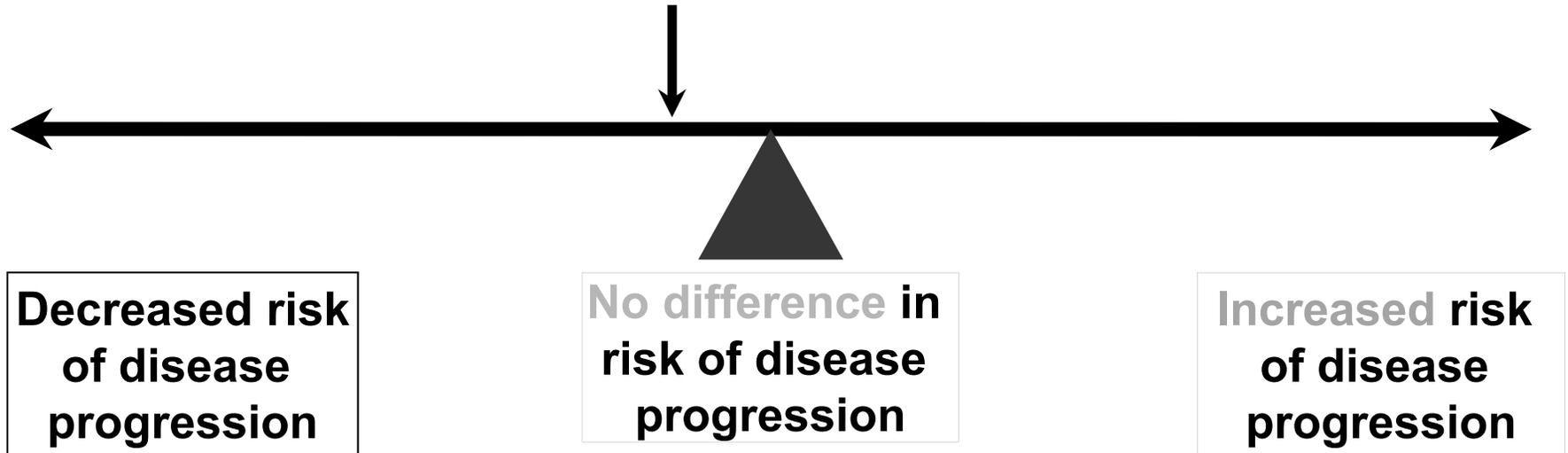↓ kidney size. ↓ renal blood flow,↓ number of functioning nephrons,↓ renal tubular secretion

Result: Lower glomerular filtration rate

Capecitabine: Tolerability data
Led to Renal Impairment Guidelines

Renal impairment	Calculated creatinine clearance (mL/min)	Starting dose (mg/m^2 twice daily)
None	>80	1,250
Mild	51–80	1,250[†]
Moderate	30–50	950[†]
Severe	<30	Contra-indicated

Poole C et al. Cancer Chemother Pharmacol 2002;49:225–34

Capecitabine Efficacy is Maintained Following Adjustments to Individual Tolerable Dose

Xeloda
HR=0.987
(0.70–1.39)
p=0.940

Decreased risk of disease progression

No difference in **risk of disease progression**

Increased risk of disease progression

HR = hazard ratio for disease progression in patients with versus without dose reduction

O'Shaughnessy et al

Elderly Patients With Cancer: Adapting to Renal Function

- Elderly patients are at greater risk for chemotherapy-induced toxicities

- Reluctance to give standard chemotherapy treatment often results in undertreatment

- Adapting to renal function allows safe and equipotent drug usage

Clinical Example #2

- How does decreased physiologic reserve affect older adults with cancer?
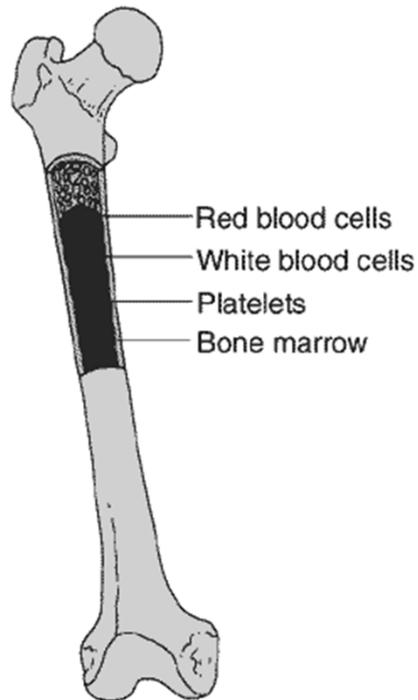
Bone Marrow Reserve and Aging

- Bone marrow change with aging
  - Appears that hematopoiesis is maintained at older ages, while the response to stresses of the stem cell gradually declines

- Risk of febrile neutropenia
  - Meta-analysis identified older age and comorbidiites such as renal and cardiovascular disease as risk factors for febrile neutropenia

Globerson. Exp Gerontol, 1999.
Lyman et al, Crit Rev Oncology/Hematology, 2014

Hemotologic Toxicity and Age: Non-Hodgkin's Lymphoma

- Studies of patients $\geq$ 70 with NHL treated with CHOP or CHOP-like regimens
  - Higher incidence of grade 3, 4 neutropenia
  - Two-fold increase in neutropenic infections
  - Increased incidence of anemia and thrombocytopenia

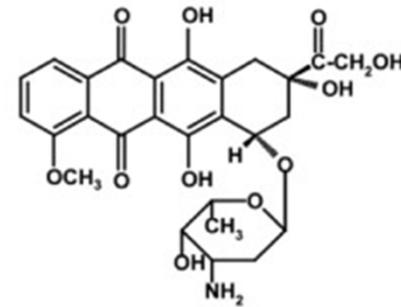# Bone Marrow Reserve and Aging

- In patients over 70 years, primary prophylaxis with hematopoietic growth factors should be considered depending on regimen
- Successive doses should be adjusted according to toxicity

Clinical Example #3

- How does comorbidity affect toxicity risk in older adults with cancer?

Doxorubicin

Anthracycline Cardiotoxicity

- Comorbidity and aging are among the risk factors for anthracycline cardiotoxicity:
  - Pre-existing cardiac diseases associated with myocardial strain
    - Hypertension, valvular hear disease
  - Increasing age

Prevention of Cardiotoxicity

- Medical management
  - Angiotensin inhibition and Beta-blockade
- Monitor LVEF and clinical symptoms
- Alternative drugs (e.g., liposomal anthracyclines)
- Lifetime dose limits
- Cardio-oncology evaluation

Conclusion

- Older adults with cancer frequently have comorbid conditions that can affect:
  - An individual's physiologic reserve
  - An individual's life expectancy independent of cancer
  - Cancer related outcomes such as tolerance to treatment and toxicity
- Attention to comorbidities and development of appropriate supportive care strategies is important for older adults with cancer