Cancer Treatment Decisions in Older Adults with Multiple Chronic Conditions

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City of Hope Comprehensive Cancer Center

HCSRN-OAICs
AGING Initiative
March 6, 2018
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Association Between Treatment for Superficial Bladder Cancer and Ten Year Mortality in Older Adults with Multiple Chronic Conditions

Tullika Garg, MD, MPH, FACS
Clinical Investigator, Dept. of Urology
AGING Pilot Plus+ Webinar
March 6, 2018
The “Silver Tsunami” of Cancer

- Elderly population will double by 2030
Urologic Cancers are Highly Prevalent

Most Common Cancers in the U.S.

1. Breast
2. Lung & Bronchus
3. Prostate
4. Colorectal
5. Bladder

* Kidney cancer is number 9.
Urologic Cancers are Highly Prevalent

- 25% of all cancer survivors
- 40% of all cancers in men
- Bladder cancer incidence projected to increase 54% by 2030

Majority of Older Cancer Patients Have Multiple Chronic Conditions (MCC)

- MCC definition:
  - Presence of two or more conditions lasting over 1 year that require ongoing medical attention and/or limit activities of daily living
  - Cancer is a chronic condition

- 90% of Medicare patients with cancer meet criteria for MCC
MCC Impacts Older Cancer Patients

- Treatment decision-making
- Health care utilization
- Quality of life
- Caregiver concerns
Superficial Bladder Cancer is Ideal for Examining Interplay Between MCC & Cancer Treatment

• Highest median age at diagnosis
  – 73 years

• Smoking is the main modifiable risk factor
  – Smoking-related MCC
  – Median of 8 chronic conditions

• High recurrence rate, low risk of death
  – Frequent surveillance & treatment
  – Frequent ambulatory surgery/anesthesia

Lack of Information for Decision-Making in Older Adults with Cancer

• Limited enrollment of older, medically complex patients in clinical trials
• Gaps in knowledge of cancer treatment outcomes
• Lack of data leads to variation
  – Under/overtreatment
**Patient Perspective:**
“Ok doc, I got superficial bladder cancer. How bad am I going to feel after that treatment? Do I have to go to a nursing home or rehab? I’d rather be independent at home. Will I be able to take care of my sick spouse? How am I going to make it back and forth to all of those appointments you’re setting up? My adult children have to take too much time off work to take care of me. What are the chances this treatment is going to be a cure? I got 3 stents in my heart and wear home oxygen? Will I die before the bladder cancer is an issue? Are you old enough to be a doctor???”

**Doctor Perspective:**
“Ok, my patient has superficial bladder cancer. He’s got some medical issues. 3 stents! Wheelchair! Home O2! Super high risk for surgery. Will the heart/lungs or SBC get him first? Clinic appointments q 3 months. BCG treatments qweek for 6 weeks. Not sure if those BCG treatments will work at his age. NCCN Guidelines say I have to recommend treatment. Have to figure this out in a 10 minute clinic appointment. Hard decisions, I should have been a pathologist!!!”
NCCN Guidelines Version 2.2017
Older Adult Oncology

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Bladder Cancer

- BCG treatment for superficial bladder carcinoma has decreased efficacy in the very old (older than 80 years).\(^1,2\)

- Age alone should not be a criterion for decisions regarding cystectomy, radiation therapy, and chemotherapy in older patients.\(^3,4\)

- The improvement in disease-specific survival from neoadjuvant chemotherapy is preserved with age.\(^4\)

- Older patients in RTOG protocols appear to have similar response rates and disease-specific survival compared to younger patients following curative intent selective bladder preservation.\(^5\)

- Older age does not appear to be associated with worse late pelvic toxicity after curative intent selective bladder preservation.\(^6\)

See NCCN Guidelines for Bladder Cancer
Research Objective

• To estimate the association between standard SBC treatment and 10 year mortality among older adults with adjustment for MCC and other confounders.
Study Design

• Retrospective cohort study
• 2 community-based health systems
  – Geisinger
  – Kaiser Permanente Northwest
• Superficial bladder cancer patients (Stage <=1)
  – 2003-2014
  – >=60 years at dx
  – N=1800
Comparison Groups

• 2 groups: treatment and observation
• Treatment defined by CPT codes
  – Within 6 months of diagnosis
  – TURBT: 52204, 52224, 52235, 52240
  – Intravesical treatment: 90586, 51720
MCC Measurement

• Extracted all ICD-9 codes attached to encounters:
  – Inpatient, outpatient, lab orders, pharmacy orders, problem lists, procedures
• AHRQ Chronic Condition Indicator
• AHRQ Clinical Classifications Software
• 3 outpatient or 1 inpatient code in 1 year
MCC Measurement cont.

• Identified 48 chronic conditions *a priori*
  – AHRQ MCC Chartbook
  – Literature review

• MCC defined as 2+ chronic conditions
  – Binary variable: Yes/No
Other Covariates

- Age at diagnosis
- Sex
- Race/ethnicity: white and non-white
- Body mass index
- Smoking status (Current, Never, Unknown)
- Health system (Geisinger, KPNW)
- AJCC stage/grade: 0a low grade, 0a high grade, 0is, and 1
Statistical Analysis

• Descriptive statistics
  – Fisher’s exact test, Pearson’s chi-square tests for categorical data
  – Two-sample $t$ tests for continuous data

• Cox proportional hazards models
  – Truncated data at 10 years

• Propensity score analysis
  – Standardized inverse probability of treatment weights (SIPTW) to balance covariates
Results

• 1800 patients
• Treatment group: 1485 (82.5%)
• Observation group: 315 (17.5%)
• Median follow up time for whole cohort 6.6 years (95% CI 6.26-7.07)
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (N=1800)</th>
<th>Treatment</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (N=315)</td>
<td>Yes (N=1485)</td>
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<td><strong>Age at Dx (mean, SD)</strong></td>
<td>73.6</td>
<td>74.1</td>
<td>73.5</td>
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<td><strong>Sex, Male (N, %)</strong></td>
<td>1418</td>
<td>248</td>
<td>1170</td>
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<td><strong>Race, White (N, %)</strong></td>
<td>1757</td>
<td>312</td>
<td>1445</td>
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<td><strong>Center (N, %)</strong></td>
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<tr>
<td>Geisinger (GHS)</td>
<td>938</td>
<td>243</td>
<td>695</td>
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<td>Kaiser Permanente Northwest (KPNW)</td>
<td>862</td>
<td>72</td>
<td>790</td>
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<td><strong>BMI, Overweight/Normal/Underweight (N, %)</strong></td>
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<td>235</td>
<td>971</td>
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<td><strong>Smoking Status (N, %)</strong></td>
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<td>Current/Former Smoker</td>
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<td>219</td>
<td>1103</td>
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<tr>
<td>Never Smoker</td>
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<td>364</td>
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<tr>
<td>Never Assessed/ Unknown if Ever Smoked</td>
<td>43</td>
<td>25</td>
<td>364</td>
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<tr>
<td><strong>Multiple Chronic Conditions at Baseline, Yes (N, %)</strong></td>
<td>1204</td>
<td>159</td>
<td>1045</td>
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<tr>
<td><strong>Status, Alive within 10 years of index date (N, %)</strong></td>
<td>1075</td>
<td>143</td>
<td>932</td>
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<tr>
<td><strong>Stage/ Grade (N, %)</strong></td>
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<td>0A – Low Grade</td>
<td>921</td>
<td>216</td>
<td>705</td>
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<tr>
<td>0A – High Grade</td>
<td>318</td>
<td>22</td>
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<td>92</td>
<td>16</td>
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<td>1</td>
<td>451</td>
<td>60</td>
<td>391</td>
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<tr>
<td>Unknown</td>
<td>18</td>
<td>1</td>
<td>17</td>
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</tbody>
</table>
Kaplan-Meier Curve for Entire Cohort
Kaplan-Meier Curve Stratified by Treatment Group

Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

Time from Diagnosis Date (Years)

Treatment 0 [No] 1 [Yes]

Geisinger
## Cox Model Using SIPTW

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.08 (1.07, 1.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>Female v. Male (ref)</td>
<td>0.77 (0.62, 0.96)</td>
<td>0.02</td>
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<tr>
<td>Center</td>
<td>KPNW v. GHS (ref)</td>
<td>1.14 (0.95, 1.37)</td>
<td>0.16</td>
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<tr>
<td>Race</td>
<td>Non-White v. White (ref)</td>
<td>1.20 (0.84, 1.73)</td>
<td>0.31</td>
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<tr>
<td>Stage/Grade</td>
<td>OA, High v. OA, Low (ref)</td>
<td>1.13 (0.89, 1.44)</td>
<td>0.30</td>
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<tr>
<td></td>
<td>OIS v. OA, Low (ref)</td>
<td>1.10 (0.78, 1.54)</td>
<td>0.60</td>
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<tr>
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<td>1 v. OA, Low (ref)</td>
<td>1.68 (1.38, 2.04)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Multiple Chronic Conditions at Baseline</td>
<td>Yes v. No (ref)</td>
<td>1.76 (1.46, 2.13)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Treatment 6 months post diagnosis</td>
<td>Yes v. No (ref)</td>
<td>0.66 (0.52, 0.84)</td>
<td>0.0006</td>
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</tbody>
</table>
Conclusions

• Cancer treatment associated with survival benefit in older adults with SBC
• Hazard of death associated with MCC was much greater
Strengths and Limitations

**Strengths**

- Community-based health systems
- Two geographically disparate systems
- Evaluating the outcome of cancer treatment in medically complex older adults

**Limitations**

- Predominantly white cohort
- Don’t have cause of death data
- Retrospective study
Clinical Context

• Provides data about treatment outcome in older, medically complex adults with SBC

• Decision-making
  – Goals and preferences
  – Data to help patients and physicians

• Future ideas
  – Chronic condition clustering
  – Chronic condition profiles
  – Personalized decisions
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  – HCSRN-OAIC AGING Initiative Pilot Projects

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  – Maureen O’Keeffe-Rosetti (Kaiser Permanente)
  – Amanda Young (Geisinger)
Thank You!

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Addressing the Needs of an Aging Nation: Merging Geriatrics and Oncology

Arti Hurria, MD, FASCO
Vice Provost of Clinical Faculty
Director, Center for Cancer and Aging
The George Tsai Family Chair in Geriatric Oncology
City of Hope
Outline

- Demographics of Aging and Cancer

- Impact of Cancer Therapy on the Aging Trajectory
  - Premature Aging Syndrome

- Utilizing Geriatric Assessment in Oncology Practice to:
  - Identify Risk of Chemotherapy Toxicity
  - Deploy Interventions Aimed at Decreasing the Risk
Projected Rise in Cancer Incidence from 2010 to 2030

- 67% in patients 65+
- 11% in patients <65

Smith et al, J Clin Oncol, 2009
Most Survivors are Older Adults

Older Cancer Survivors: Males: 77%   Females: 68%
Younger Cancer Survivors: Males: 23%   Females: 32%

Division of CCPS, National Cancer Institute, 2014
The Population is Aging

The Number of Older Adults With Cancer is on the Rise

Number of Survivors is on the Rise

Are We Prepared?
Clinical Trial Data Limited in Older Adults

No Change in Age Distribution of NCI Cooperative Group Clinical Treatment Trials (Phase 2 and Phase 3)

NCI/DCTD Clinical Data Update System, 2012
Under-representation of Older Adults on FDA Registration Trials (ASCO 2017)

- 10-yr perspective
  - 2005-2015
- 105 FDA registration trials
- 224,766 patients

Disparity is Greatest for Patients Age ≥ 75

Singh et al, ASCO Annual Meeting, 2017
Do We Address the Questions that Patients Want to Know?

Doctor, if I take the therapy…
- Will I be hospitalized?
- Will I be functionally impaired?
- Will I be cognitively impaired?
- What does my family need to prepare for?
- What is the quality of my survival?

Will I become frail?
A Phenotype of Frailty

Factors Defining Frailty:

- Weight loss
- Weakness
- Poor energy/endurance
- Slowness
- Low physical activity

Frail: 7%
Intermediate: 47%
Not Frail: 47%

0 factors: Not frail
1-2 factors: Intermediate
3+ factors: Frail

“Premature Aging Syndrome”

Introduce Cancer Tx

Withdraw Cancer Tx

Will She Recover?
How Does Cancer Impact the Aging Trajectory?

**Normal Aging**

- Phase Shift Hypothesis: The trajectory of functional decline parallels normal aging.

**Accelerated Aging Hypothesis**

- The trajectory of functional decline is accelerated in comparison to normal aging.
I would rather die than take a treatment that causes:

- functional impairment: 74%
- cognitive impairment: 88%

Fried et al, NEJM 2002: 346 (14): 1061
Cancer Treatment & Clinical Markers of Aging

- Cancer Survivors Report:
  - Poorer Physical Function
    - Diemling et al. Cancer Nurs 2007
  - Poorer Quality of Life
    - Weaver et al. CEBP 2012
  - Increased # of Comorbidities
    - Mariotto et al. CEBP 2007
  - Cognitive Decline
    - Mandelblatt et al. J Clin Oncol 2014
    - Wildiers et al. J Clin Oncol 2014
Cancer Treatment: Creating the Frailty Phenotype

Molecular and Disease
- Oxidative stress
- Mitochondrial deletions
- Shortened Telomeres
- DNA damage
- Cell senescence
- Gene variation
- Inflammatory Diseases

Impaired Physiological
- Inflammation
- Neuroendocrine Dysregulation
  - Interleukin-6
  - Anorexia
  - Sarcopenia, Osteopenia
    - Immune function
    - Cognition
    - Clotting
    - Glucose Metabolism
  - Insulin–like growth factor-1
  - Dehydroepiandrosterone Sulfate
  - Sex steroids

Clinical
- Slowness
- Weakness
- Weight Loss
- Low Activity
- Fatigue

Walston et al., JAGS 2006
Cancer Treatment & Biological Markers of Aging

- Telomere length
  - Diker-Cohen et al. Leuk Lymphoma 2013

- $\uparrow$ p16^{INK4a} expression
  - Sanoff et al. J Natl Cancer Inst 2014

- $\uparrow$ proinflammatory cytokines
  - Pomykala et al. Brain Imaging Behav 2013
  - Kim et al. Radiat Oncol J 2014

- $\uparrow$ resting energy expenditure
  - Marín Caro et al, Clinical Nutrition 2007
  - Aoyagi et al, World J Gastrointest. Oncol 2015
Older adults are at risk for cancer therapy toxicity

Quoix et al., Lancet 2011
Muss et al., Journal of Clinical Oncology 2007
Zauderer et al., Journal of Geriatric Oncology 2013
Rocha Lima et al., Cancer 2002
Argiris et al., Journal of Clinical Oncology 2004
Hurria et al., Journal of Clinical Oncology 2011
Folprecht et al., Annals of Oncology 2011
Crivellari et al., Journal of Clinical Oncology 2000
Muss et al., Journal of Clinical Oncology 2007
Zauderer et al., Journal of Geriatric Oncology 2013
Schild et al., Journal of Clinical Oncology 2003
Goldstone et al., Blood 2001
Machtay et al., Journal of Clinical Oncology 2008
Zhu et al., Journal of the American Medical Association 2012
Quoix et al., Lancet 2011
Pinder et al., Journal of Clinical Oncology 2007
Can We Prevent Toxicity?

Introduce Cancer Tx

Overall Goal is to Identify Toxicity Risk and Prevent It if at All Possible
Rather than putting out fires…
Can we anticipate and prevent them?
Geriatric Assessment: Personalized Medicine

Factors other than chronological age that predict morbidity & mortality in older adults

- Functional status
- Comorbid medical conditions
- Cognition
- Nutritional status
- Psychological state
- Social support
- Medications (polypharmacy)
Determining the Utility of an Assessment Tool for Older Patients with Cancer
Cancer and Aging Research Group

Primary Objective:
To determine the geriatric assessment’s ability to predict risk of toxicity to chemotherapy

Secondary Objective:
To evaluate the longitudinal effect of the cancer and chemotherapy treatment on geriatric assessment parameters
Can Geriatric Assessment Predict Chemo Toxicity?

Eligibility criteria
- Age 65 or older
- Diagnosis of cancer
- To start a new chemo regimen

Timepoint 1:
- Pre-chemo Geriatric Assessment

Timepoint 2:
- Post-chemo Geriatric Assessment

Chemotherapy: toxicity grading at each visit

- Sample size: 750 patients (Chemo alone)
- 10 participating institutions (Cancer and Aging Research Group)

Hurria et al, JCO 2011 & 2016
Predictors of Toxicity

- Age ≥ 72 years
- GI/GU Cancer
- Standard Dose
- Polychemotherapy
- Hemoglobin (male: <11, female: <10)
- Creatinine Clearance (Jelliffe-ideal wt <34)
- Fall(s) in last 6 months
- Hearing impairment (fair or worse)
- Limited in walking 1 block (MOS)
- Assistance required in medication intake (IADL)
- Decreased social activity (MOS)
MD-rated KPS vs. Predictive Model

Chemotherapy Toxicity Predictive Model

Development Cohort (N=500)

- Low: 31%
- Medium: 52%
- High: 83%

Validation Cohort (N=250)

- Low: 37%
- Medium: 62%
- High: 70%

% with Grade 3-5 Toxicity

Development Cohort

- 90-100: 51%
- 80: 51%
- ≤70: 62%

Validation Cohort

- 90-100: 52%
- 80: 62%
- ≤70: 67%

P-values:

- Development Cohort: P<0.001
- Validation Cohort: P=0.25

Hurria et al. JCO 2011; Hurria et al. JCO 2016
Efficiently Integrating Geriatrics into Oncology Care

Too little time... Too much to do

Development of a Short Geriatric Assessment Tool for Oncologists
Developing a Geriatric Assessment for Oncologists

- Functional Status:
  - Activities of Daily Living (subscale of MOS Physical Health)
  - Instrumental Activities of Daily Living (subscale of the OARS)
  - Karnofsky Performance Rating Scale
  - Timed Up & Go
  - Number of Falls in Last 6 Months

- Comorbidity:
  - Physical Health Section (subscale of the OARS)

- Cognition:
  - Blessed Orientation-Memory-Concentration Test

- Psychological:
  - Hospital Anxiety and Depression Scale

- Social Functioning:
  - MOS Social Activity Limitations Measure

- Social Support:
  - MOS Social Support Survey: Emotional and Tangible Subscales
  - Seeman and Berkman Social Ties

- Nutrition:
  - Body Mass Index
  - % Unintentional Weight Loss in the Last 6 Months

- Validity
- Reliability

- Length
- Time to complete
- Ability to self-administer

- Multidisciplinary input
- Alliance Cancer in Elderly Committee
Geriatric Assessment for Older Adults with Cancer on Cooperative Group Trials
CALGB 360401 (PI: Hurria)

Eligibility Criteria
- Age 65 or older
- Diagnosis of cancer
- To start treatment on a cooperative group clinical trial

Pre-chemo
Geriatric assessment
Feasibility data

Treatment and follow-up per protocol

Geriatric Assessment is Feasible in Oncology Trials

Hurria et al, JCO 2011
Geriatric Assessment is Feasible in Oncology Trials

87% Completed patient questionnaire w/o assistance

92% Length is “Just Right”

95% Easy to comprehend
96% Not upsetting

94% Completed healthcare provider portion

Hurria et al, JCO 2011
Geriatric Assessment-Guided Care Processes for Older Adults: A Delphi Consensus of Geriatric Oncology Experts

Supriya Gupta Mohile, MD, MS; Carla Velarde, MPH; Arti Hurria, MD; Allison Magnuson, DO; Lisa Lowenstein, PhD; Chintan Pandya, MD; Anita O'Donovan; Rita Gorawara-Bhat, PhD; and William Dale, MD, PhD

**Impairment Domain**

**Assessment Options**

1. Both ADL/IADL
2. IADL
3. Gait speed
4. ADL

**Process Options**

1. Physical therapy
2. Occupational therapy
3. Home safety evaluation
4. Refer to social work
5. Evaluate fall risk
6. Exercise

**Functional status**

1. Mini Mental State Examination
2. Montreal Cognitive Assessment
3. Blessed OMC

1. Involve caregiver
2. Assess/minimize medications
3. Delirium prevention
4. Refer to social work
5. Assess capacity and ability to consent to treatment
6. Identify health care proxy
7. Cognitive testing/neuropsychology referral

Mohile et al, JNCCN 2015
Development of a Touchscreen Geriatric Assessment

- Computerized geriatric assessment
- Understand the needs of:
  - patients
  - their caregivers

Hsu et al. Cancer 2014
Assessing the Needs of the Older Patient with Cancer

Approximately 20 min. later
Identifying Interventions to Help the Older Patient with Cancer

- Geriatric Assessment Results
- List of Potential Interventions
- Chemotherapy Toxicity Risk Score is Generated

![Diagram showing grade 3-5 toxicity and potential interventions]

**GA Results**

Potential Interventions

- Nutritional Consult
- Pharmacy Consult
- Social Work
- Life Line
- Rehabilitation

**Patient Total Risk Score:** 10

**Patient Toxicity Risk:** 72%
Sharing the Results with the Patient

Reassessing Throughout the Continuum of Care
Geriatric Assessment available in:
- English
- Spanish
- Mandarin
- Japanese
- Korean
- Armenian

www.mycarg.org
Conclusions

- The majority of cancer patients are older adults
- Cancer and cancer treatment may cause a premature aging syndrome
- Care of the older patient with cancer requires an integration of geriatrics and oncology
- Tools are available to assess the older patient’s needs and identify interventions
Thank You!

Geriatrics

Geriatric Oncology

Oncology