Prediction of treatment toxicity

#MASCC18 Workshop – Prognostication in Patients with Advanced Cancer

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Treatment toxicity – What treatments?

- Surgery
- Radiotherapy
- Systemic therapy
  - Chemotherapy
  - Molecularly Targeted Agents eg oral tyrosine kinase inhibitors
  - Immunotherapy
  - Hormonal therapy - androgen deprivation, progestogens, antioestrogen
  - Radiolabelled molecules eg Radium-223, Lutate therapy.

  - Supportive care measures eg bisphosphonates

Predicting treatment toxicity – What toxicities?

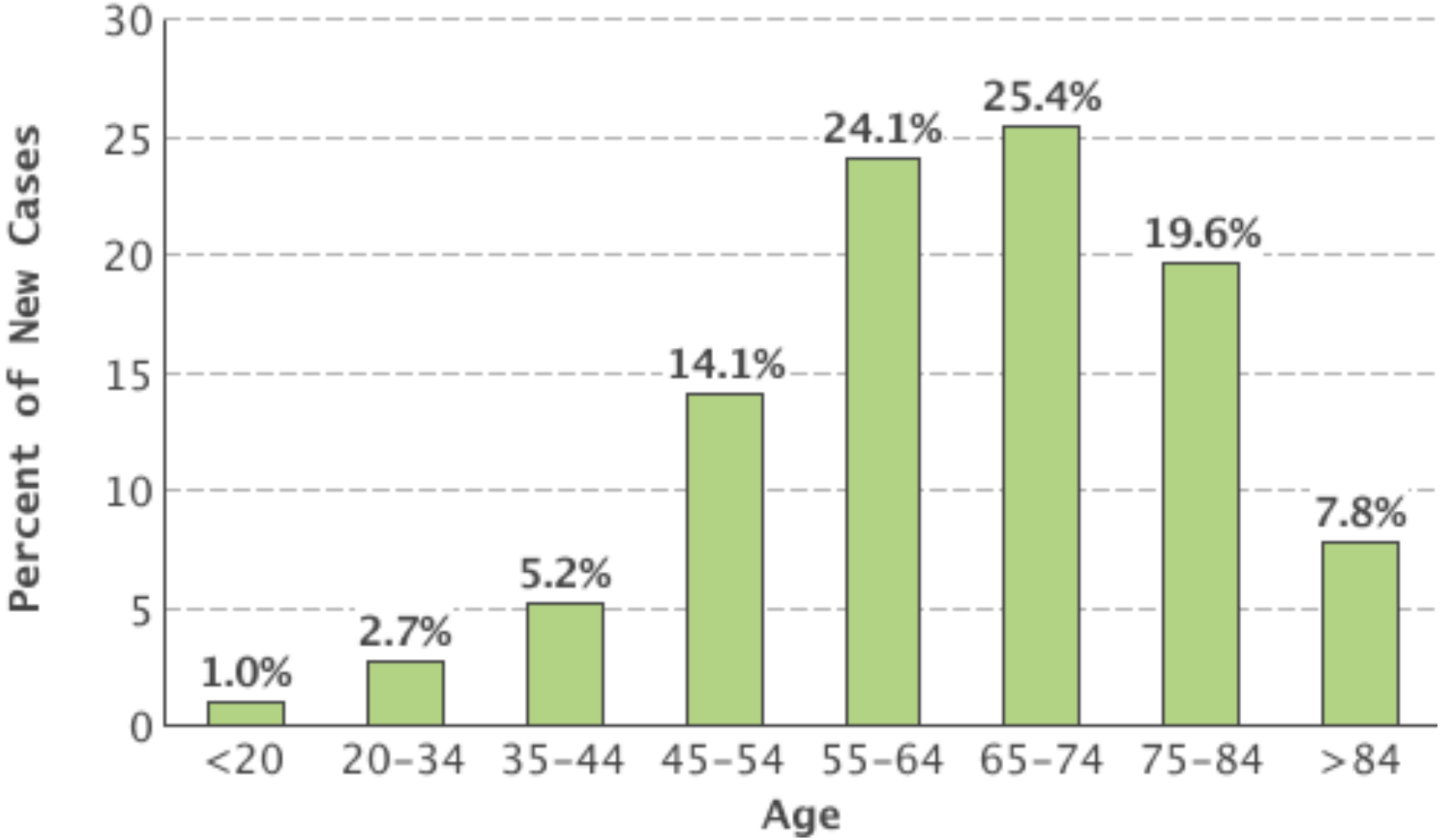
- Early vs late
- “Grade 3-4”?
- Lower grade toxicities that threaten QOL and independence
- Common and reversible
- Uncommon and catastrophic/lethal
- Reversible vs permanent (eg neuropathy)
- Asymptomatic and irrelevant eg hypertension
- Toxicity as a predictor of response?
- Clinician assessment vs patient reported
- Unplanned hospitalisation

Predicting treatment toxicity – Methods?

- Fitness
- Frailty
- Predictive models of toxicity depending on treatment modality.
- “Host factors” – comorbidities
- Genomic markers of metabolism


CHEMOTHERAPY

Cancer is a disease of older adults – NIH data

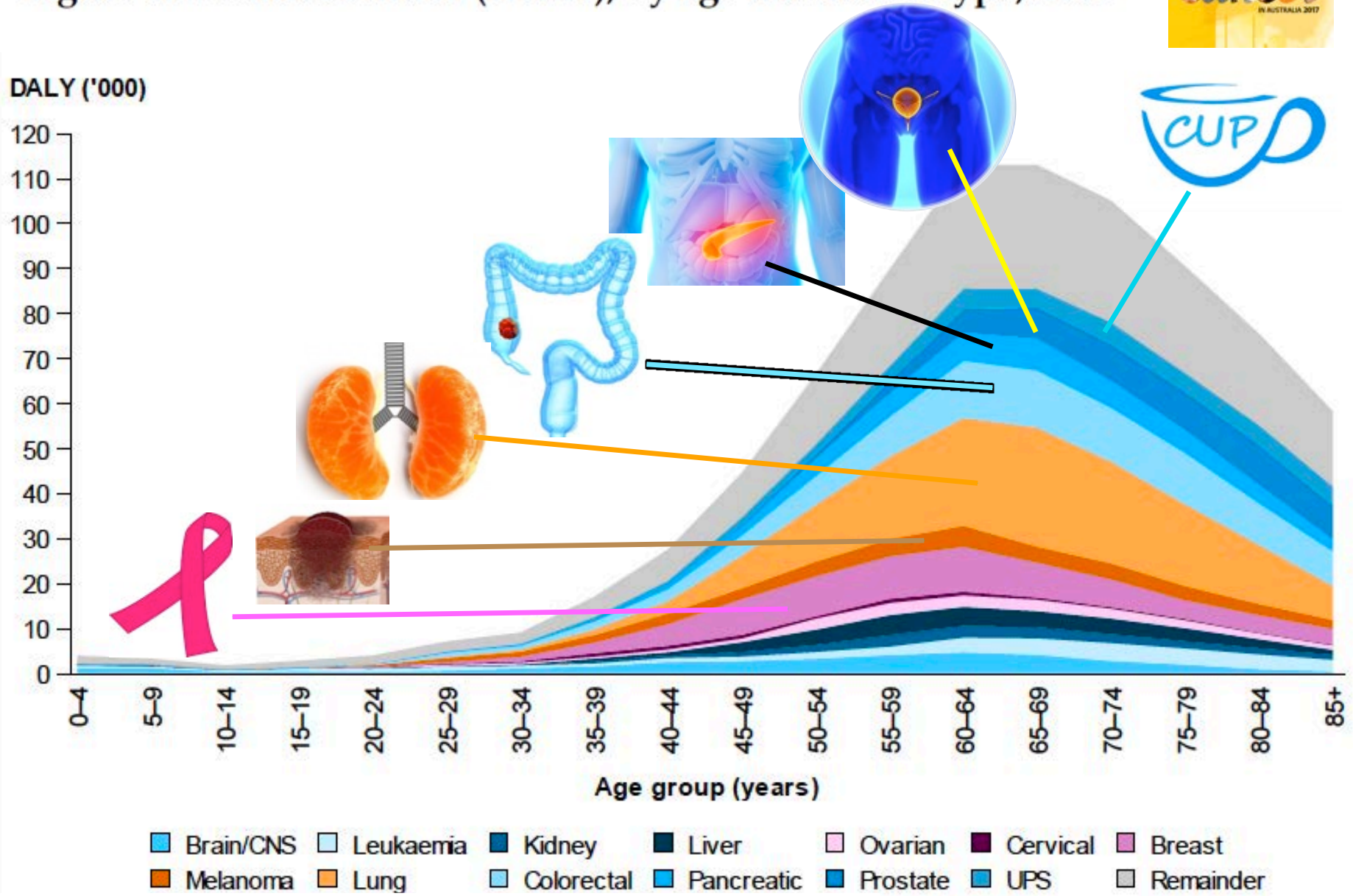


SEER 18 2007-2011, All Races, Both Sexes

https://www.cancer.gov/about-cancer/causes-prevention/risk/

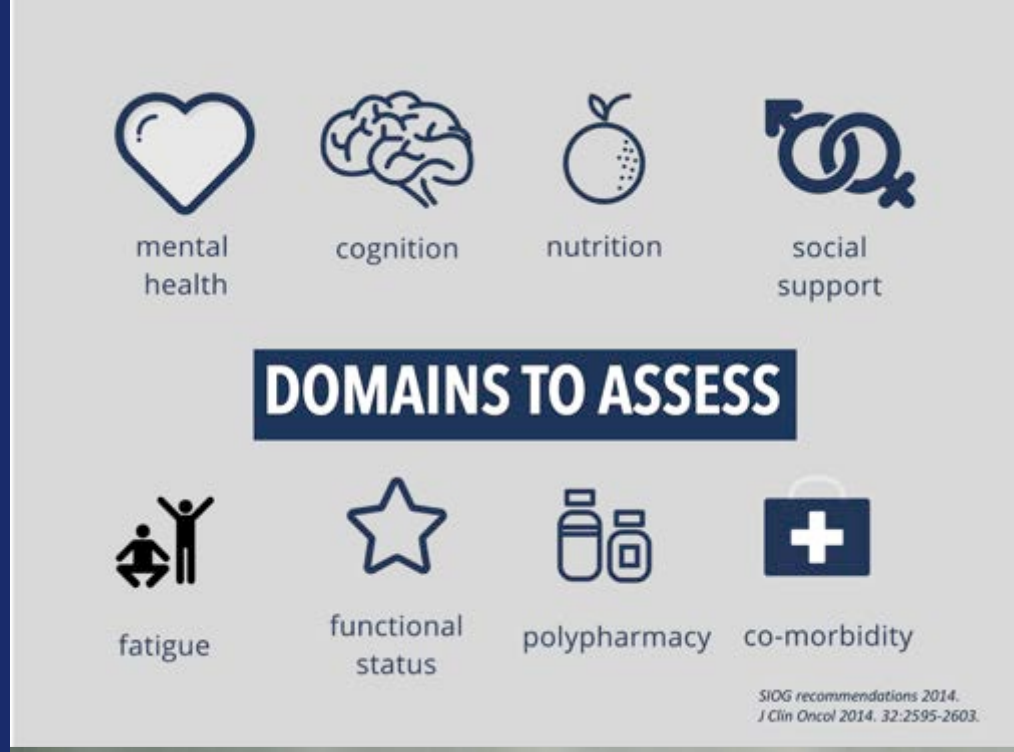
Source: AIHW Burden of Disease Database.

Figure 7.2: Cancer burden (DALY), by age and cancer type, 2011



Australian Institute of Health and Welfare 2017. Cancer in Australia 2017.


What is
GERIATRIC
ASSESSMENT?


mental health
cognition
nutrition
social support
DOMAINS TO ASSESS
fatigue
functional status
polypharmacy
co-morbidity
SIOG recommendations 2014.
J Clin Oncol 2014. 32:2595-2603.

EVIDENCE FOR GERIATRIC ASSESSMENT

IMPACT IN ONCOLOGY

01 **Identifies** deficits not otherwise detected.

02 **Optimizes** non-oncologic domains.

03 **Increases** the precision of prognostication.

04 **Influences** chemotherapy intensity.

05 **Improves** chemotherapy tolerance.

Slide courtesy of Camilla Wong

(Comprehensive) Geriatric Assessment

IMPACT IN ONCOLOGY

01 **Identifies** deficits not otherwise detected.

02 **Optimizes** non-oncologic domains.

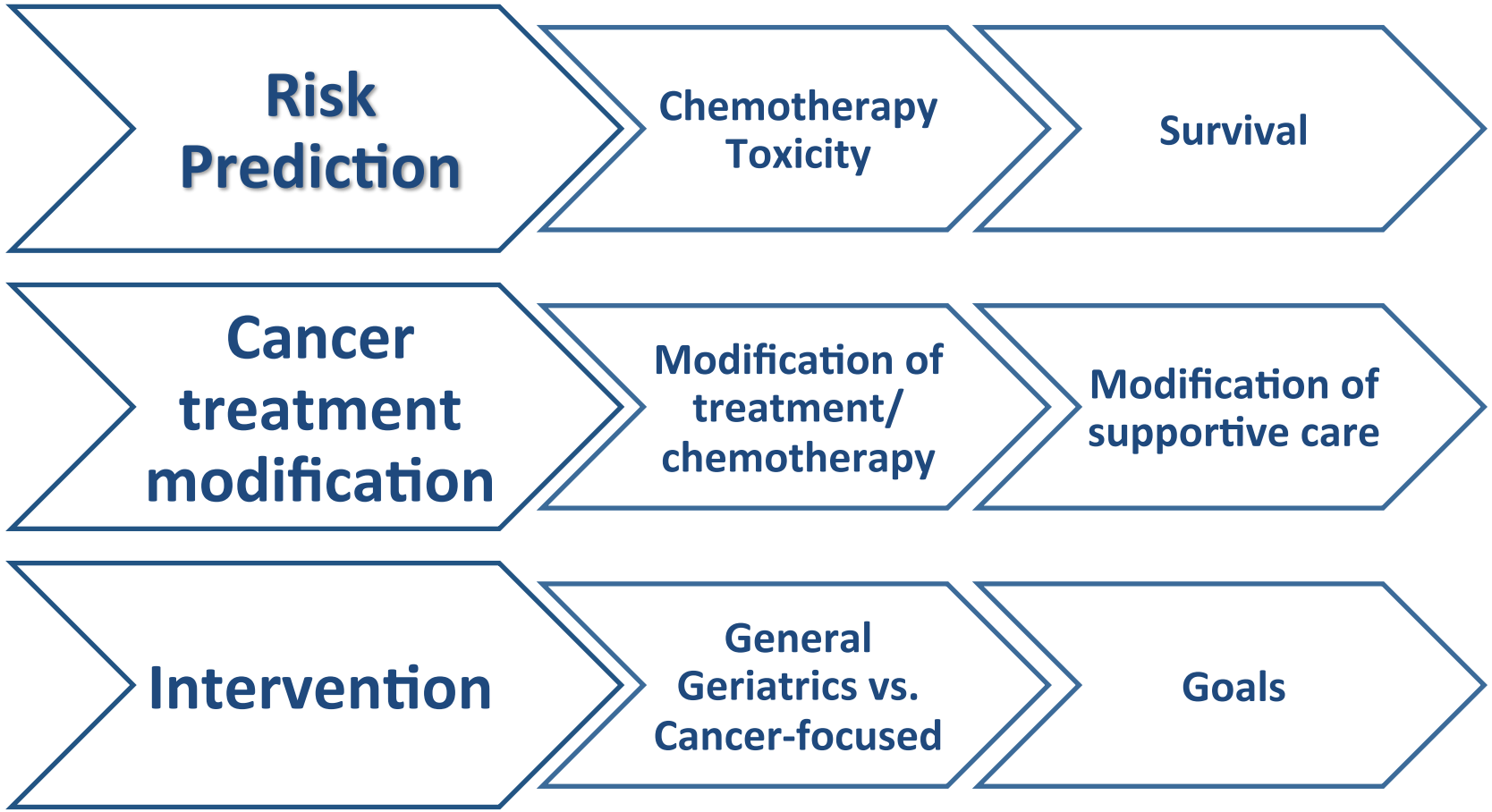
03 **Increases** the precision of prognostication.

04 **Influences** chemotherapy intensity.

05 **Improves** chemotherapy tolerance.

Slide courtesy of Camilla Wong

Utility of Comprehensive Geriatric Assessment in Older Adults with Cancer



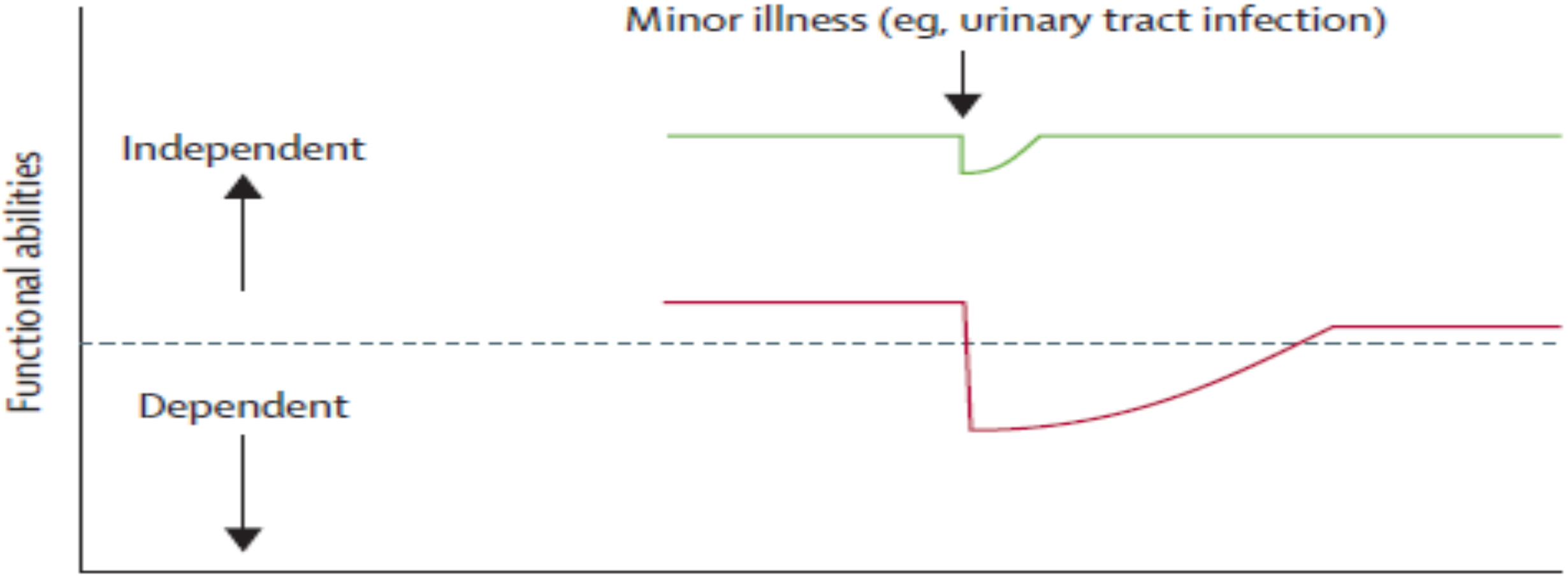
Slide courtesy of Tanya Wildes

Fit

Frail

FRAILTY

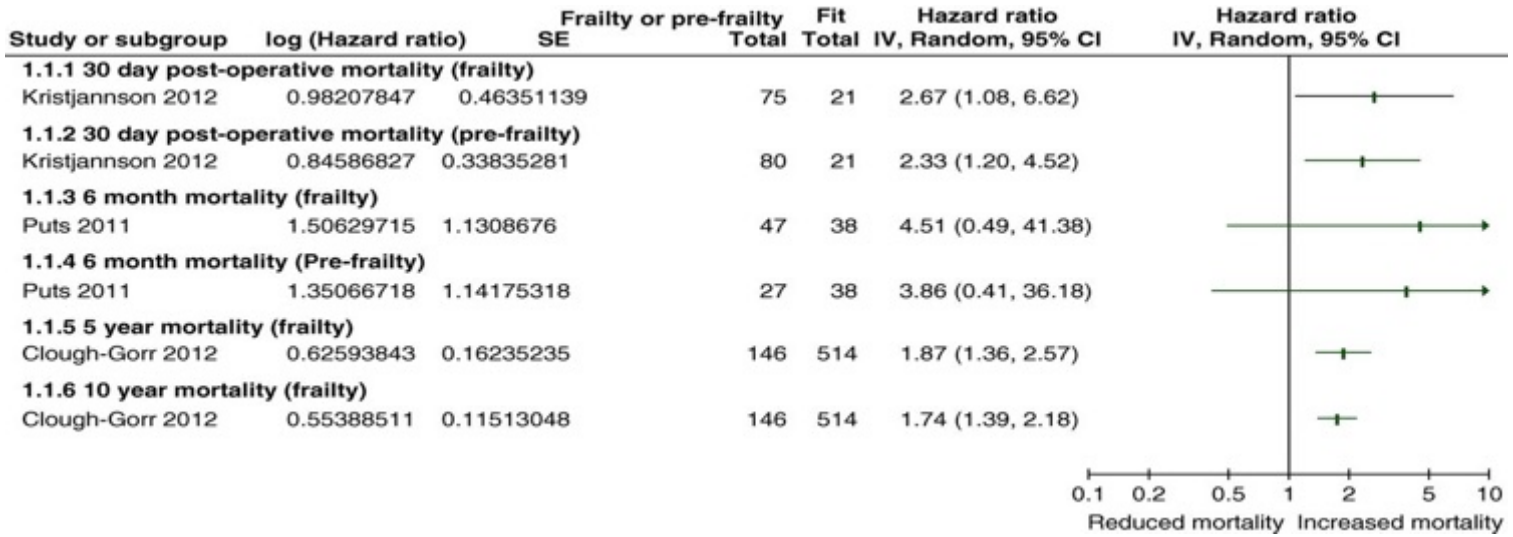
A STATE WITH HIGH VULNERABILITY TO ADVERSE HEALTH CARE OUTCOMES

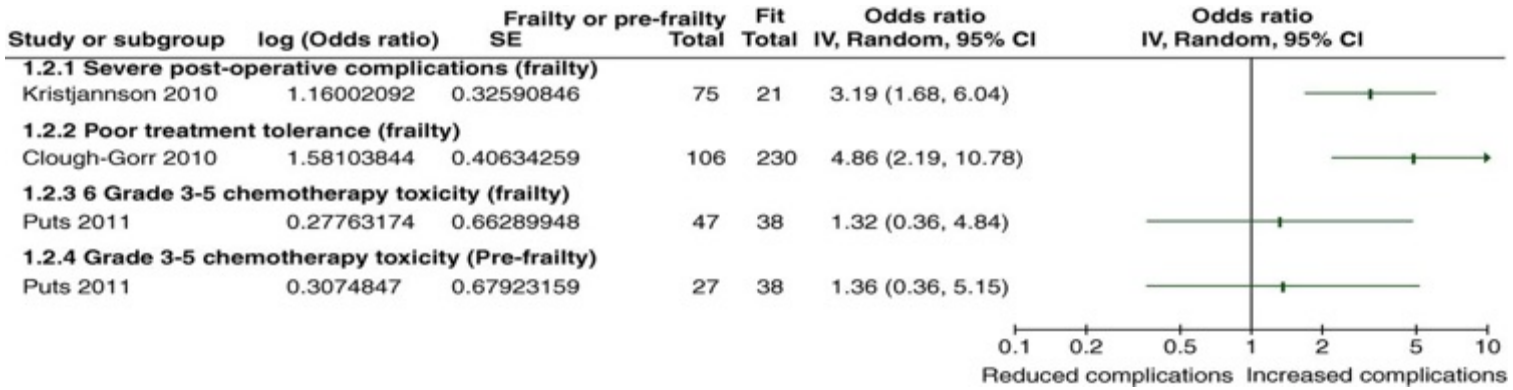


FRAILTY

A STATE WITH HIGH VULNERABILITY TO ADVERSE HEALTH CARE OUTCOMES

Slide courtesy of Camilla Wong





Ann Oncol. 2015;26(6):1091-101.

FRAILTY

IS ASSOCIATED WITH MORTALITY AND POOR TREATMENT TOLERANCE

PREDICTING TOXICITY

Cancer and Aging Research Group (CARG) Chemo-Toxicity Calculator
Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score

Risk Factor	Score
Age ≥ 72	2
GI or GU cancer	2
Chemotherapy dosing, standard dose	2
Polychemotherapy	2
Hemoglobin < 11 g/dL	3
CrCl (< 34 ml/min)	3
Hearing, fair or worse	2
≥ 1 fall in last 6 months	3
IADL: needs help with meds	1
Somewhat limited walking 1 block	2
Decreased social activity because of health	1

CARG Chemo-Toxicity Calculator

Geriatric variables increase the predictive precision

Slide courtesy of Camilla Wong

J Clin Oncol. 2011 Sep 1; 29(25): 3457–3465.


PREDICTION TOOL

Gender: Select

Patient's Age:

Patient's Height: Select Select

Patient's Weight: Select Select

Cancer Type: Choose

Dosage: Choose *

Number of chemotherapy agents: Choose

Hemoglobin: Select a value

How is your hearing (with a hearing aid, if needed)?: Choose

Number of falls in the past 6 months: Choose

Can you take your own medicines?: Choose

Does your health limit you in walking one block?: Choose

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?: Choose

Select Serum Creatinine: Choose

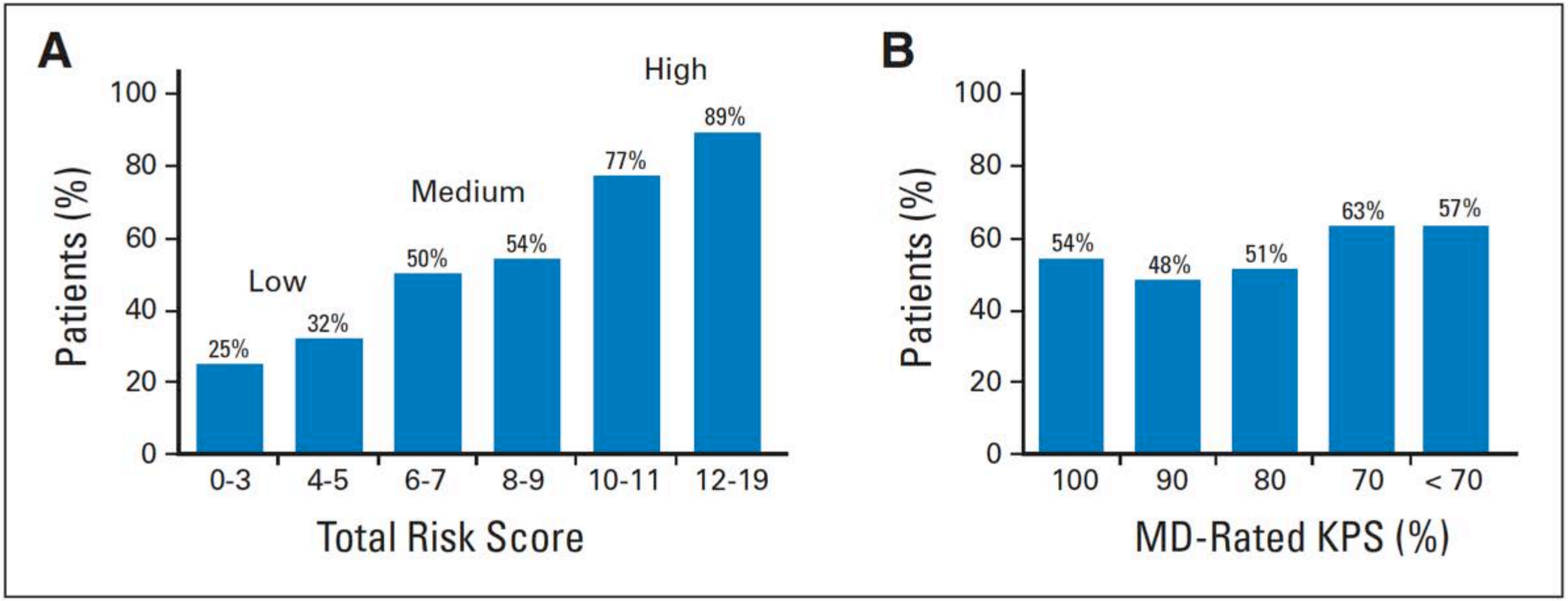
Creatinine Clearance: **

CARG Chemo-Toxicity Calculator

Geriatric variables increase the predictive precision

Slide courtesy of Camilla Wong

J Clin Oncol. 2011 Sep 1; 29(25): 3457–3465.



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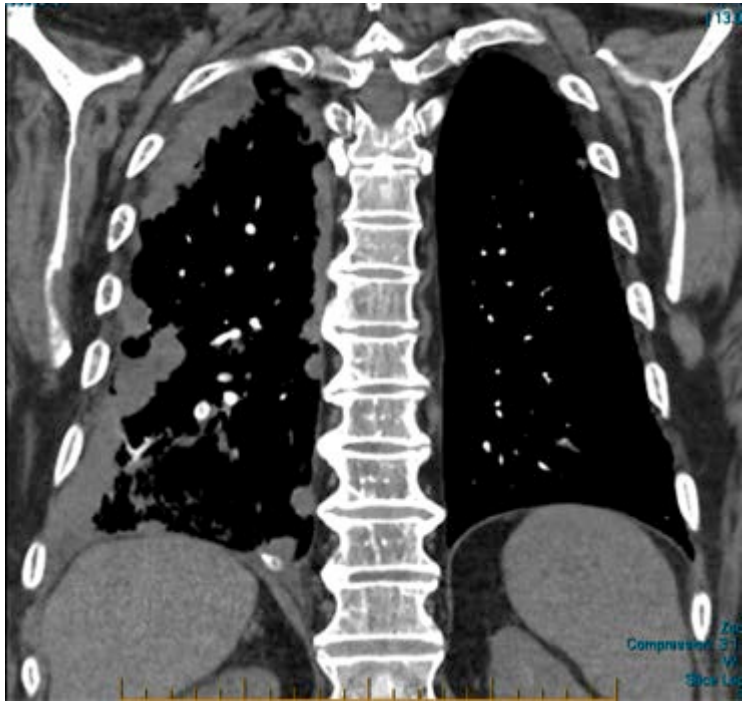
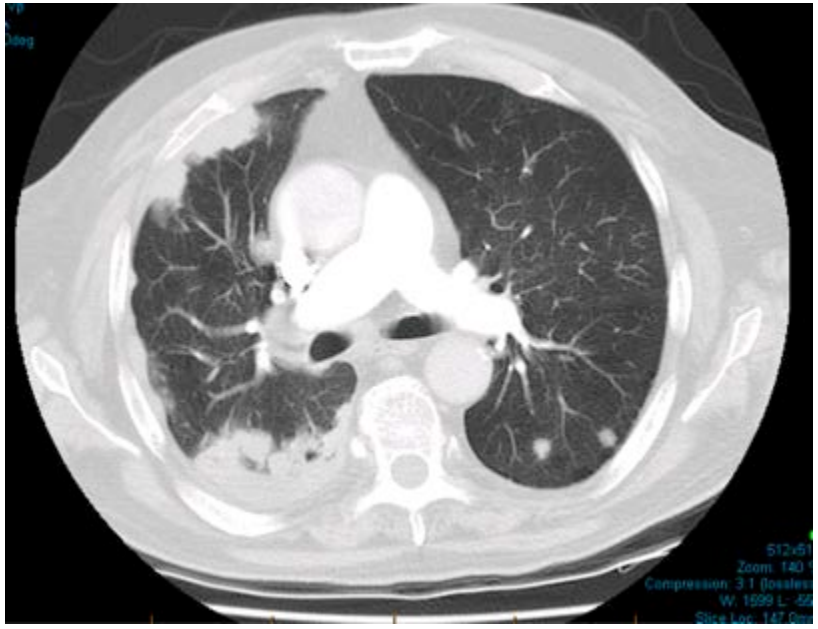




Mr PL

- 81yo
- Metastatic NSCLC
- Pleural effusion – failed VATS pleurodesis.
- TTF1+, EGFR WT, ALK -
- Lives at home with supportive wife
- Mobile but but needs to walk with frame.
- Recent falls

Mr PL

- Standard of care is combination platinum-based chemotherapy eg carboplatin gemcitabine or carboplatin and paclitaxel
- Single agent chemotherapy (eg gemcitabine or vinorelbine is an option)
- However, further testing reveals

PD-L1 = 100%

DIAGNOSIS:

Pleural biopsy: Poorly differentiated adenocarcinoma. in keeping with a lung primary.

SUPPLEMENTARY REPORT: (24/10/17)

The PD-L1 immunostain (Ventana, clone SP263) shows positive membranous staining in 100% of the tumour cells.

CARG Chemo-Toxicity Calculator

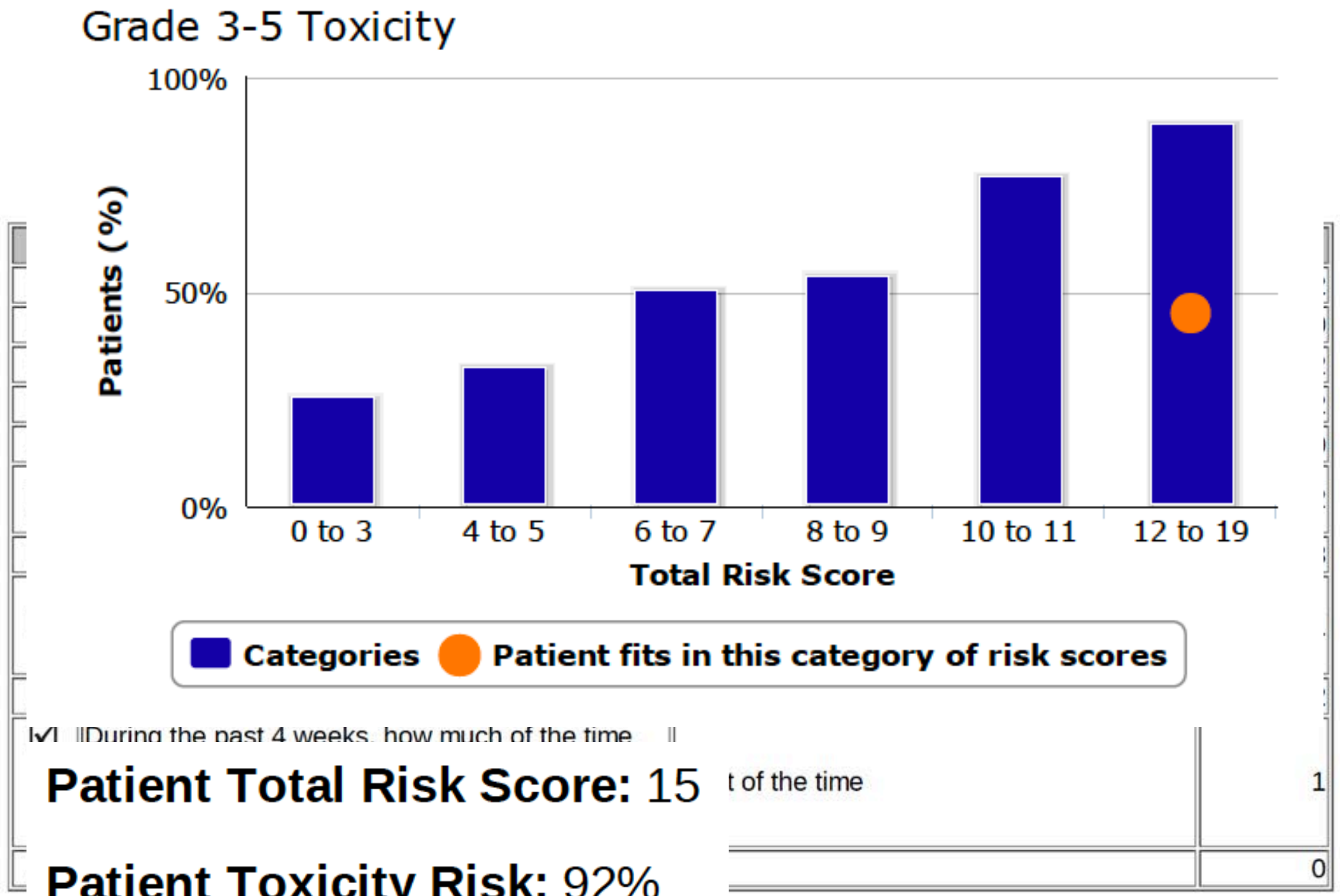
Geriatric variables increase the predictive precision

PREDICTION TOOL

Gender:	Male	
Patient's Age:	81	
Patient's Height:	Centimeters	167
Patient's Weight:	Kilograms	60
Cancer Type:	Other	
Dosage:	Standard dose *	
Number of chemotherapy agents:	Poly-chemo therapy	
Hemoglobin:	≥11 g/dL	
How is your hearing (with a hearing aid, if needed)?:	Fair	
Number of falls in the past 6 months:	1 or more	
Can you take your own medicines?:	With some help (able to take medicine if someone prepares it for you and/or reminds you	
Does your health limit you in walking one block?:	Limited a lot	
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?:	Most of the time	
Select Serum Creatinine:	0.7	
Creatinine Clearance:	70 **	
	Submit	
Toxicity Score:	15	
Risk of Chemotherapy Toxicity:	92%	
	What does this mean?	

* Dose delivered with first dose for chemotherapy

** Jeliffe formula


Grade 3-5 Toxicity
100%
50%
0%
Patients (%)
0 to 3
4 to 5
6 to 7
8 to 9
10 to 11
12 to 19
Total Risk Score
Categories
Patient fits in this category of risk scores
During the past 4 weeks, how much of the time
t of the time
1
0
Patient Total Risk Score: 15
Patient Toxicity Risk: 92%

VOLUME 34 · NUMBER 20 · JULY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer

Arti Hurria, Supriya Mohile, Ajeet Gajra, Heidi Klepin, Hyman Muss, Andrew Chapman, Tao Feng, David Smith, Can-Lan Sun, Nienke De Glas, Harvey Jay Cohen, Vani Katheria, Caroline Doan, Laura Zavala, Abrahm Levi, Chie Akiba, and William P. Tew

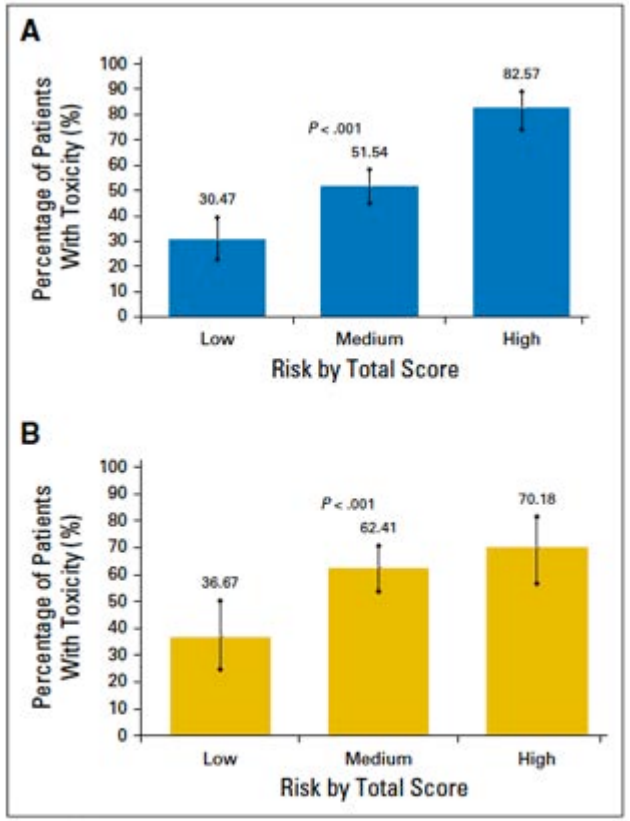


Fig 1. Risk strata versus toxicity percentage for the (A) development and (B) validation cohorts.

Table 1. Prediction Model and Scoring Algorithm for Chemotherapy Toxicity

Variable	Value/Response	Score
Age of patient	≥ 72 years	2
	< 72 years	0
Cancer type	GI or GU cancer	2
	Other cancer types	0
Planned chemotherapy dose	Standard dose	2
	Dose reduced upfront	0
Planned No. of chemotherapy drugs	Polychemotherapy	2
	Monochemotherapy	0
Hemoglobin	< 11 g/dL (male), < 10 g/dL (female)	3
	≥ 11 g/dL (male), ≥ 10 g/dL (female)	0
Creatinine clearance (Jeliffe, ideal weight)	< 34 mL/min	3
	≥ 34 mL/min	0
How is your hearing (with a hearing aid, if needed)?	Fair, poor, or totally deaf	2
	Excellent or good	0
No. of falls in the past 6 months	≥ 1	3
	None	0
Can you take your own medicine?	With some help/unable	1
	Without help	0
Does your health limit you in walking one block?	Somewhat limited/limited a lot	2
	Not limited at all	0
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?	Limited some of the time, most of the time, or all of the time	1
	Limited none of the time or a little of the time	0

NOTE. See Hurria et al.[2]
Abbreviation: GI, gastrointestinal; GU, genitourinary.

J Clin Oncol 34:2366-2371.

Available online at www.sciencedirect.com

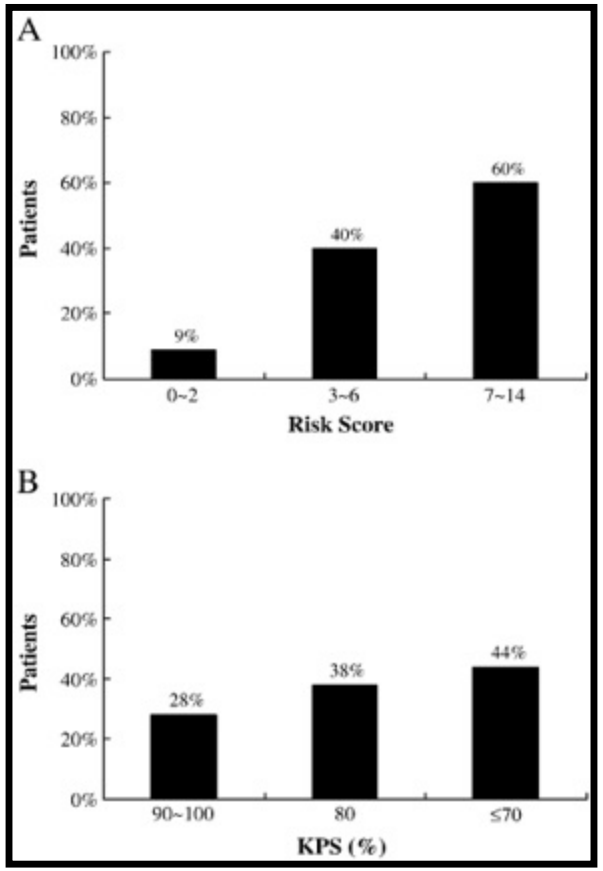
ScienceDirect

ELSEVIER

Predicting chemotherapy toxicity in older adults with lung cancer

*Xiaomeng Nie, Dan Liu, Qiang Li, Chong Bai**

Retrospective review
n = 120
Recruited over 12 months 2011-12.
Age ≥ 65 years
Scheduled to received chemotherapy



Risk score predicts grade 3-5 toxicity better than KPS in this retrospective review……..

- **But how do we use it in practice?**
- **What is the cut-off for combination therapy?**

Chemotherapy risk

Chemotherapy risk
0

Hematologic Risk Factors

Diastolic blood pressure
0

IADL
0

LDH
0

Non-Hematologic Risk Factors

ECOG PS
0

MMS
0

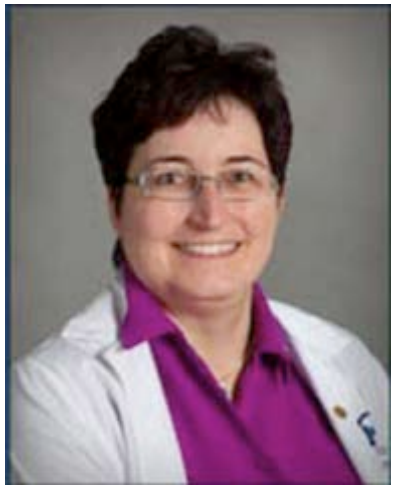
MNA
0

Submit

CRASH points (Regimens not listed should be scored by analogy)

0	1	2
Capecitabine 2g	Bendamustine +/- rituximab	5-FU/LV (Roswell-Park)
Cisplatin/pemetrexed	Capecitabine 2.5g	5-FU/LV (Mayo)
Dacarbazine	Carboplatin/gemcitabine AUC 4-6/1g d1,d8	5-FU/LV + bevacizumab
Docetaxel weekly	Carboplatin/pemetrexed	AC
FOLFIRI	Cisplatin/gemcitabine d1,8	CAF
Gemcitabine 1g 3/4 weeks	ECF	Carboplatin/docetaxel q3w Carboplatin/paclitaxel q3w
Gemcitabine 1.25g 3/4 weeks	Fludarabine	CHOP +/- rituximab
Paclitaxel weekly +/- trastuzumab	FOLFOX 85mg(e.g. FOLFOX4 or mFOLFOX6)	Cisplatin/docetaxel 75/75
Pemetrexed	Gemcitabine 7/8 weeks then 3/4	Cisplatin/etoposide
	Gemcitabine/irinotecan	Cisplatin/gemcitabine d1,8,15
	PEG doxorubicin 50mg q4w	Cisplatin/irinotecan q3w
	Topotecan weekly	Cisplatin/paclitaxel 135-24h q3w
	XELOX	CMF classic
		Docetaxel q3w
		Doxorubicin q3w

MOFFITT CANCER CENTER



https://www.moffitt.org/eforms/crashscoreform

CRASH Score

Geriatric variables increase the predictive precision

Cancer 2012;118:3377-86.

Predicting the Risk of Chemotherapy Toxicity in Older Patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score

Martine Extermann, MD[1]; Ivette Boler, ARNP[1]; Richard R. Reich, PhD[1,2]; Gary H. Lyman, MD[3]; Richard H. Brown, MD[4]; Joseph DeFelice, MD[5†]; Richard M. Levine, MD[6]; Eric T. Lubiner, MD[7]; Pablo Reyes, MD[8]; Frederic J. Schreiber III, MD[9]; and Lodovico Balducci, MD[1]

- n=518
- Patients ≥ 70 years (Mean age 75.5)
- Severe toxicity in 64% pts
- Grade 4 haem tox in 32%
- Grade 3-4 non haem tox in 56%

patient on chemotherapy. We demonstrated that patient differences contribute 2 to 3 times more than chemotherapy differences to the risk of toxicity. Our study con-

Cancer July 1, 2012

C CRASH tool

	Value	Score
Diastolic blood pressure (mm Hg)	>72	1
	≤72	0
IADL score	10–25	1
	26–29	0
LDH (μ/L)	>459	2
	0–459	0
ECOG PS	3–4	2
	1–2	1
	0	0
Mini Mental Status (cognition)	<30	2
	30	0
Mini Nutritional Assessment	<28	2
	28–30	0
Chemotox*	>0·57	2
	0·45–0·57	1
	0–0·44	0

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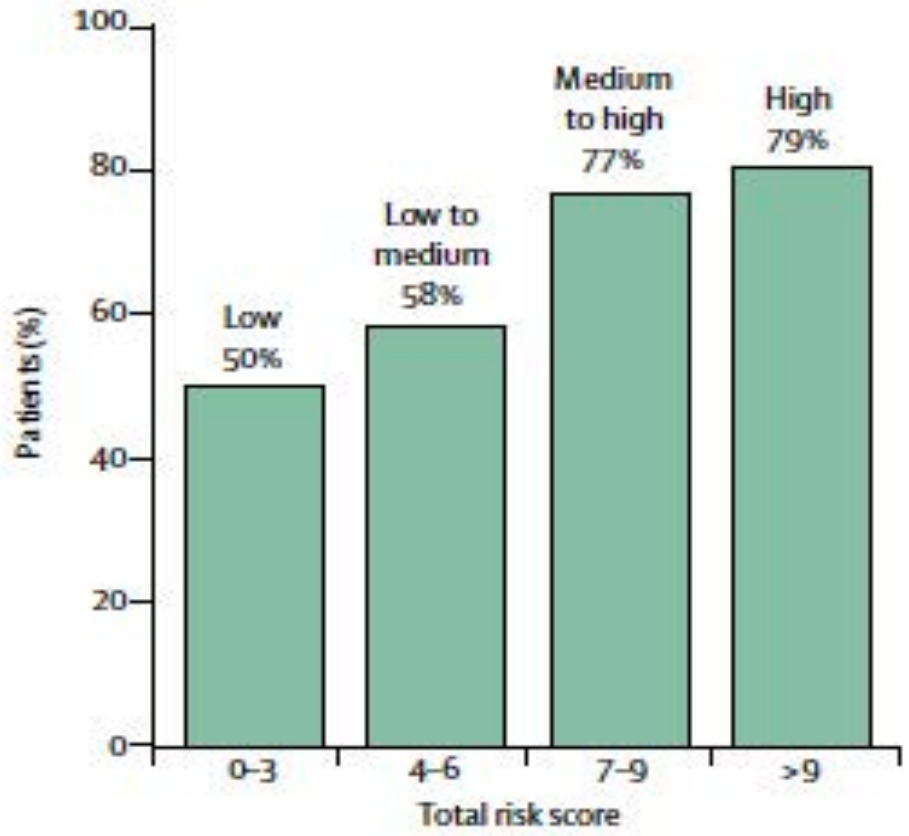


CRASH Score

Geriatric variables increase the predictive precision

Cancer 2012;118:3377-86.

Review article

Patient- and tumor-related predictors of chemotherapy intolerance in older patients with cancer: A systematic review

Doris L. van Abbema [a,b,1], Marjan van den Akker [c,d], Maryska L. Janssen-Heijnen [e,f], Franchette van den Berkmortel [g], Ann Hoeben [a], Judith de Vos-Geelen [a], Frank Buntinx [c,d], Jos Kleijnen [c], Vivianne C.G. Tjan-Heijnen [a,*]

Review of 30 articles from 27 studies in patients aged >65 years

Chemotherapy Intolerance

- Grade 3-5 toxicity
- Unplanned hospitalisation
- Chemotherapy discontinuation
- Chemotherapy dose reduction
- Functional Decline
- “Chemotherapy mortality"

J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.04.001

Review article

Patient- and tumor-related predictors of chemotherapy intolerance in older patients with cancer: A systematic review

Predictors of Toxicity

Patient-related factors

- > 1 fall in last 6 months
- Mobility problems
- Poor Performance Status
- Presence of severe comorbidities

Tumour related factors

- Certain chemotherapy regimens eg platinum, irinotecan
- “polychemotherapy vs monochemotherapy”

J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.04.001

Review article

Patient- and tumor-related predictors of chemotherapy intolerance in older patients with cancer: A systematic review

	Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) [28]	Cancer and Aging Research Group (CARG) [29]
Objective	To develop and validate a predictive score for older cancer patients receiving chemotherapy	To identify risk factors for chemotherapy toxicity in older cancer patients and develop a risk stratification score for chemotherapy toxicity
Setting	6 hospitals of the Moffitt Affiliate Research Network (USA)	7 outpatient oncology practices (USA)
Population	n = 518 (derivation cohort, $N = 331$; validation cohort, $N = 187$) Patients aged ≥70 years	$N = 500$ Patients aged ≥65 years, scheduled to receive a new chemotherapy cycles
Exclusion	Planned concomitant radiation therapy, dementia, and aplasia-inducing chemotherapy	No fluent English
Design	Prospective cohort study	Prospective cohort study
Measurement times	Patients were followed throughout the chemotherapy to a maximum of 1 month after the last cycle. If chemotherapy was continued beyond 6 months, follow-up was ended at 6 months.	
Predictors used	Demographics; nutrition; diastolic blood pressure; comorbid conditions; polypharmacy; quality of life; performance status; functional status; mood; tumor stage; bone marrow invasion; prior chemotherapy; tumor response; chemotherapy toxicity risk score; laboratory values	Age, cancer type, chemotherapy dose, number of chemotherapy agents, Karnofsky performance status, functional status, falls in the last 6 months, nutrition, chronic liver or kidney disease, hearing problems, housework, number of medications, decreased social activity because of health or emotional problems, limited social activity, laboratory values (white blood cell, red blood cell, hemoglobin, albumin)
Outcome measurement	Non-hematologic chemotherapy toxicity grades 3–4 and hematologic chemotherapy toxicity grade 4	Chemotherapy toxicity grades 3–5
Items in the instrument	Model for hematologic toxicity: diastolic blood pressure ≥72 mm Hg; impaired IADL; lactate dehydrogenase ≥0.74 times the upper limit of normal; MAX2 score Model for non-hematologic toxicity: poor performance status; impaired cognition; malnutrition or at risk for malnutrition; MAX2 score	Age ≥72 years; gastrointestinal or genitourinary cancer; standard chemotherapy dosing; polychemotherapy; hemoglobin <11 g/dL in male and <10 g/dL in female; creatinine clearance of 34 mL/min, hearing impairment; ≥1 falls in last 6 months; walking limited to 1 block; decreased social activity because of physical or emotional health; requiring some help in taking medications
Area under the ROC curve	ROC non-hematologic toxicity = 0.76; ROC hematologic toxicity = 0.66; ROC for hematologic toxicity and non-hematologic toxicity = 0.65	ROC = 0.72

J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.04.001

Prediction of treatment-related toxicity and outcome with geriatric assessment in elderly patients with solid malignancies treated with chemotherapy: a systematic review

K. S. Versteeg[1], I. R. Konings[1], A. M. Lagaay[2], A. A. van de Loosdrecht[3] & H. M. W. Verheul[1*]

[1]Department of Medical Oncology, VU University Medical Center, Amsterdam; [2]Department of Internal Medicine, Spaarne Hospital, Hoofddorp; [3]Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands

ANNALS OF ONCOLOGY

Geriatric assessment and chemotherapy toxicity

- 13/411 publications met criteria
- 49-64% of older patients experience ≥ grade 3 toxicity
- No consistency found amongst GA criteria for chemotherapy toxicity.

Toxicity due to

- Polychemotherapy
- Nutritional status
- Poor function
- Comorbidities

GA revealed new (unknown) geriatric issue in >50% patients

- Dose modification in 21-53% patients.

Annals of Oncology 25: 1914–1918, 2014

Prediction of treatment-related toxicity and outcome with geriatric assessment in elderly patients with solid malignancies treated with chemotherapy: a systematic review

ANNALS OF ONCOLOGY

Geriatric Assessment and chemotherapy toxicity

- 49-64% of older patients experience ≥ grade 3 toxicity
- But clinical value of these numbers is unclear as:
  1. Grade 3-4 haematological toxicity often not relevant
  2. Lower grade non-haematological toxicity is of clinical importance eg fatigue and neuropathy.

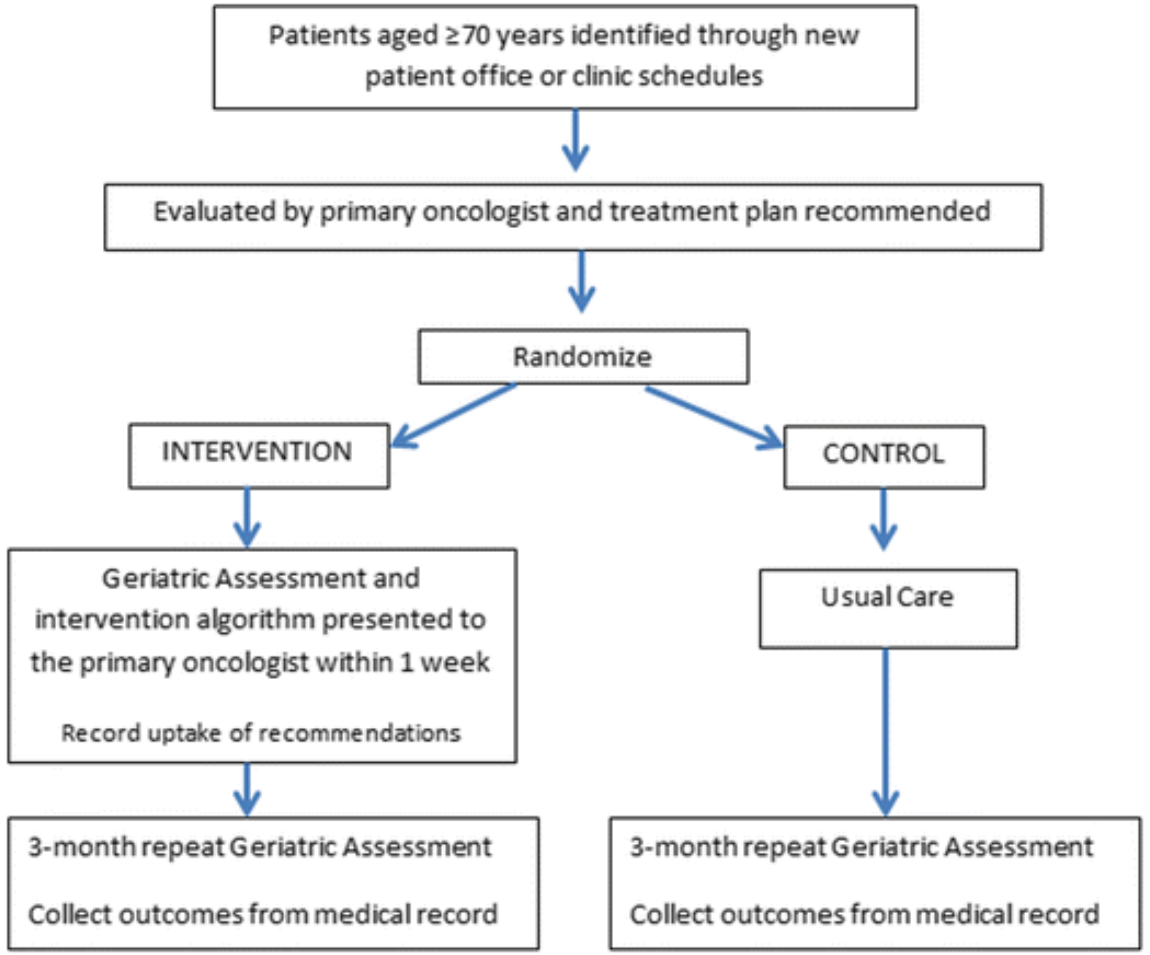
No consistency was found amongst geriatric assessment criteria for chemotherapy toxicity.

Annals of Oncology 25: 1914–1918, 2014

Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study

Allison Magnuson[1] · Tatyana Lemelman[2] · Chintan Pandya[1] · Molly Goodman[1] · Marcus Noel[1] · Mohammed Tejani[1] · David Doughtery[1] · William Dale[3] · Arti Hurria[4] · Michelle Janelsins[1] · Feng Vankee Lin[1] · Charles Heckler[1] · Supriya Mohile[1,5]

- 71 patients age >70yrs
- Multidimensional geriatric assessment
- Vulnerable population
  - 74% scoring impaired on the objective physical performance
  - 30% screening positive for cognitive impairment
  - 36% having > 3 comorbidities.



Support Care Cancer (2018) 26:605–613

Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study

Allison Magnuson[1] · Tatyana Lemelman[2] · Chintan Pandya[1] · Molly Goodman[1] · Marcus Noel[1] · Mohammed Tejani[1] · David Doughtery[1] · William Dale[3] · Arti Hurria[4] · Michelle Janelsins[1] · Feng Vankee Lin[1] · Charles Heckler[1] · Supriya Mohile[1,5]

- 71 patients age >70yrs
- Multidimensional geriatric assessment
- Including the CARG score
  for prediction of grade 3-5 toxicity
- Predicted toxicity of 58-60%
- Observed toxicity 57-61%

Toxicity based upon CARG chemotherapy score

The baseline CARG chemotherapy toxicity score was used to evaluate the likelihood of chemotherapy toxicity for each patient and averaged for each arm [9, 11]. The average CARG chemotherapy toxicity score for the usual care arm was 8.06, with a mean likelihood of toxicity of 58%. Compared to the anticipated toxicity of 58%, observed toxicity in the usual care arm was 61% ($p = 0.56$). The average CARG chemotherapy toxicity score for the intervention group was 8.78, with a mean likelihood of toxicity of 60%. Compared to the anticipated toxicity of 60%, observed toxicity in the intervention group was 57% ($p = 0.55$).

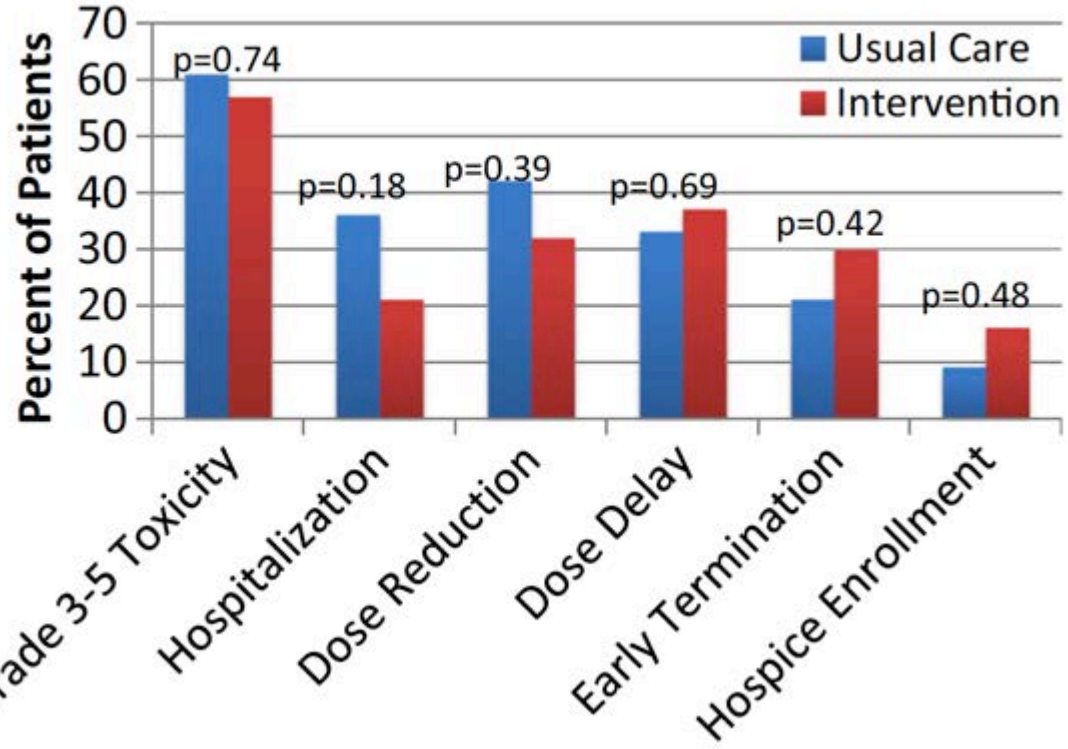
Support Care Cancer (2018) 26:605–613

Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study

Allison Magnuson[1] · Tatyana Lemelman[2] · Chintan Pandya[1] · Molly Goodman[1] · Marcus Noel[1] · Mohammed Tejani[1] · David Doughtery[1] · William Dale[3] · Arti Hurria[4] · Michelle Janelsins[1] · Feng Vankee Lin[1] · Charles Heckler[1] · Supriya Mohile[1,5]

Study underpowered to detect a difference between the 2 arms.

Uptake of guided interventions was 35.4%



Support Care Cancer (2018) 26:605–613

Predicting cumulative incidence of adverse events in older patients with cancer undergoing first-line palliative chemotherapy: Korean Cancer Study Group (KCSG) multicentre prospective study

Jin Won Kim[1], Yun-Gyoo Lee[2], In Gyu Hwang[3], Hong Suk Song[4], Su Jin Koh[5], Yoon Ho Ko[6], Seong Hoon Shin[7], In Sook Woo[8], Soojung Hong[9], Tae-Yong Kim[10], Sun Young Kim[11], Byung-Ho Nam[11], Hyun Jung Kim[12], Hyo Jung Kim[13], Myung Ah Lee[14], Jung Hye Kwon[15], Yong Sang Hong[16], Sung Hwa Bae[17], Dong-Hoe Koo[2], Kwang-Il Kim[1] and Jee Hyun Kim[1]

BJC British Journal of Cancer

British Journal of Cancer (2018) 118:1169–1175;

- Patients over the age of 70yrs with solid tumours
- N = 301
- Undergoing chemotherapy
- Geriatric assessment prior

Table 3. Common adverse events ≥ G3

Variable	*N* (%)
Haematologic adverse events, ≥G3	
Neutropaenia	85 (28.2)
Anaemia	35 (11.6)
Thrombocytopaenia	25 (8.3)
Febrile neutropaenia	13 (4.3)
Non-haematologic adverse events, ≥G3	
Fatigue	23 (7.6)
Anorexia	19 (6.3)
Abdominal pain	15 (5.0)
Nausea	14 (4.7)
Diarrhoea	10 (3.3)

Predicting cumulative incidence of adverse events in older patients with cancer undergoing first-line palliative chemotherapy: Korean Cancer Study Group (KCSG) multicentre prospective study

BJC British Journal of Cancer

British Journal of Cancer (2018) 118:1169–1175;

53.8% of patients experienced grade ≥ 3 toxicity.

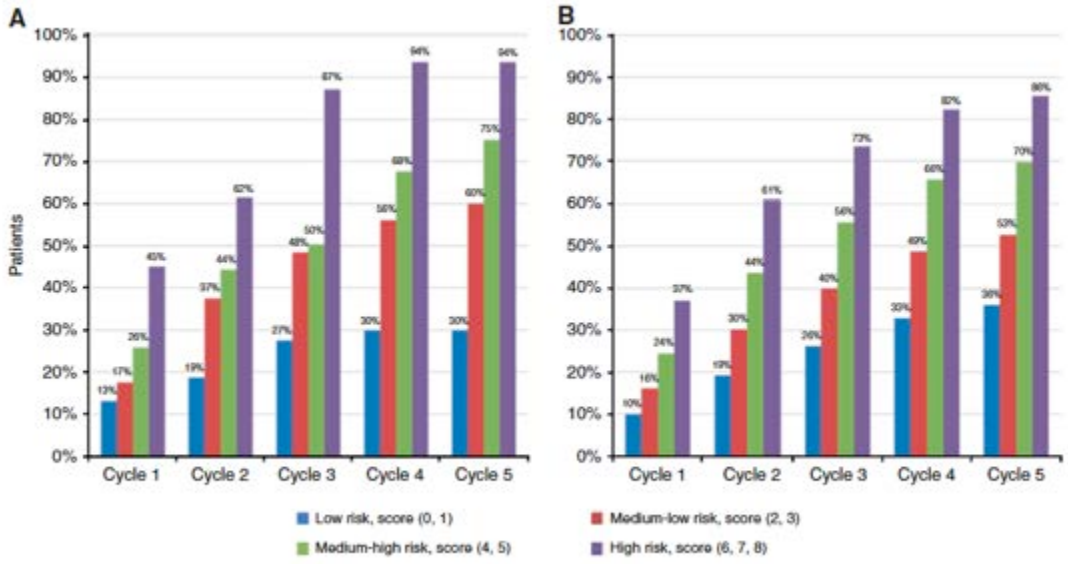


Fig. 1 Actual incidence (a) and predicted incidence (b) of adverse events ≥ G3 according to the risk group and cycle

Risk factors

- Serum protein <6.7g/dL
- Initial full dose chemotherapy
- Psychological stress or acute disease in last 3 months
- Water consumption <3 cups/day
- Unable to obey simple command
- Self perception of poor health

Chemotherapy Toxicity Risk Score for Treatment Decisions in Older Adults with Advanced Solid Tumors

TOMOHIRO F. NISHIJIMA,[a,b] ALLISON M. DEAL,[a] GRANT R. WILLIAMS,[c] HANNA K. SANOFF,[a,b] KIRSTEN A. NYROP,[a,b] HYMAN B. MUSS[a,b]
[a]Lineberger Comprehensive Cancer Center and [b]Department of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [c]Department of Medicine, Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, Alabama, USA

The Oncologist®

Chemotherapy Toxicity Risk Score (CTRS)

- n= 51 patients aged ≥65yrs
- Patients given chemotherapy (standard or reduced dose)
- Clinician blinded to result

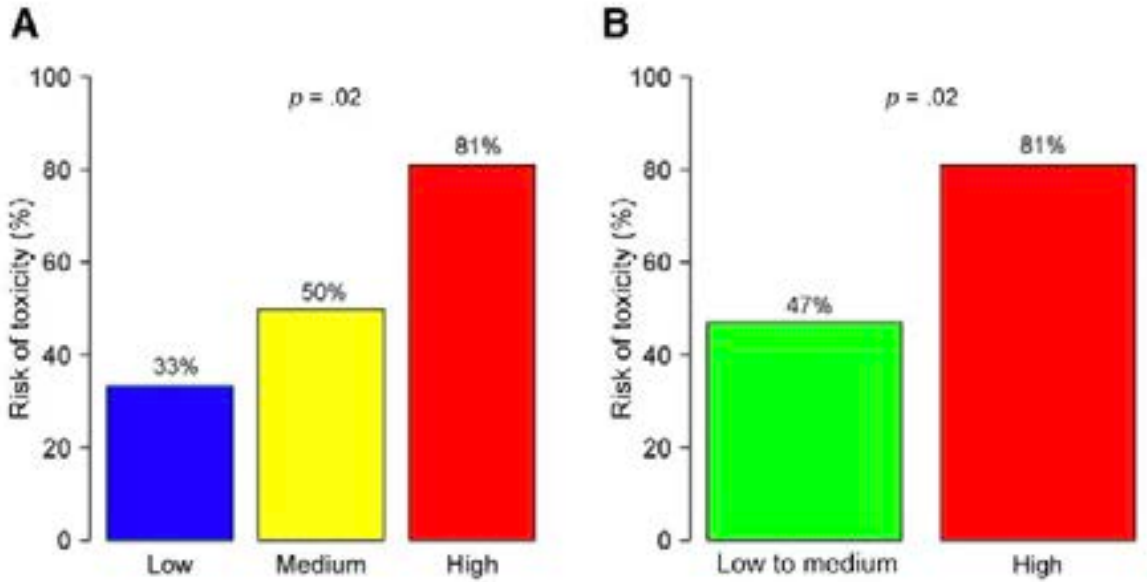


Figure 1. Ability of the chemotherapy toxicity risk score (CTRS) to predict chemotherapy toxicity. **(A)**: Three CTRS categories, low (0 to 5 points), medium (6 to 9 points), or high risk (10 to 19 points), versus toxicity risk. **(B)**: Two CTRS categories, low and medium risk combined (0 to 9 points) or high risk (10 to 19 points), versus toxicity risk.

The Oncologist®

Geriatric Oncology

Chemotherapy Toxicity Risk Score for Treatment Decisions in Older Adults with Advanced Solid Tumors

Tomohiro F. Nishijima,[a,b] Allison M. Deal,[a] Grant R. Williams,[c] Hanna K. Sanoff,[a,b] Kirsten A. Nyrop,[a,b] Hyman B. Muss[a,b]
[a]Lineberger Comprehensive Cancer Center and [b]Department of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [c]Department of Medicine, Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, Alabama, USA

CTRS ≥ 10 = high risk

CTRS < 10 = non-high risk

Table 5. Comparison of toxicity outcomes between concordant and discordant treatment decisions

Chemotherapy choice	Risk score	Gr 3–4 AEs, %	*p* value	Hospitalization, %	*p* value
Standard therapy	≥10 ($n = 16$)	***88***	***.006***	***50%***	***.03***
	<10 ($n = 20$)	***40***		***15%***	
Reduced therapy	≥10 ($n = 11$)	55	1.00	27%	1.00
	<10 ($n = 8$)	50		25%	

The bold-italic values show statistically significant differences ($p < .05$).
Abbreviations: AEs, adverse events; Gr, grade.

Life Expectancy

	Life Expectancy (years)	
Age	Men	Women
65	18.3	21.5
70	14.5	17.3
75	11.1	13.4
80	8.2	9.9
85	5.9	7.1

3302.0.55.001 - Life Tables, Australia, 2006

Latest ISSUE 09/11/2007

http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3302.0.55.001

Geriatric oncology 2

Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer

Enrique Soto-Perez-de-Celis, Daneng Li*, Yuan Yuan, Yat Ming Lau, Arti Hurria*

Norman Barrett - Barrett's esophagus

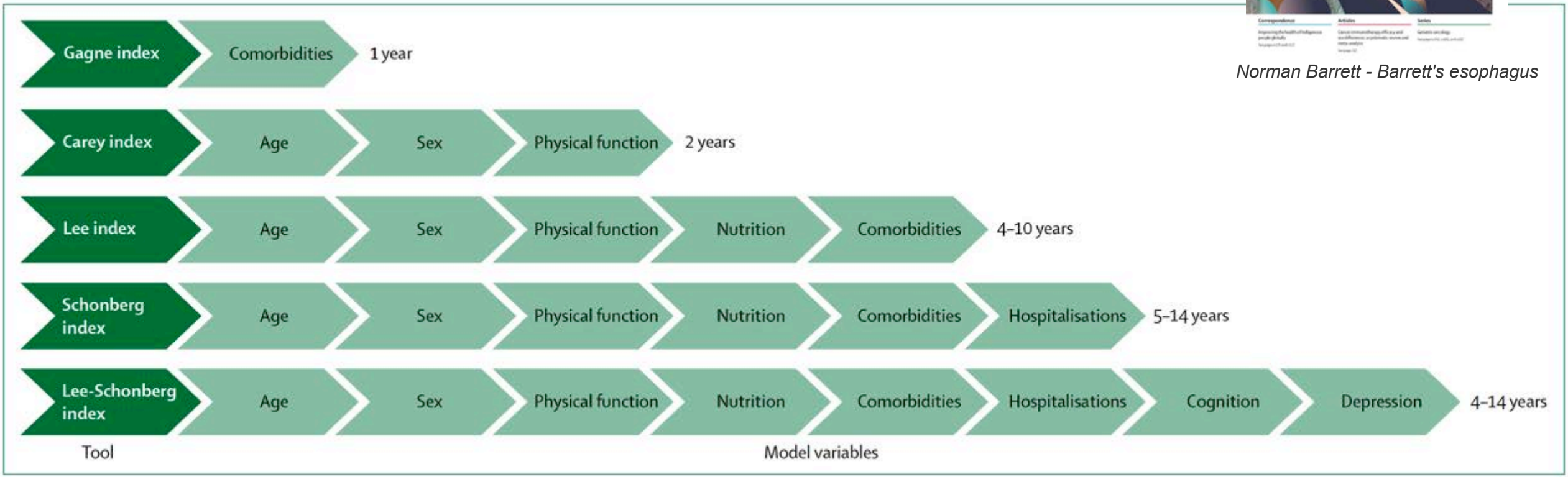


Figure 4: Selected life expectancy calculation tools for community-dwelling older people[68,69]

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ePrognosis

Estimating Prognosis for Elders

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Combined Lee Schonberg Index

- Population: Community dwelling adults aged 50 and older
- Outcome: All cause 4, 5, 10 and 14 year mortality

Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).

Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality)
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.

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Schonberg Scale: 11 items

- Age
- Sex
- Smoking
- BMI
- Prior cancer
- Diabetes
- COPD
- **Hospitalizations in the past 12 mths**
- **Self-rated health**
- **Dependent in 1+ IADL**
- **Difficulty walking a few blocks (1/4 mile)**

J Gen Intern Med 24(10):1115–22

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Mortality Risk for Schonberg Index

Points	Risk of FIVE YEAR mortality	Risk of TEN YEAR mortality	Risk of FOURTEEN YEAR mortality
0 - 1	<3%	5 - 11%	19 - 21%
2 - 3	3 - 6%	9 - 12%	19 - 24%
4 - 5	7 - 8%	15 - 21%	27 - 36%
6 - 7	10 - 12%	26 - 37%	42 - 52%
8 - 9	17 - 27%	37 - 44%	42 - 52%
10 - 11	26 - 29%	53 - 60	74 - 78%
12 - 13	37 - 41%	60 - 68	81 - 83%
14 - 15	47 - 52%	74 - 76	87 - 88%
16 - 17	60 - 61%	86 - 87	100%
≥17	70%	92%	100%

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Non-chemotherapy?

VOLUME 26 · NUMBER 8 · MARCH 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Nomograms to Predict Serious Adverse Events in Phase II Clinical Trials of Molecularly Targeted Agents

Gregory R. Pond, Lillian L. Siu, Malcolm Moore, Amit Oza, Hal W. Hirte, Eric Winquist, Glenwood Goss, Gary Hudes, and Carol A. Townsley

Q: What are the risks of serious adverse events in patients on treatment that is not chemotherapy?

- MTA's – Molecularly Targeted Agents

(NB This is 2008 so *pre-immunotherapy)*

J Clin Oncol 26:1324-1330.

VOLUME 26 · NUMBER 8 · MARCH 10 2008

JOURNAL OF CLINICAL ONCOLOGY

MTA's

EGFR inhibitors

VEGFR inhibitors

Proteosome inhibitors

Cyclin dependent kinases

RAF, multikinases

mTOR

J Clin Oncol 26:1324-1330.

Table 1. List of MTAs

Trial No.	MTA	Target
002	Erlotinib/cisplatin	Epidermal growth factor receptor
003	Erlotinib	Epidermal growth factor receptor
005	UCN-01/topotecan	Cyclin-dependent kinases
007	Tipifarnib	Farnesyl protein transferase
009	Imatinib mesylate	C-Kit, BCR-ABL, PDGFR, multikinases
011	Oblimersen sodium/ doxorubicin	Bcl-2
012	Bortezomib	Proteasome
014	Perifosine	Cellular membranes, Akt
015	Perifosine	Cellular membranes, Akt
017	GTI-2040/docetaxel	Ribonucleotide reductase R2 component
018	Bortezomib	Proteasome
019	UCN-01/topotecan	Cyclin-dependent kinases
021	Temsirolimus	mTOR
023	Triapine/gemcitabine	Ribonucleotide reductase
024	GTI-2040/docetaxel	Ribonucleotide reductase R2 component
025	Sorafenib/gemcitabine	Raf, VEGFR, multikinases
028	Lapatinib	Epidermal growth factor receptor, HER2
030	Lapatinib	Epidermal growth factor receptor, HER2
031	Ispinesib	Mitotic kinesin spindle protein
032	UCN-01/topotecan	Cyclin-dependent kinases
036	Sorafenib	Raf, VEGFR, multikinases
037	AZD2171	VEGFR, multikinases
038	AZD2171	VEGFR, multikinases
039	AZD2171	VEGFR, multikinases
040	Vorinostat	Histone deacetylases
042	Sorafenib/erlotinib	Raf, VEGFR, multikinases; epidermal growth factor receptor
BAY-HN	Sorafenib	Raf, VEGFR, multikinases

Nomograms to Predict Serious Adverse Events in Phase II Clinical Trials of Molecularly Targeted Agents

Predictors

- ECOG
- Age
- Comorbidities
- LDH
- Albumin
- Disease burden
- Creatinine (not CrCl?)
- BSA = dose?

Table 3. Predictors via Multivariate Analysis of Cycle 1 Dose-Limiting Toxicities

	Odds Ratio	95% CI	*P*
Predictors of all SAEs			
ECOG performance status	1.91	1.36 to 2.69	< .001
Age/10-year increase	0.90	0.78 to 1.05	.181
Charlson score	1.18	0.94 to 1.49	.158
Prior radiotherapy	0.79	0.56 to 1.11	.176
No. of target lesions	1.06	0.98 to 1.14	.161
log (LDH ULN)	1.39	1.03 to 1.88	.030
Albumin ULN	0.13	0.02 to 0.93	.043
Predictors of attributable SAEs			
ECOG performance status	1.37	1.01 to 1.88	.046
Body-surface area	0.27	0.10 to 0.70	.007
Charlson score	1.20	0.98 to 1.48	.079
Prior radiotherapy	0.72	0.46 to 1.14	.164
log (LDH ULN)	1.23	0.93 to 1.63	.152
Creatinine ULN	2.91	1.14 to 7.44	.026
No. of prior systemic chemotherapy regimens	1.21	0.91 to 1.60	.184

J Clin Oncol 26:1324-1330.

Nomograms to Predict Serious Adverse Events in Phase II Clinical Trials of Molecularly Targeted Agents

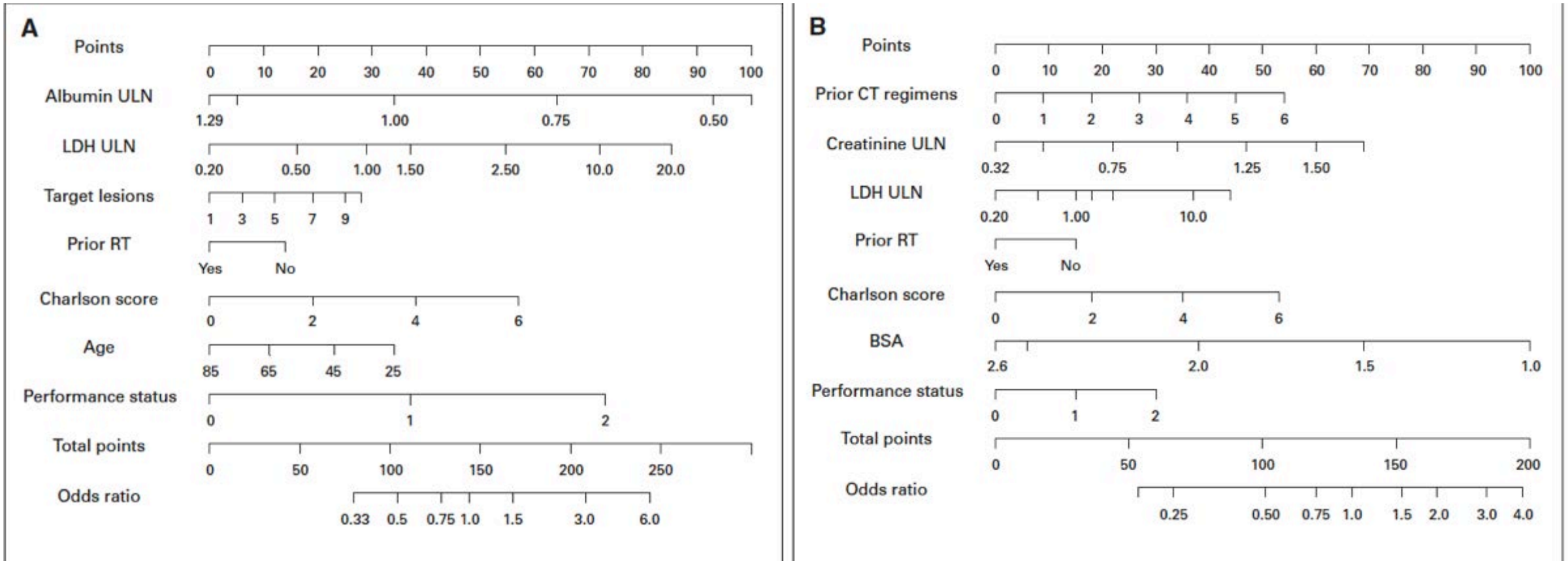


Fig 1. (A) Nomogram for predicting any serious adverse event during cycle 1. (B) Nomogram for predicting any attributable serious adverse event during cycle. Abbreviations: ULN, upper limit of normal; LDH, lactate dehydrogenase; RT, radiation therapy; BSA, body-surface area.

J Clin Oncol 26:1324-1330.

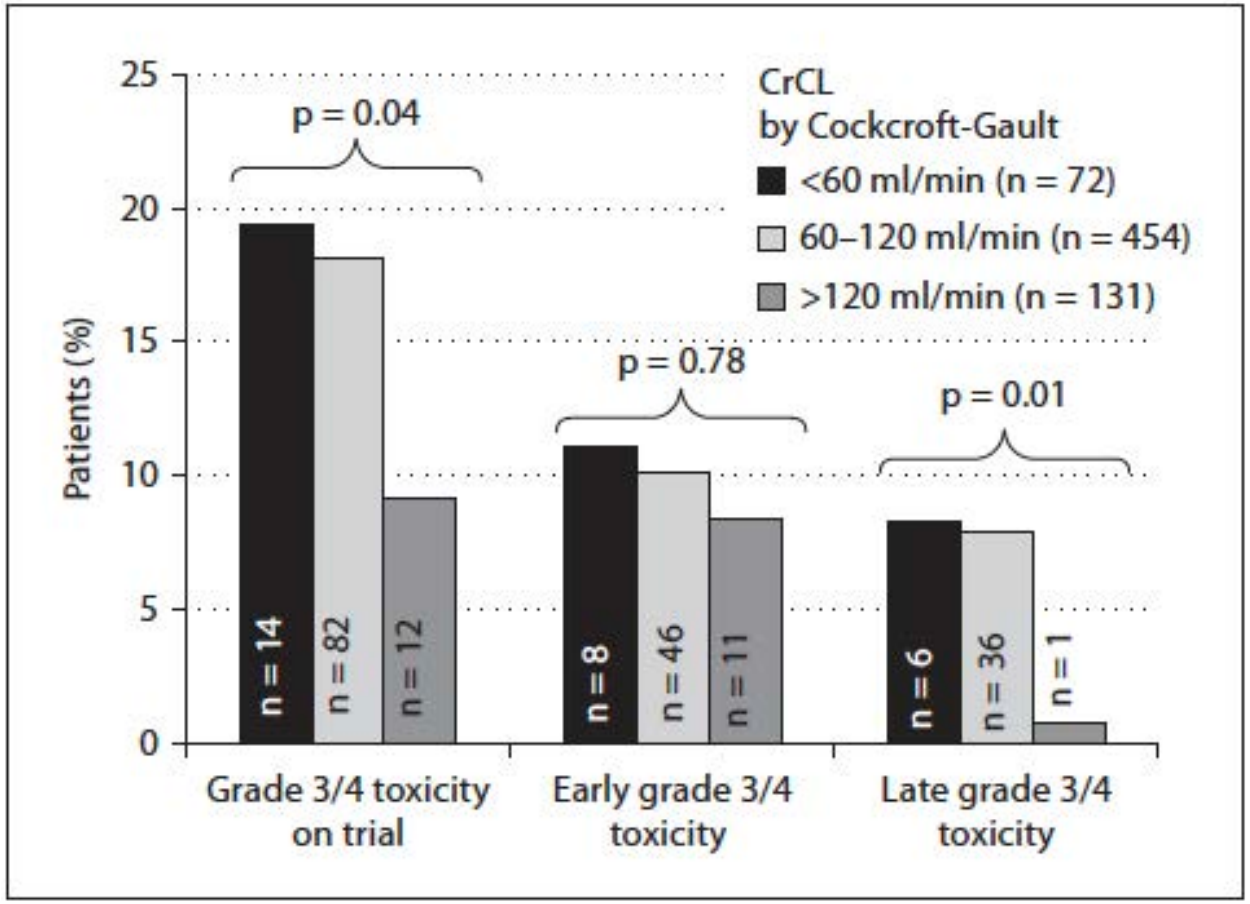
Creatinine Clearance Is Associated with Toxicity from Molecularly Targeted Agents in Phase I Trials

B. Basu[a] J. Vitfell-Pedersen[a] V. Moreno Garcia[a] M. Puglisi[a] A. Tjokrowidjaja[a]
K. Shah[a] S. Malvankar[a] B. Anghan[a] J.S. de Bono[a, b] S.B. Kaye[a, b] L.R. Molife[a]
U. Banerji[a, b]

Lower CrCl associated with increased grade 3/4 toxicities of MTA's in phase 1 trials

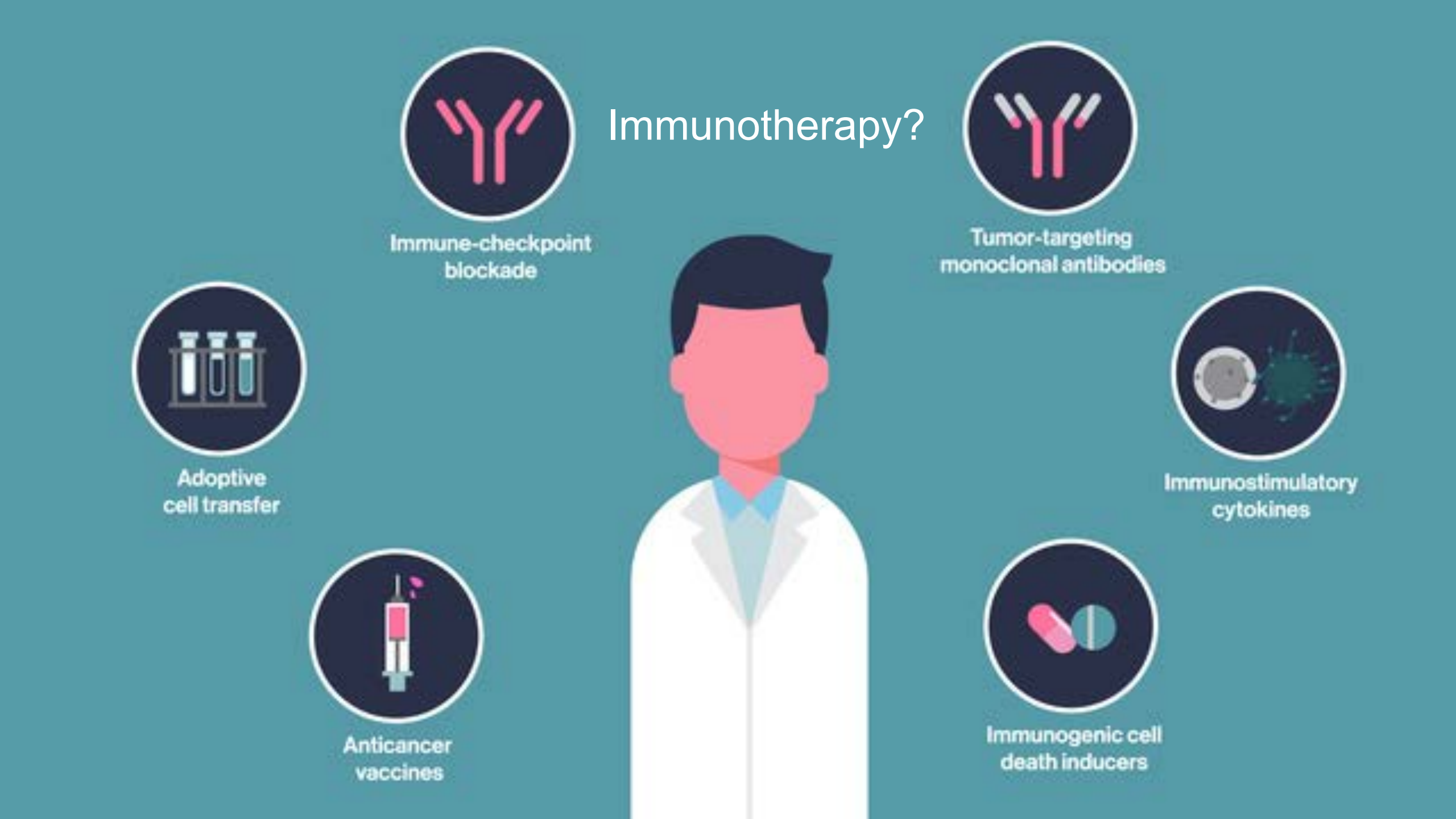
Table 2. Phase I trial agents

Target	Number of trials	Number of patients (% of total)	Early toxicity (% of target)	Late toxicity (% of target)
Cell cycle and apoptosis	6	53 (7)	5 (9)	3 (6)
Chromatin remodelling	8	97 (13)	13 (13)	6 (6)
Anti-sense	2	3 (1)	0	1 (33)
Cytoplasmic signalling protein	9	123 (17)	18 (15)	9 (7)
DNA repair	3	71 (10)	3 (4)	4 (6)
Growth factor receptors	14	206 (29)	21 (10)	13 (6)
Oncolytic virus	5	41 (6)	6 (15)	1 (2)
Protein folding and degradation	4	29 (4)	3 (10)	2 (7)
Anti-angiogenic/vascular	4	24 (3)	1 (4)	2 (8)
Other	4	75 (10)	2 (3)	3 (4)



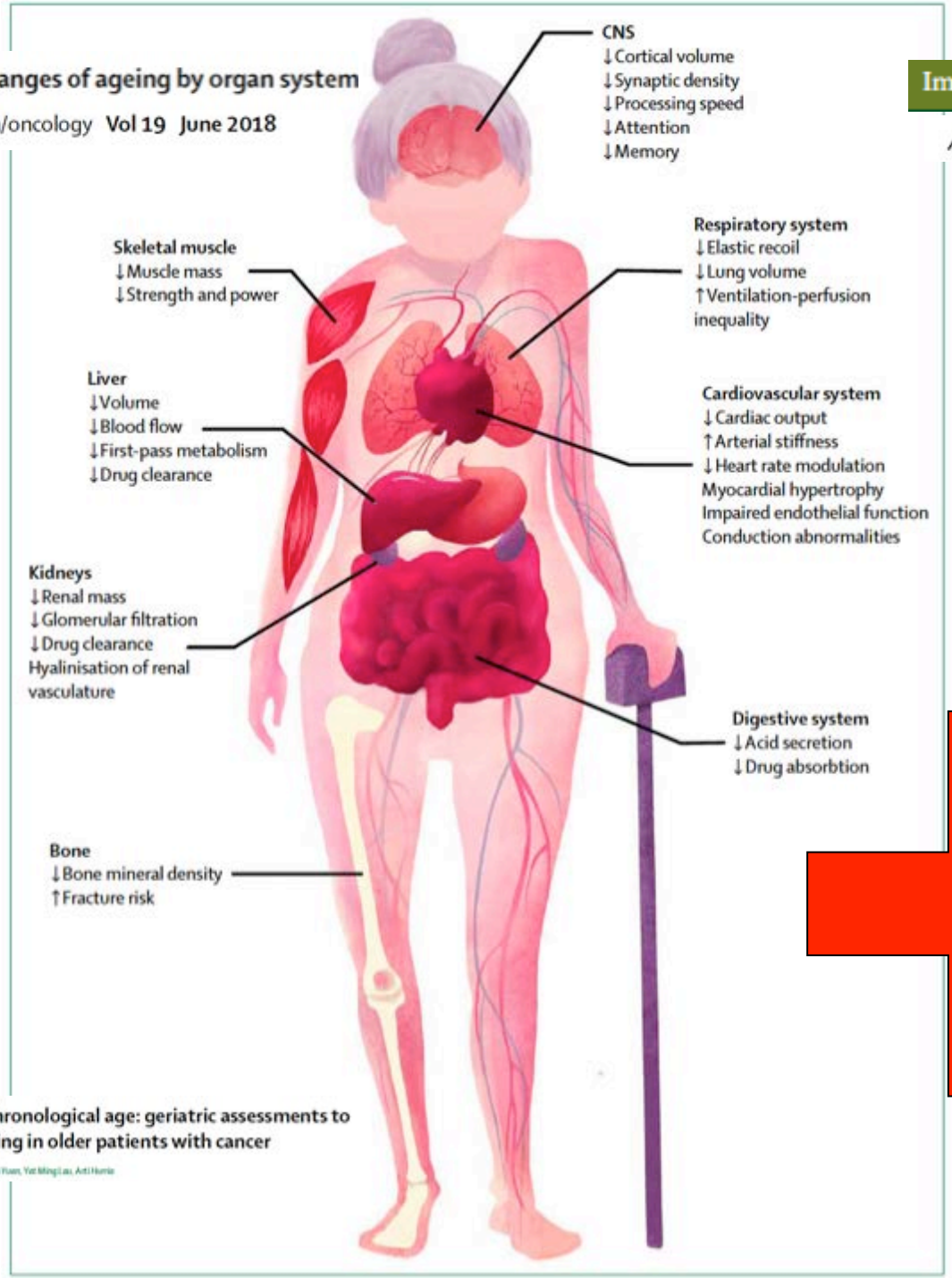
Oncology 2012;83:177–182

Immunotherapy?



Physiological changes of ageing by organ system

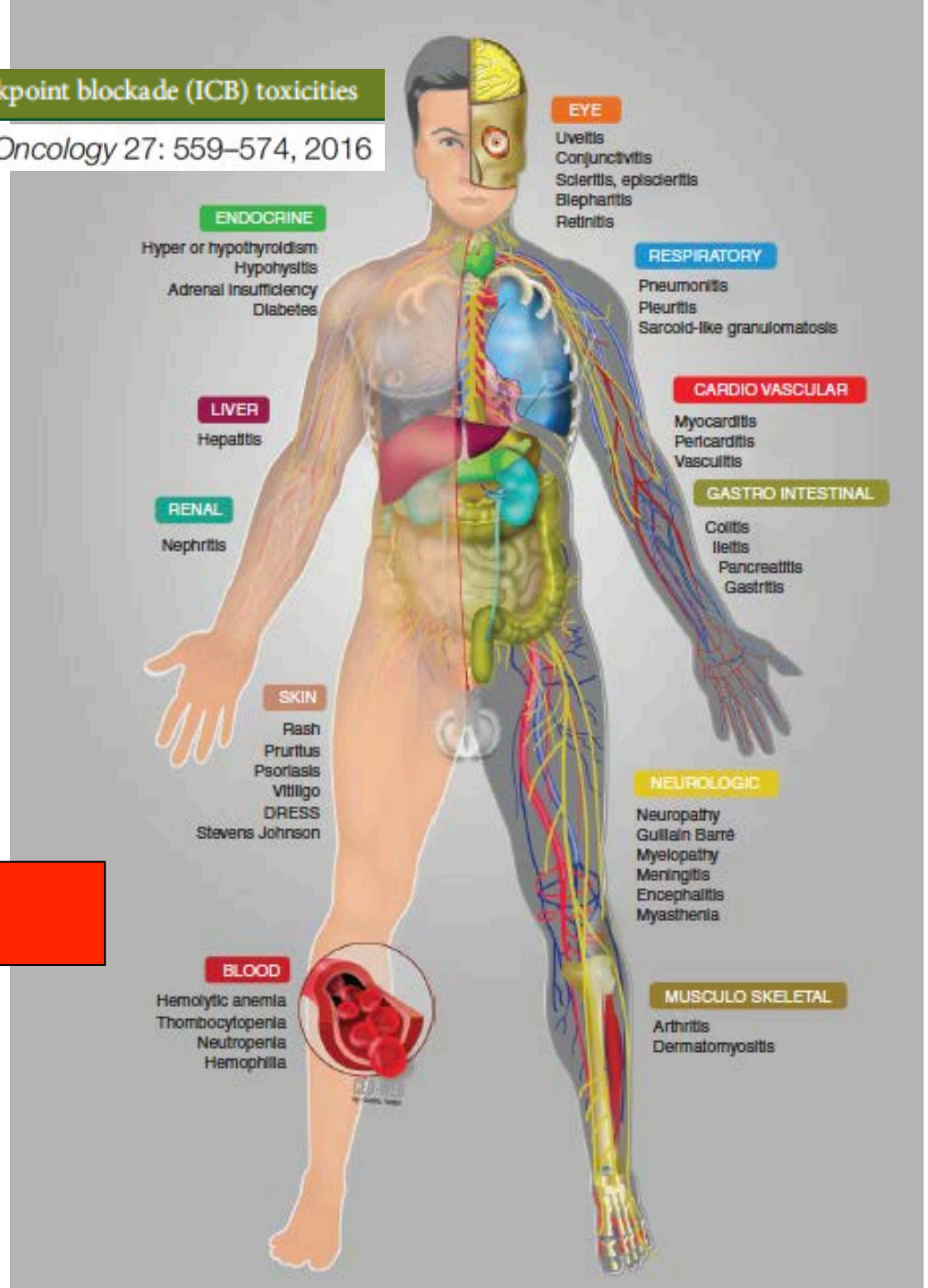
www.thelancet.com/oncology **Vol 19 June 2018**



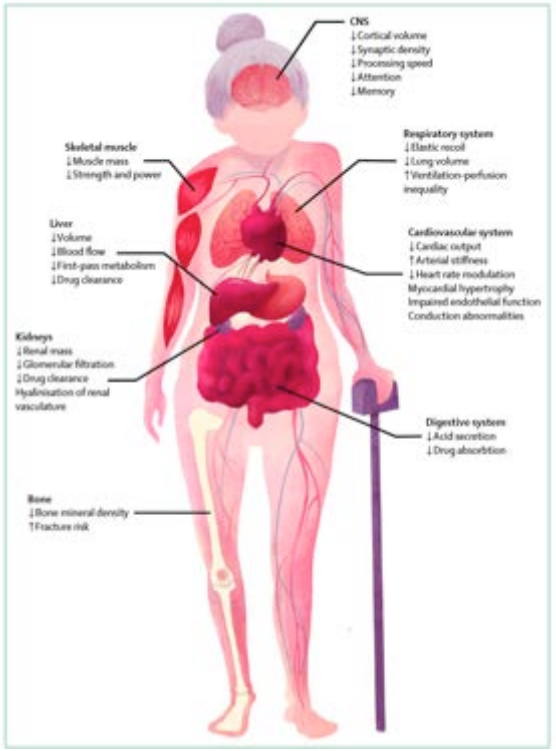
Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer

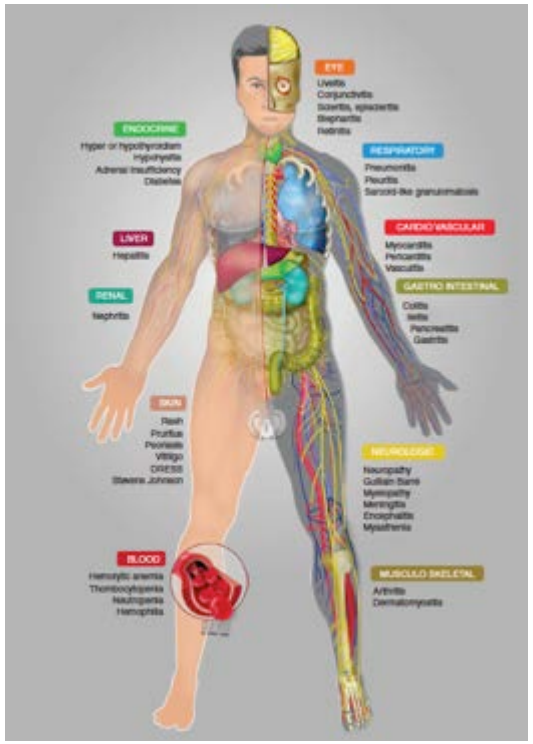
Immune checkpoint blockade (ICB) toxicities

Annals of Oncology 27: 559–574, 2016



Immunotherapy in older adults with cancer





Decreased functional reserve

Autoimmunity

Decreased ability to cope with toxicity

Not necessarily increased incidence of autoimmunity

Autoimmune disease and ipilumumab

Research

Original Investigation

Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Douglas B. Johnson, MD; Ryan J. Sullivan, MD; Patrick A. Ott, MD, PhD; Matteo S. Carlino, MBBS; Nikhil I. Khushalani, MD; Fei Ye, PhD; Alexander Guminski, MD, PhD; Igor Puzanov, MD; Donald P. Lawrence, MD; Elizabeth I. Buchbinder, MD; Tejaswi Mudigonda, BS; Kristen Spencer, DO; Carolin Bender, MD; Jenny Lee, MBBS; Howard L. Kaufman, MD; Alexander M. Menzies, MBBS; Jessica C. Hassel, MD; Janice M. Mehnert, MD; Jeffrey A. Sosman, MD; Georgina V. Long, MBBS; Joseph I. Clark, MD

Johnson DB, et al. JAMA Oncol. 2016;2(2):234-40.

AID and ipilimumab

Characteristic	No. (%)[a] (N = 30)
Age, median (range), y	59.5 (30-80)
Autoimmune disorder[b]	
Rheumatoid arthritis	6 (20)
Psoriasis	5 (17)
Multiple sclerosis	2 (7)
Crohn disease or ulcerative colitis	6 (20)
Systemic lupus erythematosus	2 (7)
Thyroiditis	3 (10)
Sarcoidosis	2 (7)
Other	7 (23)
Prior systemic therapies for autoimmune disorder	
Any	22 (73)
Corticosteroid	10 (33)
Disease-modifying antirheumatic	13 (43)
Ongoing therapies	
Steroids	6 (20)
Other	7 (23)
Time since autoimmune diagnosis, median (range), y	13.5 (0.25-60)

- 27% AID flare
- 33% conventional irAEs
- Toxicities resolved quickly with standard Rx
- Several patients with IBD had low-grade flares, responded to steroids
- ORR 20%

Johnson DB, et al. JAMA Oncol. 2016;2(2):234-40.

AID and PD-1 inhibitors

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 368–376, 2017
doi:10.1093/annonc/mdw443
Published online 29 September 2016

ORIGINAL ARTICLE

Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab

A. M. Menzies[1,2*], D. B. Johnson[3], S. Ramanujam[1], V. G. Atkinson[4], A. N. M. Wong[5], J. J. Park[6], J. L. McQuade[7], A. N. Shoushtari[8], K. K. Tsai[9], Z. Eroglu[10], O. Klein[11], J. C. Hassel[12], J. A. Sosman[3], A. Guminski[1,2], R. J. Sullivan[13], A. Ribas[14], M. S. Carlino[1,6], M. A. Davies[7], S. K. Sandhu[5] & G. V. Long[1,2]

European Journal of Cancer 75 (2017) 24–32

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity

Ralf Gutzmer [a,*], Anika Koop [a], Friedegund Meier [b], Jessica C. Hassel [c], Patrick Terheyden [d], Lisa Zimmer [e], Lucie Heinzerling [f], Selma Ugurel [e], Claudia Pföhler [g], Anja Gesierich [h], Elisabeth Livingstone [e], Imke Satzger [a], Katharina C. Kähler [i], for the German Dermatooncology Group (DeCOG)

Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab

N = 52

AI disorder[a]		
Rheumatologic	27 (52%)	RA 13, sarcoidosis 3, PMR 3, SLE 2, scleroderma 2, psoriatic arthritis 2, Sjogren's 2
Dermatologic	8 (15%)	psoriasis 6, eczema, erythema nodosum
Gastrointestinal	6 (12%)	CD 3, UC with colectomy 2, celiac disease 1
Neurologic	5 (10%)	GBS 2, CIDP 1, MG 1, Bell's palsy 1
Endocrine	4 (8%)	Graves' disease 4
Respiratory	2 (4%)	Asthma 2 (1 severe on long-term oral steroids)
Hematologic	2 (4%)	ITP 2
Activity of AI disorder at PD1 start		
Not clinically active	37 (71%)	
Clinically active	15 (29%)	11 rheumatologic (RA 5, psoriatic arthritis 2, Sjogrens 2, sarcoidosis 1, PMR 1), 3 psoriasis, 1 severe asthma
Treatment of AI disorder at PD1 start		
No immunosuppresion	32 (62%)	
Corticosteroids	9 (17%)	
Steroid-sparing agent	5 (10%)	Mesalamine 2, leflunomide, hydroxychloroquine, apremilast
Steroids and SSAs	5 (10%)	Sulfasalazine, leflunomide, hydroxychloroquine, methotrexate, ibuprofen
IVIG	1 (2%)	

Menzies AM et al. Ann Oncol. 2017;28(2):368-76.

European Journal of Cancer 75 (2017) 24–32

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity

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N=19

Gutzmer R et al. Eur J Cancer. 2017;75:24-32.

Melanoma Institute Australia

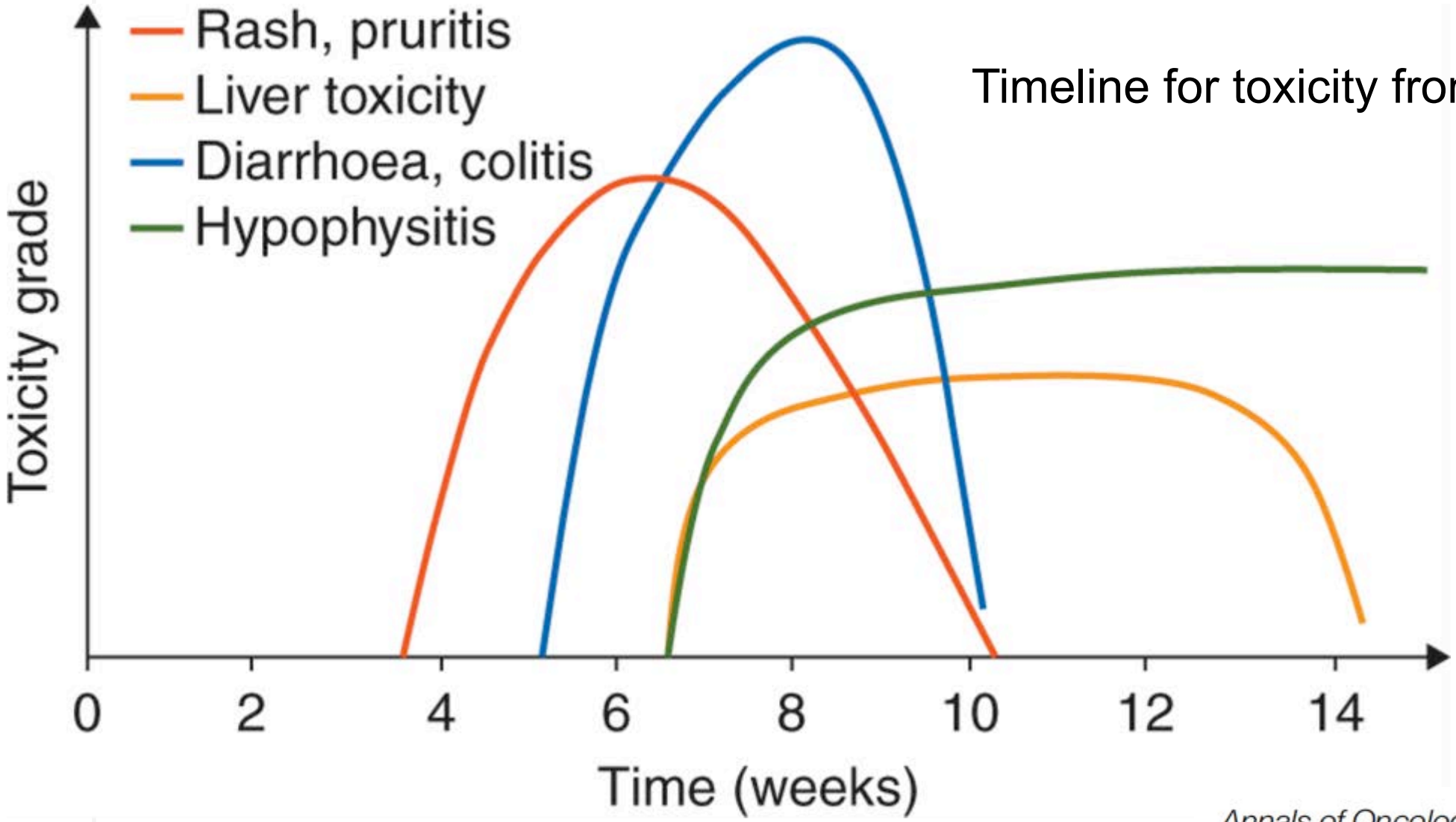
71/m/N	Psoriasis vulgaris	None
64/m/P	Psoriasis vulgaris	Topical steroids and vitamin D analogues
53/m/P	1) Psoriasis vulgaris 2) Ankylosing spondylitis	Methotrexate, Prednisolone, Etanercept
38/m/N	Spondylarthropathy	None
75/m/N	Polymyalgia rheumatica	Prednisolone
54/m/P	Myositis	None
39/m/P	Rheumatoid arthritis	Prednisolone
62/f/N	1) Seronegative rheumatoid spondylarthritis, 2) Autoimmune thyroiditis	1) None 2) L-thyroxine
68/f/N	Autoimmune thyroiditis	L-thyroxine
45/f/N	Autoimmune thyroiditis	L-thyroxine
52/f/N	Autoimmune thyroiditis	L-thyroxine
39/f/N	Autoimmune thyroiditis	L-thyroxine
51/f/P	Autoimmune thyroiditis	L-thyroxine
47/f/N	Sarcoidosis	None
76/m/N	Sarcoidosis	None
59/f/N	Multiple sclerosis	None
64/f/P	Guillain–Barré-Syndrome	None
51/f/N	Ulcerative colitis	Sulfasalazine, Budesonide
68/m/P	Churg Strauss vasculitis	Prednisolone

AID and PD-1 inhibitors

	Menzies et al.	Gutzmer et al.
N.	52	19
Active	29%	n/a
On IS	38%	32%
Flare (discontinuation)	38% (4%)	42% (0)
Other irAEs (discontinuation)	29% (8%)	16% (0)
ORR	33%	32%

- Rheumatologic, skin conditions flare often (~50%). GI, neuro seldom.
- More likely to flare if AID active or on IS at PD1 start
- Lower ORR if on IS at PD1 start

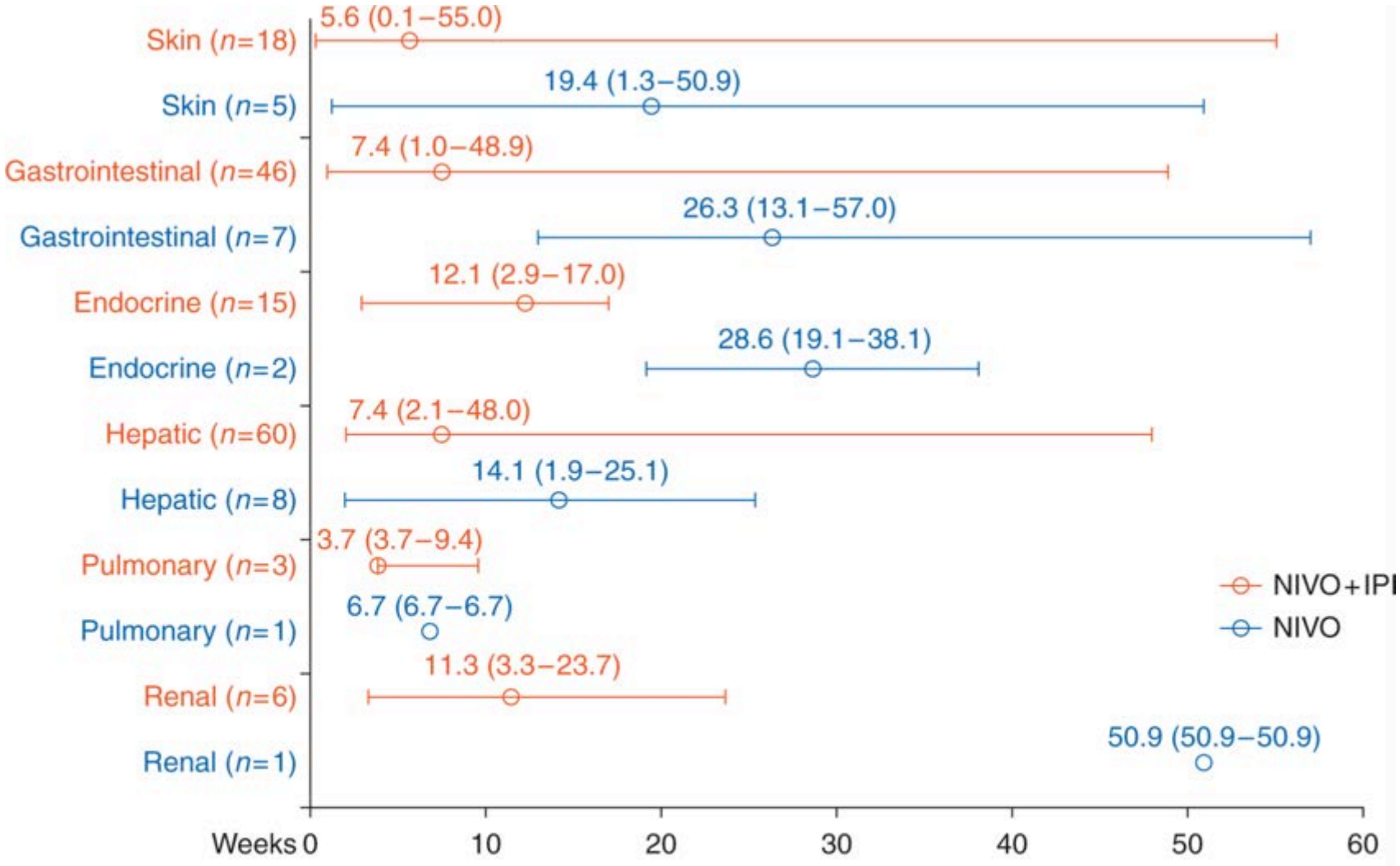
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



Timeline for toxicity from ipilimumab

Annals of Oncology 27: 559–574, 2016

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



Circles represent medians; bars signify ranges

Combination ipilimumab + nivolumab:

Single agent nivolumab:

Annals of Oncology 27: 559–574, 2016

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SIOG 2017 ANNUAL CONFERENCE

SIOG Annual Conference - November 09-11, 2017

SIOG 2018 ADVANCED COURSE

The **2018 edition of the SIOG Avanced Course** will


Supportive care in cancer.
Which bridge would you
rather cross?
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