MODIFYING CHEMOTHERAPY FOR THE OLDER PATIENT

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SIOG INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY | YOUNG SIOG

DISCLOSURE

- No conflicts of interest.

OUTLINE

- Introduction
- Challenges specific to older patients
- Specific malignancies
  - Breast cancer
  - Non-small cell lung cancer
  - Colon cancer
  - Lymphoma
- CGA and chemotherapy toxicity prediction
- Conclusions

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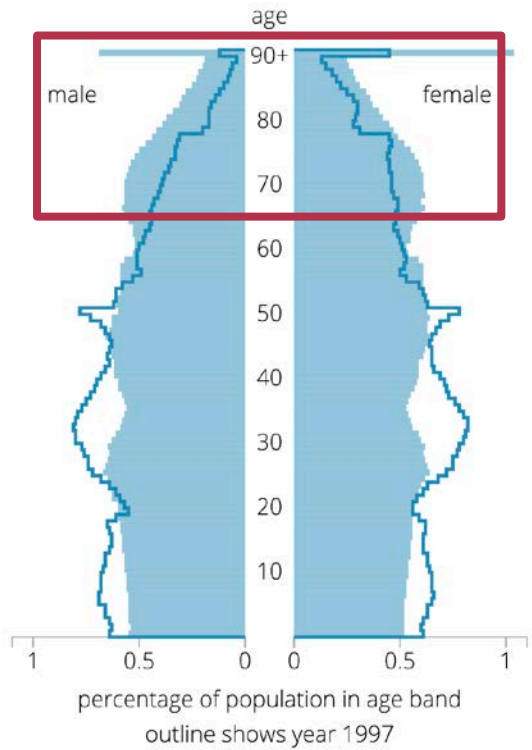
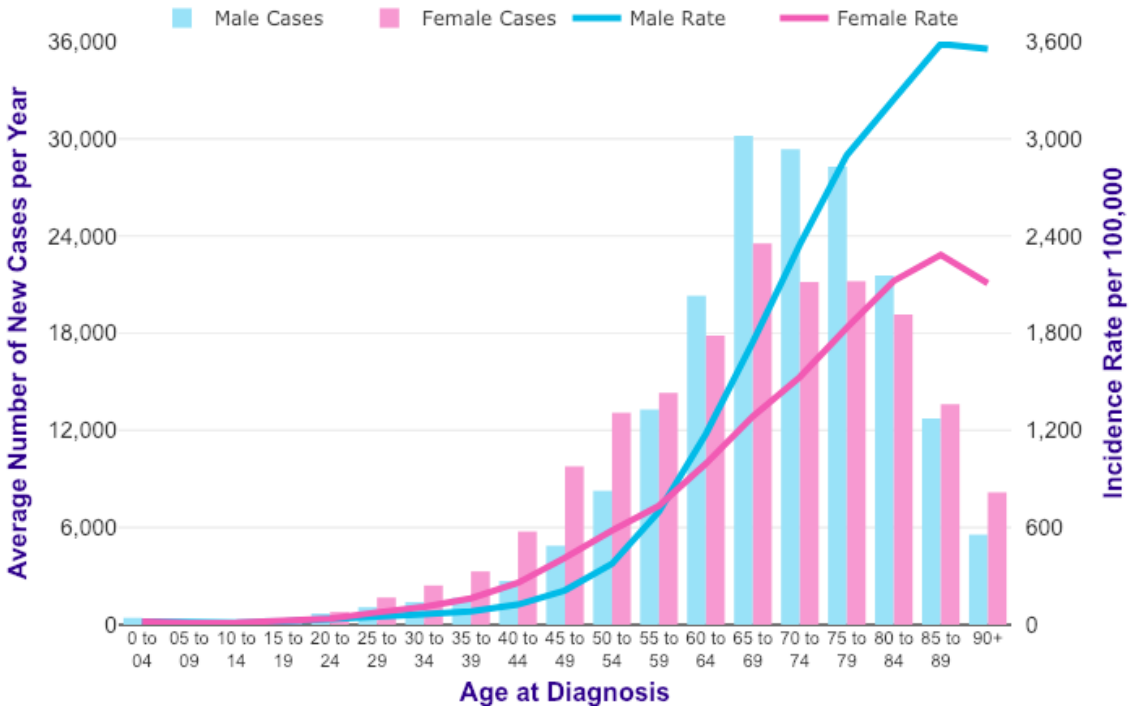
CANCER IS A DISEASE OF OLDER ADULTS

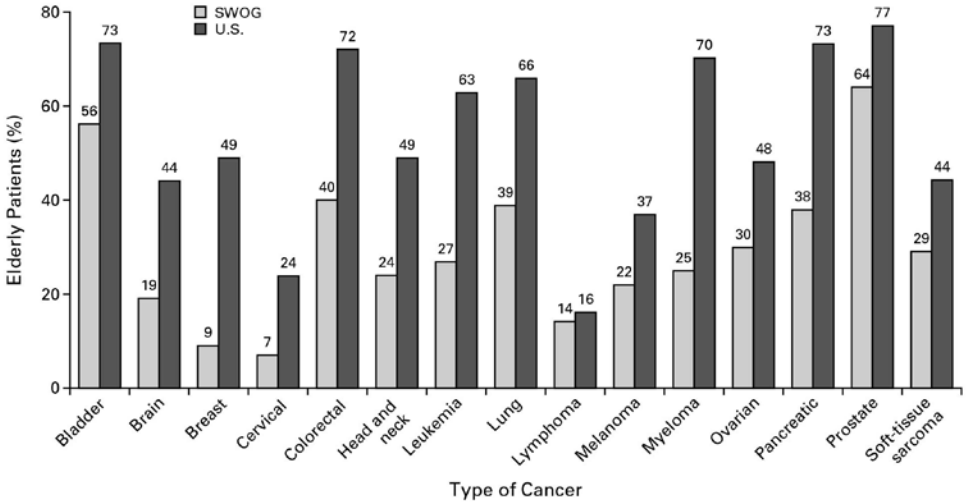
1997 - 2037
15.9% - 24.0%



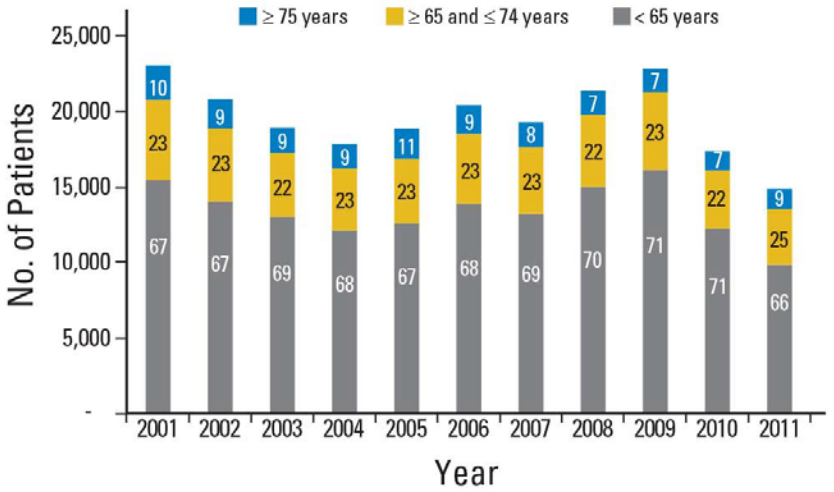


Source: Office for National Statistics; Cancer Research UK

OLDER ADULTS ARE UNDER-REPRESENTED IN CLINICAL TRIALS



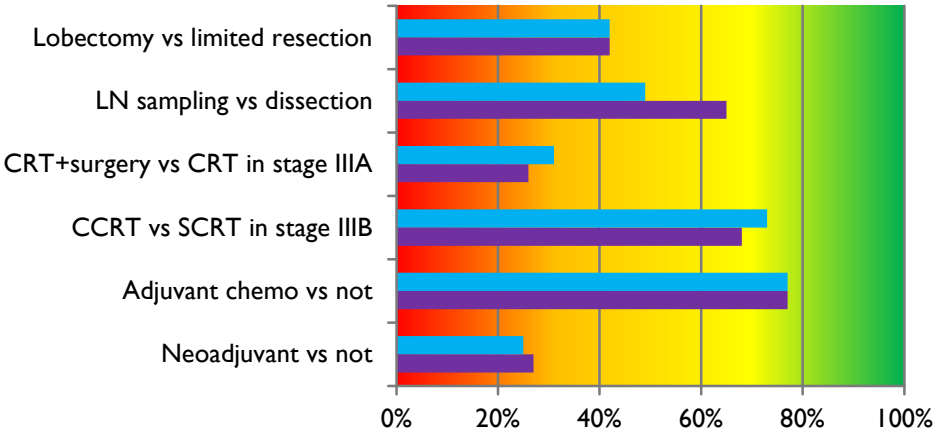
25% patients enrolled in 164 SWOG studies were 65+ vs 63% in the US cancer patient population

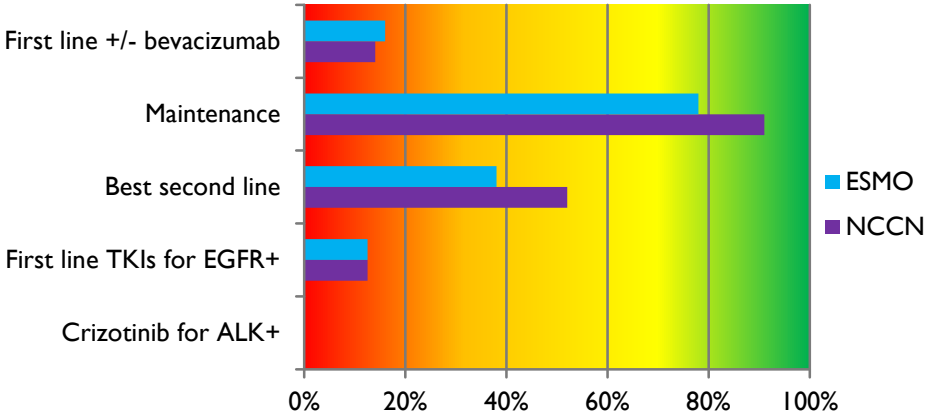


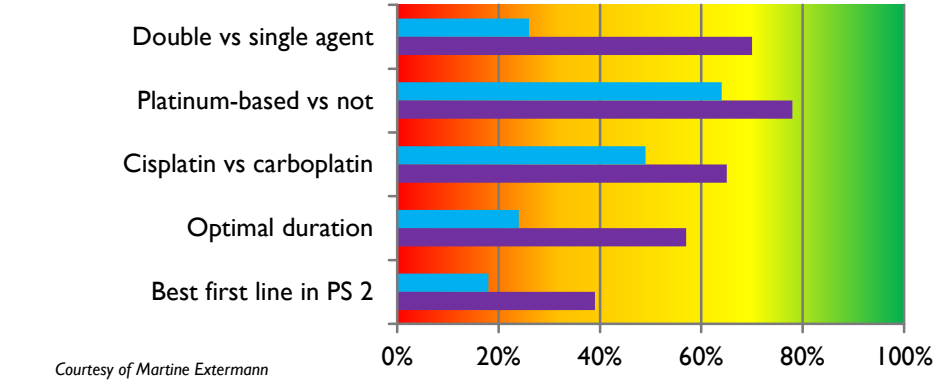
<10% of patients enrolled in NCI phase II-III trials are 75+ vs 28% of cancer patients overall

Hutchins, NEJM, 1999; Hurria, JCO, 2014

THE APPLICABILITY OF EVIDENCE TO THE MANAGEMENT OF CANCER IN OLDER ADULTS IS LIMITED







NCCN National Comprehensive Cancer Network®

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NCCN NSCLC guidelines version 4.2014; ESMO early & LA NSCLC guidelines July 2013; ESMO advanced NSCLC guidelines August 2014

Battisti et al, Clin Lung Cancer, 2017

Courtesy of Martine Extermann

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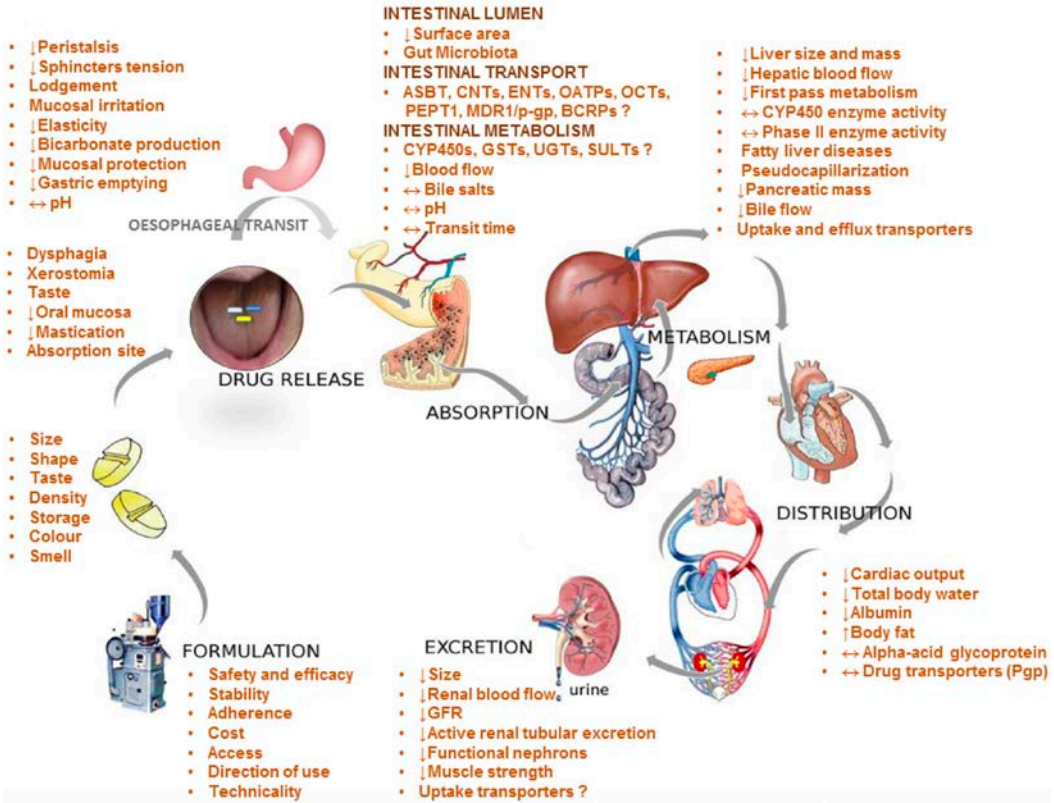
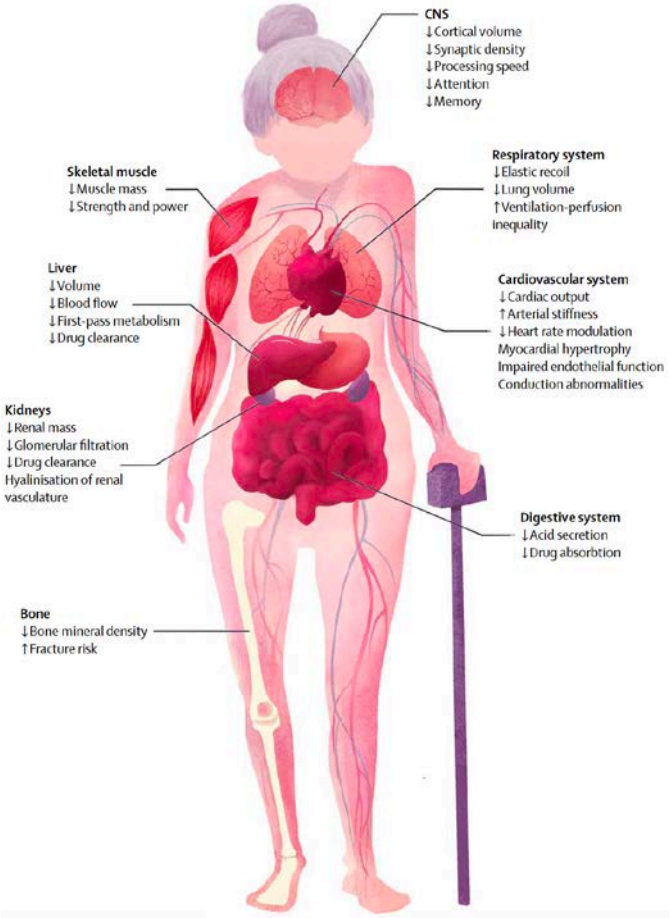
ORGAN FUNCTION DECLINE

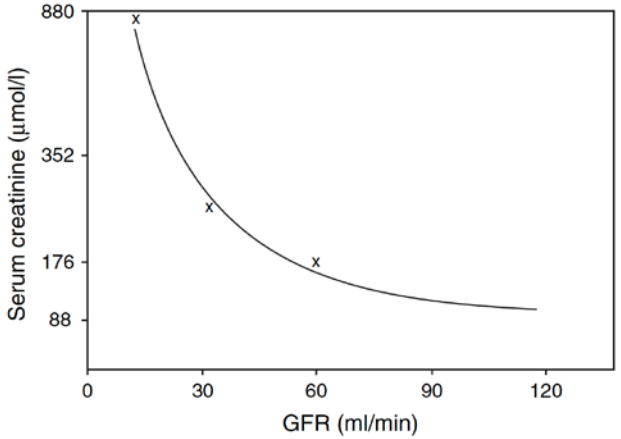




Soto-Perez-de-Celis, Lancet Oncol, 2018; Khan, Adv Drug Deliv Rev, 2018

RENAL FUNCTION AND DRUG EXCRETION

- **Gradual decline in GFR <60 mL/min/1.73m^2** in a significant proportion of patients
- **Higher peak drug levels and more prolonged chemo exposure**
- Increased toxicities for renally excreted drugs
- Concurrent use of NSAIDs
- Serum creatinine ≠ reliable renal function measure owing to loss of muscle mass
  - Estimate **creatinine clearance** instead - Cockcroft-Gault equation
- Chemotherapy may be **safely administered with dose adjustments**



review

Annals of Oncology 18: 1314–1321, 2007
doi:10.1093/annonc/mdm011
Published online 13 July 2007

Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations

V. Launay-Vacher[1], E. Chatelut[2], S. M. Lichtman[3], H. Wildiers[4], C. Steer[5] & M. Aapro[6]*

[1]Hôpital Pitié-Salpétrière, Paris; [2]Université Paul-Sabatier and Institut Claudius-Regaud, Toulouse, France; [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [4]University Hospital Gasthuisberg, Leuven, Belgium; [5]Murray Valley Private Hospital, Wodonga, Australia; [6]Clinique de Genolier, Geneva, Switzerland

Received 11 October 2006; revised 21 November 2006; accepted 27 November 2006

Cytotoxics

Arsenic trioxide
Bendamustine
Bleomycin
Capecitabine
Carboplatin
Carmustine (BiCNU)
Cisplatin
Cladribine
Clofarabine
Cyclophosphamide
Cytarabine (high dose)
Daunorubicin
Epirubicin
Eribulin
Etoposide
Fludarabine
Hydroxyurea
Ifosfamide
Irinotecan (controversial)
Ixazomib
Lenalidomide
Lomustine (CCNU)
Melphalan
Methotrexate
Mitomycin
Oxaliplatin
Pemetrexed
Pentostatin
Pomalidomide
Pralatrexate
Streptozocin
Topotecan
Trabectedin
Vinorelbine

Targeted agents

Afatinib
Bosutinib
Brentuximab
Crizotinib
Imatinib
Lenvatinib
Olaparib
Sorafenib
Sunitinib
Talazoparib
Vandetanib

LIVER FUNCTION AND METABOLISM

- **Liver size and hepatic blood flow decline** – usually not enough to warrant routine dose modifications
- Concurrent **hepatic impairment (malignancy, comorbidities, con meds)** may require dose adjustments
- Relevant for a number of commonly used drugs:
  - **Anthracyclines**
  - **5-FU**
  - **Taxanes**
  - **Cyclophosphamide**
  - **Methotrexate**

Egorin, Semin Oncol, 1993

DISTRIBUTION AND ABSORPTION

- **Body composition changes**
  - Increasing fat content and decrease in intracellular water
  - Peak blood concentrations: higher for more polar drugs and lower (and longer half-life) for lipid-soluble drugs
  - Decrease in plasma albumin and RBC may also affect PK of agents bound to albumin or erythrocytes
  - Usually **not warranting dose modifications** based on age
- **Absorption**
  - Intestinal mucosa atrophy, GI motility decrease, visceral blood flow decline and digestive enzyme secretion decrease
  - Magnitude of these changes **does not usually require dose adjustments**
  - **Compliance to oral treatments**

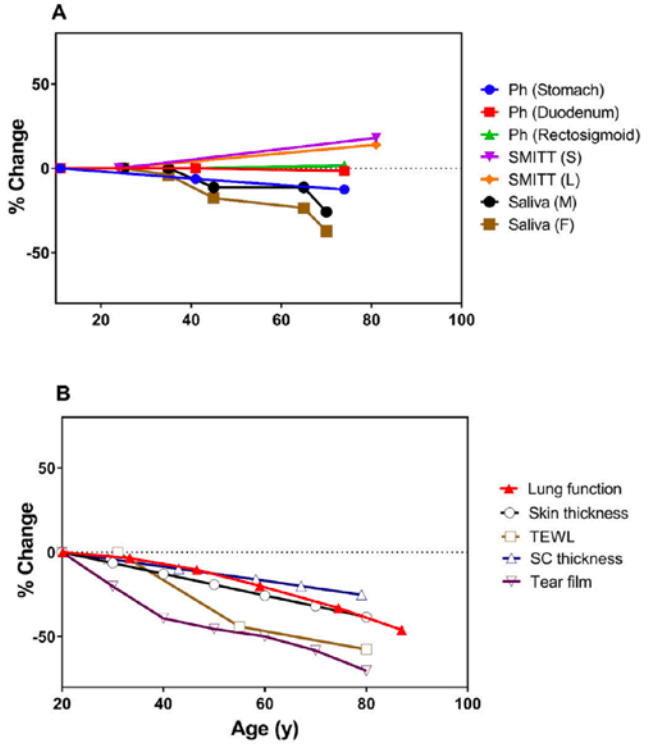
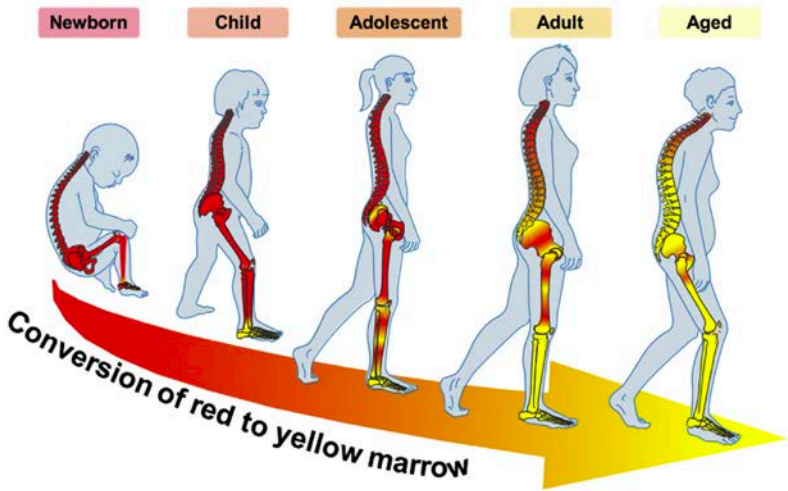


Fig. 3. Physiological changes in absorption sites with ageing [94–100]. A. Oral absorption sites – SMITT: Small intestine transit time; F: Female; M: Males; S: Solid; L: Liquid. B. Other routes of administration – Lung function here is the reduction in forced expiration volume in one second (FEV1); SC: Stratum corneum; TEWL: Transepidermal water loss. Percentage change is relative to the reference values in young age group as reported. Negative value represents decline in function. AAG results are from two different studies.

Egorin, Semin Oncol, 1993; Baker, Clin Geriatr Med, 1997; Khan, Adv Drug Deliv Rev, 2018

REDUCED BONE MARROW RESERVE

- **Bone marrow stem cell reserve decreases with aging**
- **Increased rates of haematological toxicities** in older patients
  - More frequent infectious complications, hospitalizations and mortality
- **Neutropenia**
  - **Dose reductions and G-CSF** are used to avoid severe neutropenia
  - ASCO guidelines: G-CSF are recommended if risk of febrile neutropenia ≥20%
  - NCCN guidelines: G-CSF are indicated if older adults treated with curative intent
- **Anaemia**
  - Can impair functional status and its incidence increases with age
  - ESAs may be useful if anaemia is due to chemotherapy
    - Risk of thrombosis and shorter survival
    - **Treatment intent - curative vs palliative?**



Dees, Cancer Invest, 2000; Baraldi-Junkins, Hematol Oncol Clin North Am, 2000; Anía, J Am Geriatr Soc,1997; Hoffman, Bone, 2019

HEART FUNCTION

- **Pre-existing occult heart disease** is more frequent
- Increased risk of
  - **Heart failure** associated with anthracyclines and trastuzumab
  - **Coronary artery vasospasm** due to fluoropyrimidines
- **Radiotherapy to the chest wall** may also contribute

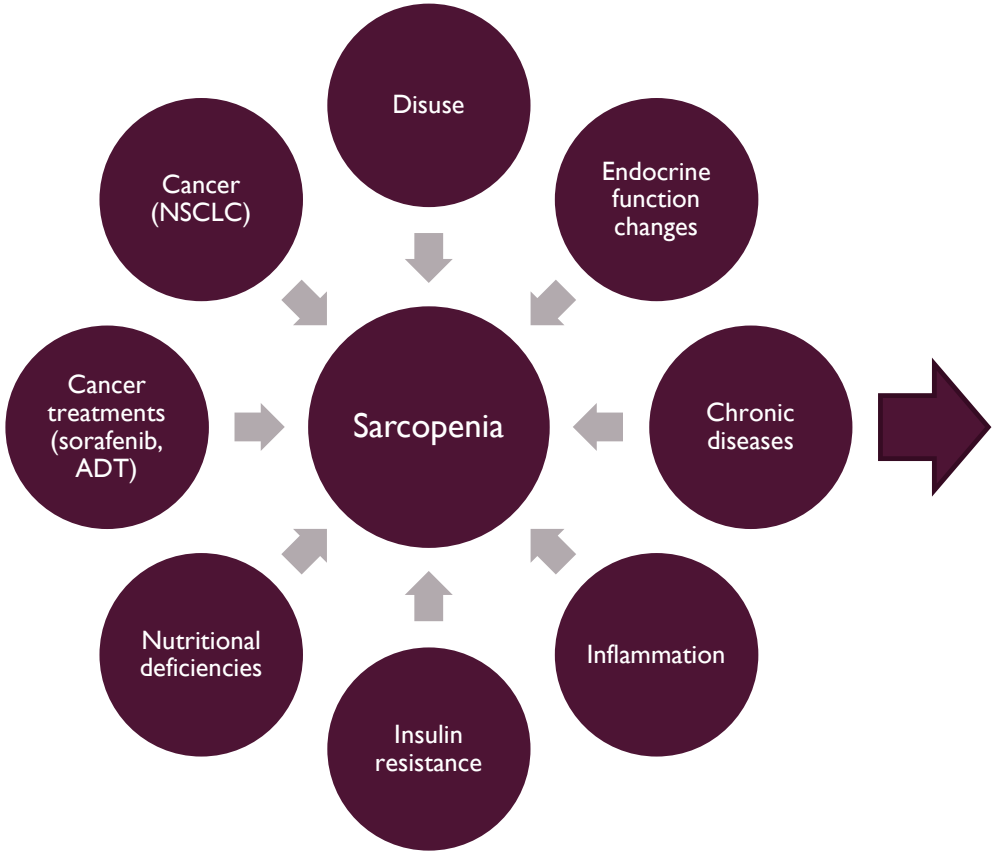
Table 2 – Cardiac toxicity of anticancer agents.

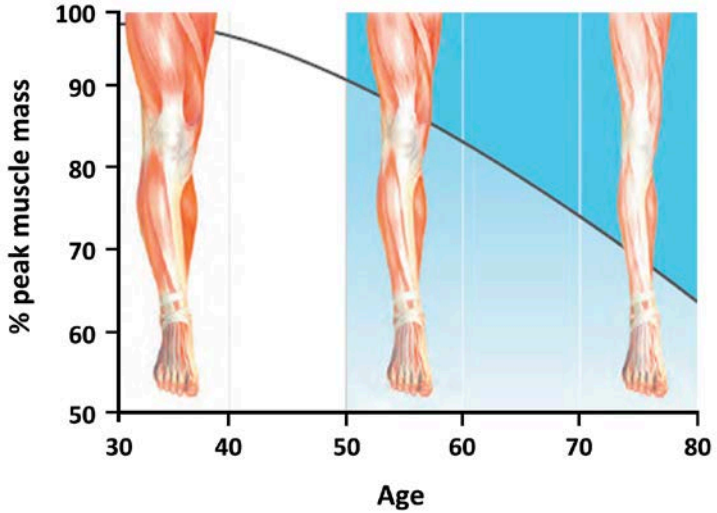
Agent	Mechanism	Toxicity
Anthracyclines	Free radical cellular damage Myocyte apoptosis	CHF, LV systolic dysfunction Advanced age is a risk factor
Trastuzumab	Inhibition of cardiomyocyte HER2 ATP depletion Myofibrillar disarray	CHF, LV systolic dysfunction Age >50 is a risk factor
VEGF-receptor ligand Ab Bevacizumab	Inhibition of nitric oxide Vasoconstriction Endothelial cell proliferation	Hypertension, ischemia, MI Ventricular arrhythmias CHF, LV dysfunction Arterial thrombosis Age >59 is a risk factor
VEGF-TKI Sunitinib, Imatinib and Sorafenib	Inhibition of nitric oxide Vasoconstriction Mitochondrial damage of cardiomyocytes	Hypertension, ischemia, MI CHF, LV dysfunction Adverse events more common in elderly
TKI Imatinib	Inhibition of c-Abl, which appears to have a survival function in cardiomyocytes	CHF, LV dysfunction Advanced age and CV RF increase risk
Fluoropyrimidines 5-FU and Capecitabine	Thrombosis, arteritis, vasospasm Direct toxicity to myocardium Myocyte apoptosis	Myocardial ischemia, MI
Alkylating agents Cyclophosphamide	May cause direct endothelial injury Coronary vasospasm	CHF, LV dysfunction Pericardial effusion/tamponade
Cisplatin	Platelet activation and aggregation Altered endothelial cell integrity Vasospasm	Hemorrhagic myocarditis CHF, LV dysfunction Hypertension Venous thrombosis (PE, DVT)

Abbreviations: 5-FU, 5-fluorouracil; Ab, antibody; ATP, adenosine triphosphate; CHF, congestive heart failure; HER2, human epidermal growth factor 2; CV, cardiovascular; DVT, deep vein thrombosis; LV, left ventricular; MI, myocardial infarction; RF, risk factors; PE, pulmonary embolism; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Sawhney R, Cancer J. 2005; Gupta, J Geriatr Oncol, 2017; Hershman, JCO, 2008; Carver, JCO, 2008

MUSCLE MASS AND FUNCTION





- Decreased immunity
- Increased risk of infections
- Impaired wound healing
- Increased muscle weakness
- Pressure ulcers
- Increased mortality

Colloca G, J Geriatr Oncol, 2018

FUNCTIONAL STATUS

- Karnofsky or ECOG **PS scales under-represent the degree of functional impairment** in older patients
- **ADL and IADL scales** offer a more comprehensive understanding of functional status
- **Functional disability is common** in older cancer patients
  - 17% of the patients had a limitation for ADL and 59% for IADL
  - Leading to increased healthcare utilization
- **Independence in IADLs** (and better QOL) associated with **improved OS** (MILES study)
- Functional status influences also risk of **chemotherapy toxicity**

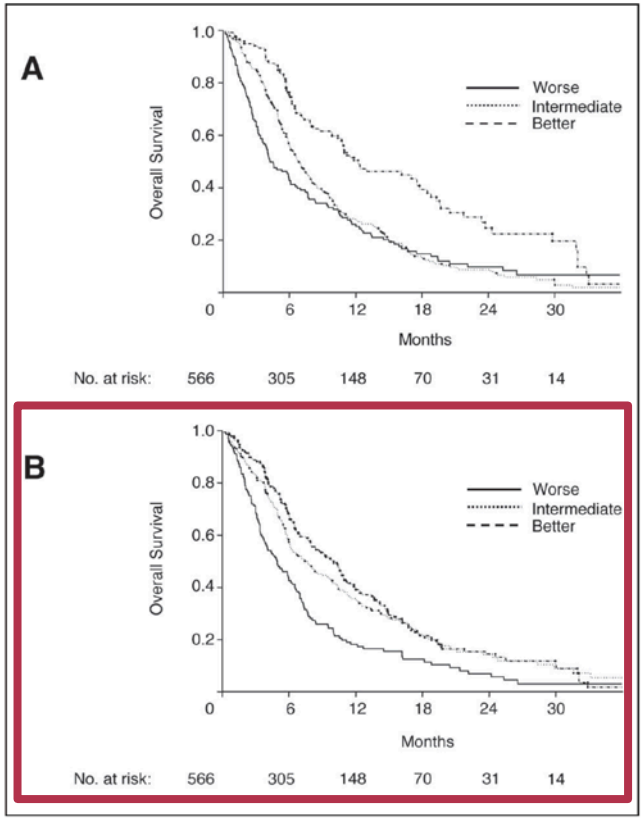
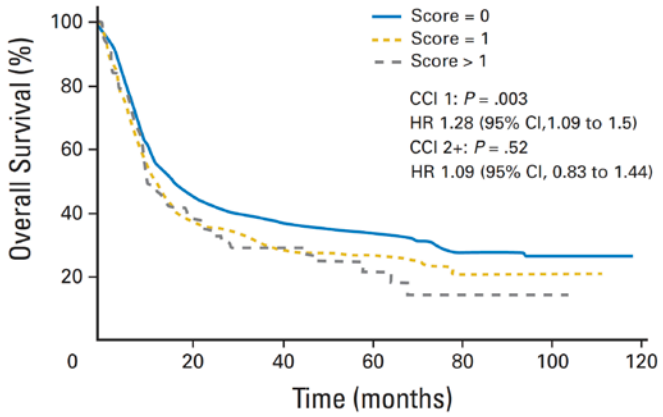


Fig 2. Kaplan-Meier–estimated overall survival curves according to pre-treatment (A) quality of life (QoL) and (B) intermediate Activities of Daily Living (IADL) categories.

Stafford, Cancer, 1997; Serraino, Crit Rev Oncol Hematol, 2001; Maione, JCO, 2005

COMORBIDITIES

- Increase with age
- Impact on life expectancy and treatment tolerance
- **Impact on mortality** in 3 large series of breast cancer, NSCLC and colorectal cancer patients
- **Comorbidity and functional status are independent variables in older cancer patients**
  - Assessing both is mandatory



No. at risk							
Score = 0	865	318	220	134	61	16	0
Score = 1	310	98	65	33	9	2	0
Score > 1	81	24	13	6	3	2	0

Table 3. Spearman Rank Correlation Between Comorbidity Scores, Functional Scores, Age, and Tumor Stage

ρ	Age	Tumor Stage	ADL	IADL	ECOG PS	Charlson	CIRS-cat	CIRS-score	CIRS-mean	CIRS 3+4
Age	1									
Tumor stage	−0.09	1								
ADL	0.12	0.16	1							
IADL	0.22	0.13	0.60	1						
ECOG PS	0.07	0.20	0.51	0.61	1					
Charlson	0.15	0.01	0.20	0.18	0.14	1				
CIRS-cat	0.18	−0.08	0.14	0.19	0.13	0.30	1			
CIRS-score	0.15	−0.05	0.18	0.23	0.16	0.39	0.89	1		
CIRS-mean	0.04	0.05	0.12	0.11	0.12	0.30	0.07	0.46	1	
CIRS 3+4	0.02	−0.01	0.27	0.18	0.10	0.25	0.35	0.62	0.67	1

NOTE. All correlations of 0.14 or more are significantly different from 0 ($t_{(201)} > 1.980$; 2-sided $P < .05$).

Satariano, Ann Intern Med, 1994; Asmis, JCO, 2008; Hines, JCO, 2009; Extermann, JCO, 1998

POLYPHARMACY

- Older ambulatory patients use **3x as many medications compared with younger patients** and ≥90% take ≥1 medication
- Increased risk of **drug interactions** – eg, via cytochrome P450
- Impact on **compliance**
- Regular and comprehensive review of all medications (both prescription and OTC) mandatory
  - Lipid-lowering medications after terminal cancer diagnosis?
- Increased risk of **medication errors** due to medication changes, complex regimens and incomplete information sharing between providers

Vestal, Cancer, 1997; Tam-McDevitt, Oncology, 2008; Maggiore, The Oncologist, 2010; Nightingale, JCO, 2015

Drug interaction	Type of interaction	Result	Comments
5FU/etoposide/carboplatin/ gemcitabine based regimens & coumadin	Protein binding Inhibition of coumarins metabolism	Increased INR	Follow INR closely
PPIs and tyrosine kinase inhibitors	Absorption	TKIs need acid for absorption	Stop if possible, or if needed, give e.g. omeprazole at least 2 hours after TKI or 10 hours before
Penicillins & methotrexate (MTX)	Renal tubular secretion	Elevated MTX levels	Monitor for toxicities of methotrexate if a penicillin is initiated or the dose is increased
Ketoconazole & irinotecan	Inhibition of CYP3A4 Inhibition of UGT1A1	Increased exposure to irinotecan active metabolite	Avoid administration of strong CYP3A4 inhibitors during and within 1 week prior to irinotecan, unless needed.
Delvairdine and squinavir & paclitaxel	CYP3A inhibition	Severe paclitaxel toxicity	Consider an alternative for one of the interacting drugs in order to avoid toxicity of the substrate and monitor for toxicities.
NSAIDs & methotrexate	Renal tubular secretion	Elevated MTX levels	Consider alternative anti-inflammatory therapy. Lower risk with COX-2 inhibitors. Monitor for hematologic toxicity (frequent CBC), nephrotoxicity (frequent creatinine), and hepatotoxicity (LFTs).
Herbal supplements (St John's wort) & imatinib and irinotecan	Induction of CYP3A4	Decreased plasma concentrations of imatinib and irinotecan active metabolite	Avoid concomitant use. Monitor for decreased effects of imatinib.. Discontinue St Johns Wort at least 2 weeks prior to irinotecan.
Doxorubicin & sotalol/amiodarone/clarithromycin/levofloxacin	CYP2D6 inhibition P-glycoprotein/ABCB1 inhibition	QT interval prolongation	Seek alternative drugs.
Quinolones & carboplatin/etoposide/ mitoxantrone/vincristine/ cisplatin/cyclophosphamide/ doxorubicin	Gastrointestinal mucosa damage P-glycoprotein/ABCB1 induction	Decreased quinolones absorption QT interval prolongation	Monitor for decreased effects of chemo and for QT prolongation (EKG).
Hydrochlorotiazide & cyclophosphamide/5-FU	Enhanced chemo toxicity	Increased myelosuppression	Monitor for higher rates of granulocytopenia
Phenytoin & cyclophosphamide/etoposide/vincristine/doxorubicin	CYP2B6 induction	Altered plasma concentrations of phenytoin or cytostatic agents	Consider alternatives to avoid therapeutic failure. If needed, adjust dosage and monitor for decreased chemo effects.
Valproic acid & cisplatin/doxorubicin/ bleomycin	Altered gastrointestinal absorption Increased metabolism	Lower AUC valproic acid	Adjust dosage.
Cyclophosphamide & allopurinol	Bone marrow depression	Increased chemo toxicity	Monitor for changes in CBC if allopurinol is initiated or the dose is increased, especially in long-term therapies (eg, for gout).

Battisti, Extermann, Multidisciplinary management, including chemotherapy of solid tumours (chapter 93), Oxford Textbook of Geriatric Medicine, 2018

COGNITION

- Dementia increases the risk of late **cancer diagnosis** in older adults
  - Colon cancer patients affected by dementia are more likely to have a cancer diagnosis reported after death based upon either autopsy or death certificate and are less likely to receive biopsy or surgery or chemotherapy
  - Patients with Alzheimer's disease and breast cancer are more likely to be diagnosed with a later stage of breast cancer and less likely to receive treatment for their malignancy
- Cognition is **key for compliance with oral chemotherapy and supportive medications** and for patients to understand and remember to **seek medical attention if they experience side effects**
- **Chemotherapy-related cognitive impairment**
  - Few studies focused on its prevalence in older cancer patients
  - Its biologic drivers are unknown
  - Impact of treatment on cognition is **not routinely measured in therapeutic studies** on older cancer patients
  - Few randomized trials of treatment or prevention of CRCI in older cancer patients

Gupta, J Am Geriatr Soc, 2004; Gorin, J Am Geriatr Soc, 2005; Loh, J Geriatr Oncol, 2016

NUTRITION

- Weight loss during anti-cancer therapy
- Malnutrition during advanced disease
- Obesity during survivorship

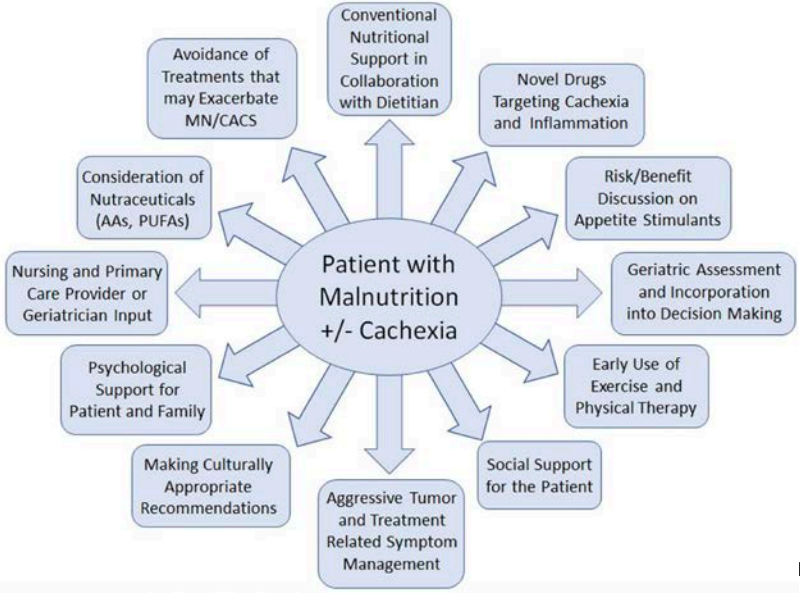


TABLE III Effect of Weight Loss Subcategories on Median Survival

Tumor Type	Median Survival (wk)				P Value*
	None	Weight Loss 0–5%	Weight Loss 5–10%	Weight Loss >10%	
Nonsmall cell lung	20	17	13	11	<0.01
Prostate	46	30	18	9	<0.05
Colorectal	43	27	15	20	<0.01

* Based on a simultaneous statistical test of the null hypothesis that median survival is not affected by weight loss.

Table 3 – Factors to consider when assessing weight loss and malnutrition in elderly patients with cancer.

- Fatigue
- Functional dependence
- Anemia
- Anorexia
- Dry mouth
- Dysosmia
- Dysgeusia
- Impaired mobility
- Nausea
- Early satiety
- Poor vision
- Dental issues
- Oral candidiasis
- Hand, foot, and mouth syndrome
- Poor dentition, ill-fitting dentures
- Cognitive function
- Mental health
- Polypharmacy
- Social support
- Vomiting
- Diarrhea
- Specific cancer diagnosis which limit oral intake: head and neck, esophageal, gastric

Presley, J Geriatr Oncol, 2016; Jain, Curr Oncol Rep, 2017; Newman, J Am Geriatr Soc, 2001; Dewys, Am J Med, 1980

PSYCHOLOGICAL STATUS AND SOCIAL SUPPORT

- **1/3 of older cancer patients** experience psychological distress
  - Most typically **depression in 3-25%** of older cancer patients
- Psychological distress is associated with:
  - **Poor QOL**
  - Reduced **treatment adherence and response**
  - Longer **hospitalizations**
  - **Increased utilization of healthcare resources** (ED visit, overnight hospitalizations and 30-day re-admissions)
  - **Shorter survival**
  - Increased risk of **functional decline**
- Patients with inadequate **social support** are most vulnerable to psychological distress
- Social isolation is also an independent predictor of mortality in the geriatric population

Kua, Ann Acad Med Singapore, 2005; Penninx, JAMA, 1998; Kornblith, Cancer, 2003

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BREAST CANCER – EARLY AND LOCALLY ADVANCED STAGE

- Consider non anthracycline-based regimens for patients not suitable
  - **Docetaxel + Cyclophosphamide (TC)**
  - **Weekly Paclitaxel**
- **No role for Capecitabine alone**
  - ICE: no difference with Capecitabine versus Ibandronate (plus endocrine treatment)
  - CALGB 49907: worse RFS and OS with Capecitabine versus standard chemotherapy

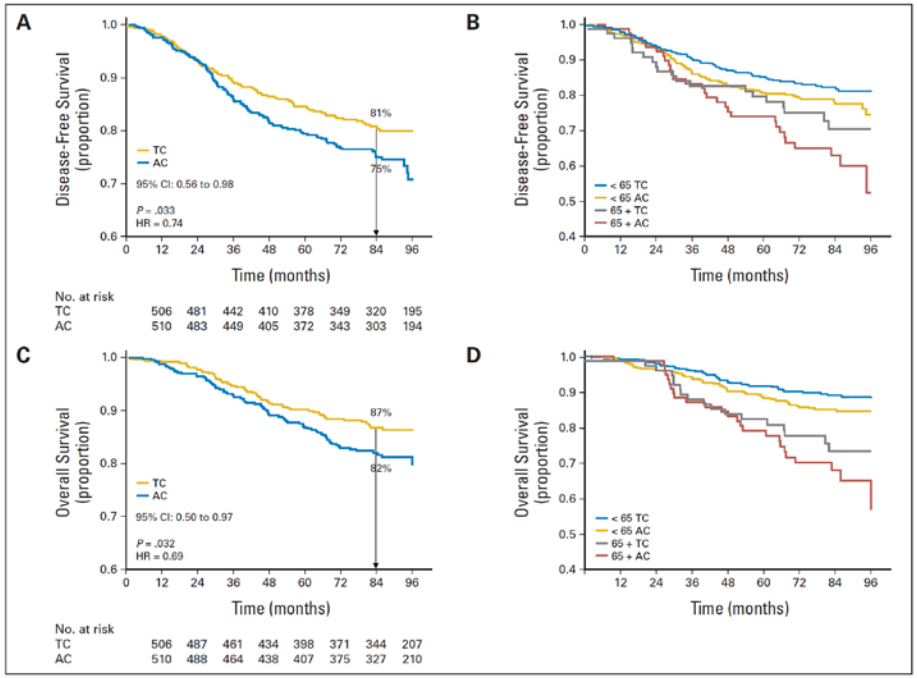


Fig 1. Disease-free survival (DFS) and overall survival (OS) (A) DFS by treatment; (B) DFS by treatment and age; (C) OS by treatment: 1 day; (D) OS by treatment and age. TC, docetaxel/cyclophosphamide; AC, doxorubicin/cyclophosphamide.

Jones, JCO, 2009; von Minckwitz, SABCS, 2014; Muss, NEJM, 2009; Coltelli, The Breast, 2017

BREAST CANCER – ADVANCED STAGE

- Sequential single-agent chemotherapy is recommended but no optimal sequence is defined
- **Capecitabine**
  - Effective and well tolerated at dose of **1000mg/m²**
  - Monitor **renal function** and **bilirubin**
  - In chemo-naïve MBC patients aged 65+: ORR 37% and G3+ adverse events ≤10%
- **Vinorelbine**
  - In chemo-naïve MBC patients aged 60+: ORR 38% and G3+ haem tox 80%
- **Eribulin**
  - No impact of age on OS, PFS and toxicities in a pooled analysis of 3 trials
- **Weekly paclitaxel**
  - Better CBR and TTP versus docetaxel – higher anaemia and neurotoxicity with **weekly paclitaxel**, oedema and fatigue with **docetaxel**
- **Weekly epirubicin**
- **Pegylated liposomal doxorubicin**: comparable efficacy to doxorubicin but less cardiotoxicity, myelosuppression, vomiting and alopecia

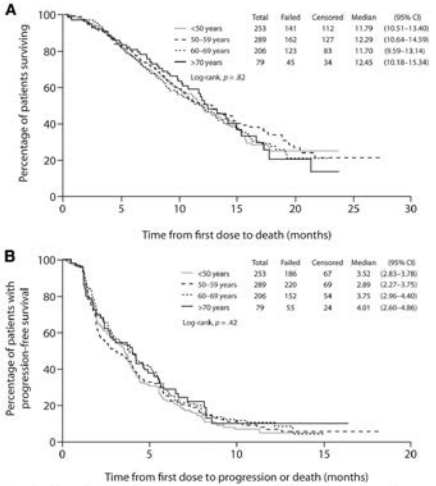


Figure 2. Kaplan-Meier graph of overall survival **(A)** and progression-free survival **(B)** by independent review. Abbreviation: CI, confidence interval.

Table 5. Treatment-related adverse events of special interest in each age cohort

Adverse event[a]	<50 years (*n* = 253)	50–59 years (*n* = 289)	60–69 years (*n* = 206)	≥70 years (*n* = 79)	Total (*N* = 827)
Asthenia/fatigue					
All	125 (49.4)	150 (51.9)	115 (55.8)	47 (59.5)	437 (52.8)
Grade 3/4	15 (5.9)	20 (6.9)	21 (10.2)	11 (13.9)	67 (8.1)
Peripheral neuropathy[b]					
All	77 (30.4)	84 (29.1)	74 (35.9)	30 (38.0)	265 (32.0)
Grade 3/4	10 (4.0)	21 (7.3)	18 (8.7)	8 (10.1)	57 (6.9)
Nausea					
All	87 (34.4)	116 (40.1)	70 (34.0)	17 (21.5)	290 (35.1)
Grade 3/4[c]	1 (0.4)	4 (1.4)	3 (1.5)	1 (1.3)	9 (1.1)
Arthralgia/myalgia					
All	38 (15.0)	36 (12.5)	26 (12.6)	7 (8.9)	107 (12.9)
Grade 3/4	0	0	3 (1.5)	0	3 (0.4)
Vomiting					
All	48 (19.0)	40 (13.8)	26 (12.6)	6 (7.6)	120 (14.5)
Grade 3/4	1 (0.4)	1 (0.3)	2 (1.0)	0	4 (0.5)

Bajetta, JCO, 2005; Vogel, Ann Oncol, 1999; Muss, Oncologist, 2014; Beuselinck, Crit Rev Oncol Hematol, 2010; Lichtman, Ann Oncol, 2012; O'Brien, Ann Oncol, 2004

BREAST CANCER – HER2-DIRECTED AGENTS

- **Early stage/LA disease**
  - Improved survival and recurrence risk (47%) and well tolerated in patients aged 60+ (5% cardiac event rate)
  - **Weekly Paclitaxel and trastuzumab**
  - 81.7% of older patients are able to complete 1 year of treatment
- **Advanced stage disease**
  - Trastuzumab improves median PFS (11.7 versus 4.6 months), but no difference in median OS
  - **Metronomic cyclophosphamide + P + T** versus P+T alone improves PFS but >50% patients on P experienced diarrhoea

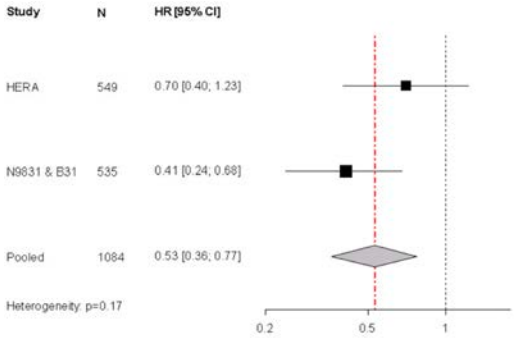
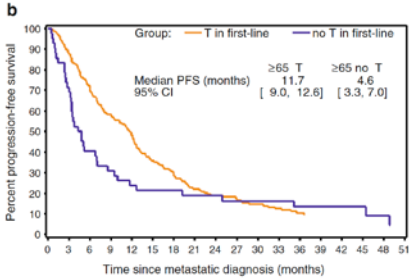
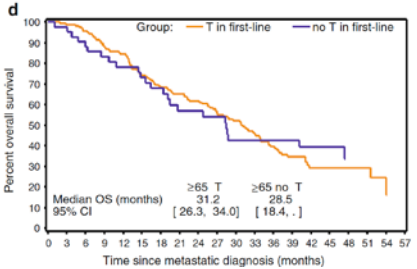


Fig. 1. Forest plot for DFS.





Brollo, Cancer Treat Rev, 2013; Vaz-Luis, JCO, 2014; Cadoo, Clin Breast Cancer, 2016; Kaufman, Breast Cancer Res Treat, 2012; Wildiers, Lancet Oncol, 2018

NSCLC – ADJUVANT CHEMOTHERAPY

- **LACE meta-analysis** and **JBR.10 study**: same efficacy and toxicity of **cisplatin** combos in 70+ patients vs <70
  - Older patients received lower doses and fewer chemo cycles
- **Carboplatin** is more appropriate in case of hearing loss

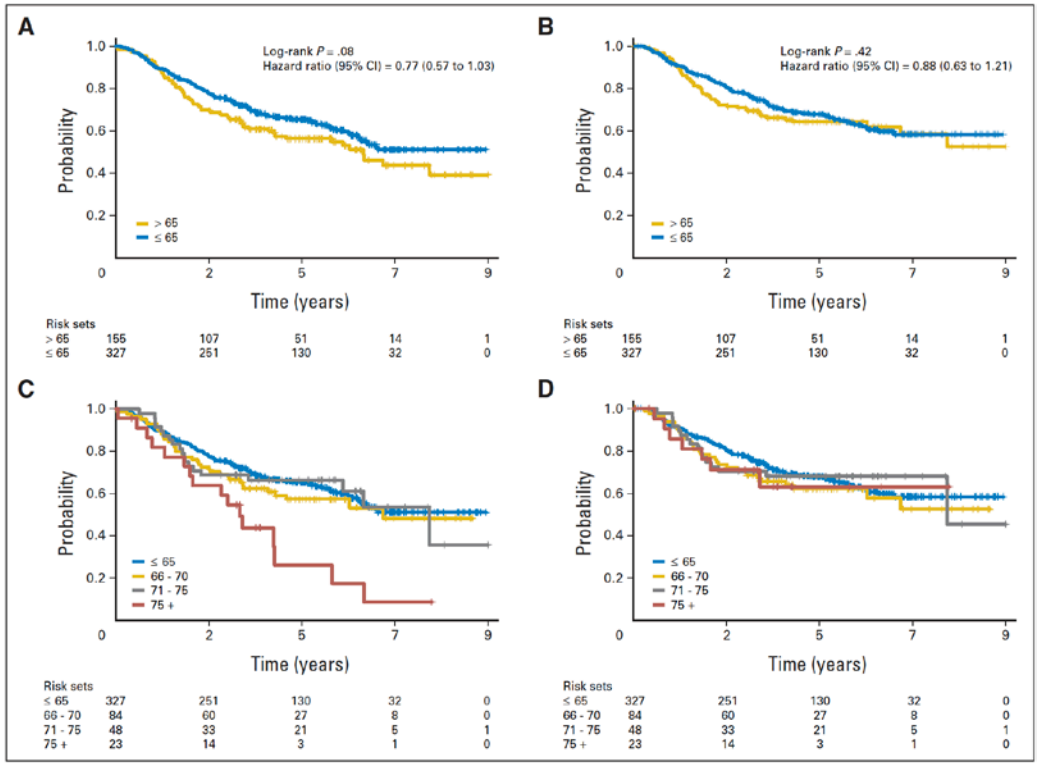


Fig 1. Overall and disease-specific survival by age group. (A, C) Overall survival by age group; (B, D) disease-specific survival by age group.

Wisnivesky, BMJ, 2011; Früh, JCO, 2008; Pepe, JCO, 2007

NSCLC – ADVANCED STAGE

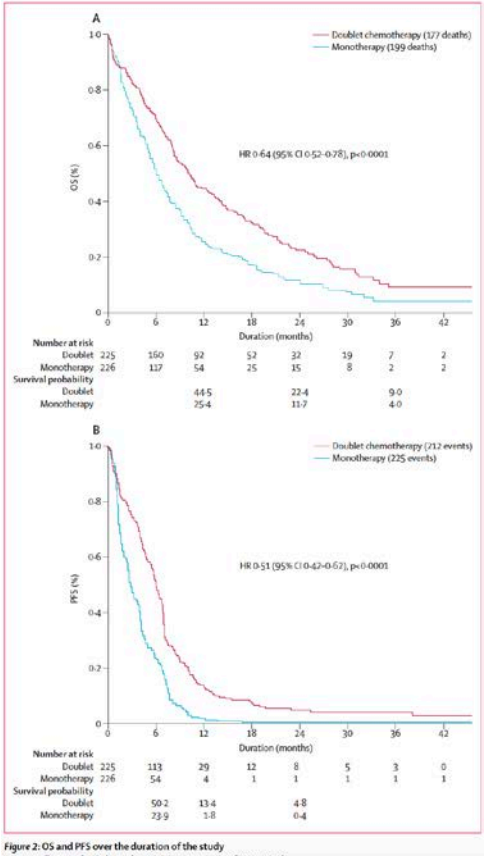
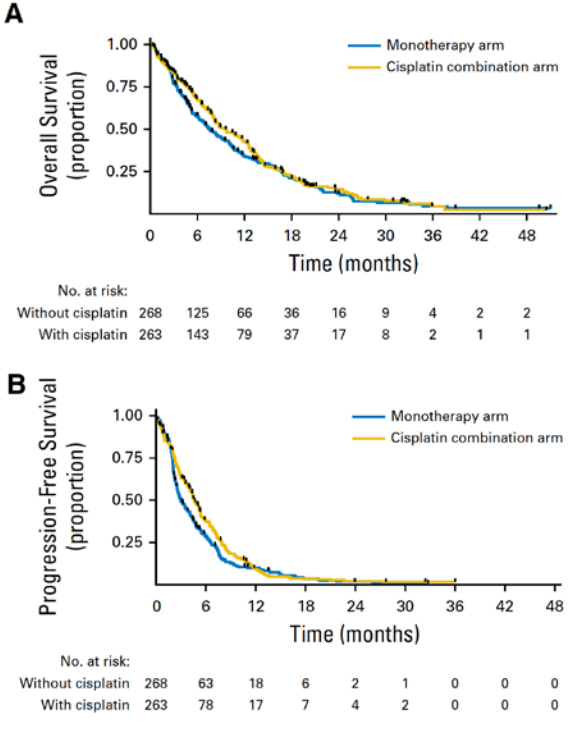


Figure 2: OS and PFS over the duration of the study
OS=overall survival. HR=hazard ratio. PFS=progression-free survival.

	Monotherapy group (n=225)			Doublet chemotherapy group (n=223)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Haematological						
Decreased neutrophil count	28 (12·4%)	15 (6·7%)	13 (5·8%)	108 (48·4%)	69 (30·9%)	39 (17·5%)
Decreased haemoglobin concentration	10 (4·4%)	10 (4·4%)	0	21 (9·4$)	21 (9·4)	0
Febrile neutropenia	6 (2·7%)	3 (1·3%)	3 (1·3%)	21 (9·4%)	12 (5·4%)	9 (4·0%)
Decreased platelet count	2 (0·9%)	2 (0·9%)	0	15 (6·7%)	11 (4·9%)	4 (1·8%)
Non-haematological						
Asthenia	13 (5·8%)	13 (5·8%)	0	23 (10·3%)	20 (9·0%)	3 (1·3%)
Anorexia	2 (0·9%)	2 (0·9%)	0	9 (4·0%)	9 (4·0%)	0
Worsening general condition	4 (1·8%)	4 (1·8%)	0	5 (2·2%)	4 (1·8%)	1 (0·4%)
Diarrhoea	2 (0·9%)	2 (0·9%)	2 (0·9%)	6 (2·7%)	6 (2·7%)	0
Nausea and vomiting	2 (0·9%)	2 (0·9%)	0	6 (2·7%)	6 (2·7%)	0
Pulmonary disorder	5 (2·2%)	5 (2·2%)	0	3 (1·3%)	3 (1·3%)	0
Sensory neuropathy	1 (0·4%)	1 (0·4%)	0	7 (3·1%)	7 (3·1%)	0
Mouth irritation	2 (0·9%)	2 (0·9%)	2 (0·9%)	2 (0·9%)	2 (0·9%)	0
Constipation	2 (0·9%)	2 (0·9%)	2 (0·9%)	1 (0·4%)	1 (0·4%)	0
Dyspnoea	1 (0·4%)	1 (0·4%)	0	1 (0·4%)	1 (0·4%)	0
Infection	1 (0·4%)	1 (0·4%)	0	1 (0·4%)	1 (0·4%)	0
Pulmonary embolism	0	0	0	2 (0·9%)	0	2 (0·9%)
Bronchitis	0	0	0	1 (0·4%)	1 (0·4%)	0
Raised γ-glutamyltransferase concentration	0	0	0	1 (0·4%)	1 (0·4%)	0
Superficial phlebitis	0	0	0	1 (0·4%)	1 (0·4%)	0

Table 5: Grade 3–4 toxic effects in patients who received at least one dose of first-line therapy



Quoix E, Lancet, 2011; Gridelli, JCO, 2018

COLON CANCER – EARLY STAGE

- **5-FU/leucovorin**
  - 24% reduction in mortality (overall survival 71% versus 64%) and a 32% reduction in stage II-III disease recurrence
  - Same rates of adverse events versus younger patients except for higher rate of G3-4 neutropenia (8% versus 4%)
  - 1/3 patients aged 65+ not able to complete 6 months of treatment
- **Capecitabine**
  - Similar efficacy compared to younger patients
  - Increased rates of diarrhoea and dehydration in 65+ patients
  - Caution in very old patients, particularly with diminished **renal function**
- **Oxaliplatin** – uncertain efficacy and safety

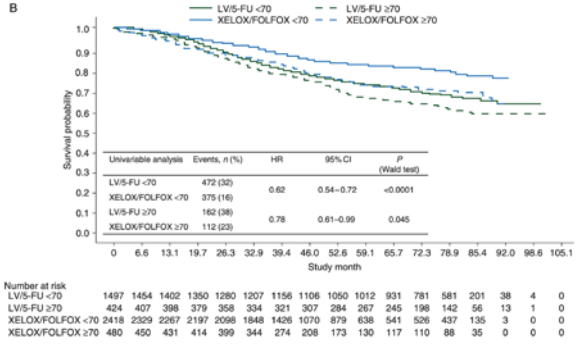


Figure 2. Kaplan–Meier plots of overall survival (A) for the intention-to-treat population, (B) by age (<70 versus ≥70 years), (C) by Charlson Comorbidity Index (≤1 versus >1), and (D) by National Cancer Institute Combined Index (≤1 versus >1). 5-FU, 5-fluorouracil; FOLFOX, leucovorin, 5-fluorouracil plus oxaliplatin; LV, leucovorin; XELOX, capecitabine plus oxaliplatin.

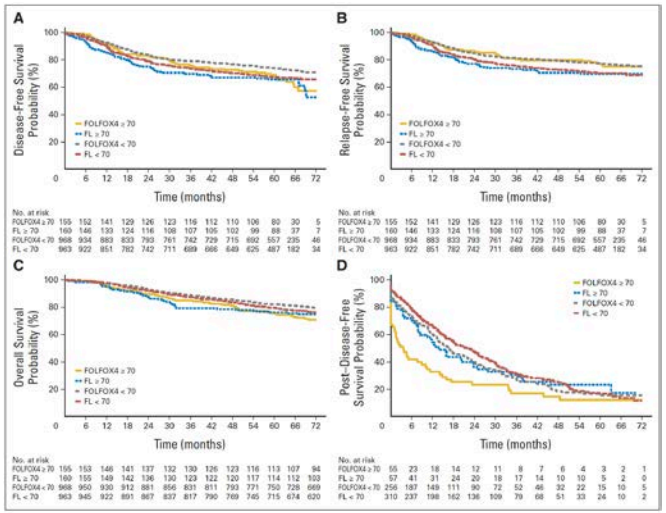


Fig 3. Rates of (A) disease-free, (B) relapse-free, (C) overall, and (D) post–disease-free survival in patients older than 70 years treated with leucovorin and fluorouracil with oxaliplatin (FOLFOX4) or without (FL).

Sargent, NEJM, 2001; Twelves, Ann Oncol, 2012; Schmoll, JCO, 2007; Tournigand, JCO, 2012; Haller, Ann Oncol, 2015

COLON CANCER – ADVANCED STAGE

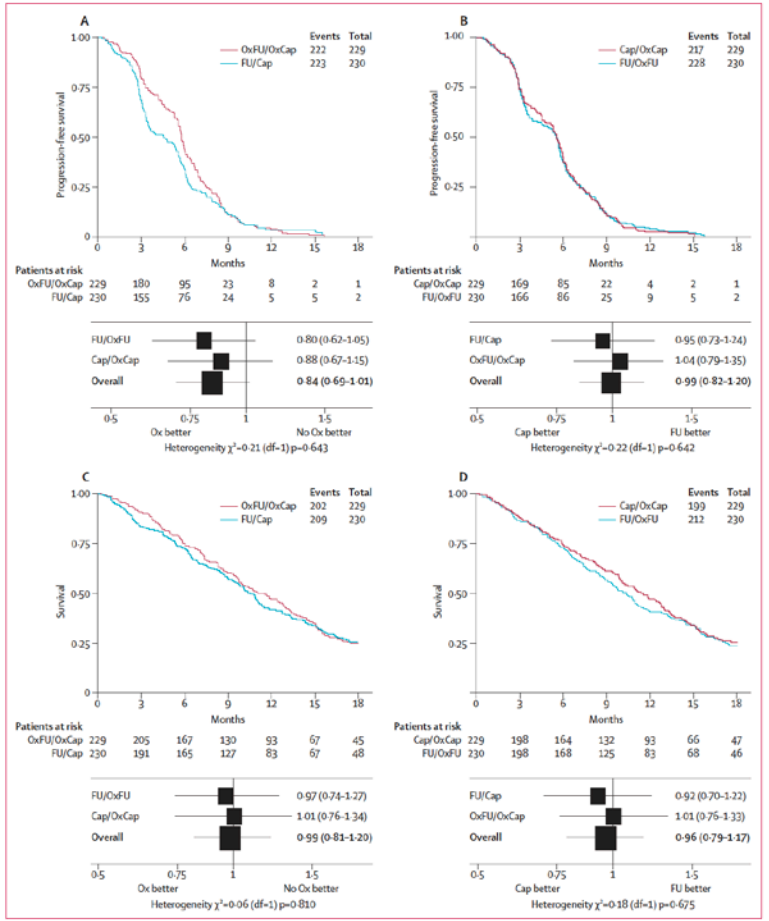
- Single-agent **5-FU**
  - Consistently tolerable and similar efficacy to younger patients – slightly higher rates of neutropenia
  - **De Gramont** better tolerated than bolus or Mayo regimen
- **Capecitabine**
  - Convenient oral dosing and similar efficacy versus 5FU - ORR 24% and G3-4 adverse events rate 12%
  - More frequent nausea, vomiting, diarrhoea, anorexia and HFS in oldest old and less fit
  - Start with **1000 mg/m²** bd and dose-escalate to tolerance

	Group A (FU; N=109)	Group B (OxFU; N=109)	Group C (Cap; N=112)	Group D (OxCap; N=110)	Factorial comparisons			
					Addition of oxaliplatin		Fluorouracil vs capecitabine	
					[A vs B]+[C vs D]	p	[A vs C]+[B vs D]	p
Any toxicity								
Grade ≥2	84 (77%)	81 (74%)	86 (77%)	94 (86%)	170 (77%) vs 175 (80%)	0·45	165 (76%) vs 180 (81%)	0·17
Grade ≥3	29 (27%)	36 (33%)	41 (37%)	47 (43%)	70 (32%) vs 83 (38%)	0·17	65 (30%) vs 88 (40%)	0·03
Nausea								
Grade ≥2	8 (7%)	17 (16%)	15 (13%)	27 (25%)	23 (10%) vs 44 (44%)	<0·0001	25 (12%) vs 42 (19%)	0·03
Grade ≥3	1 (1%)	2 (2%)	6 (5%)	5 (5%)	7 (3%) vs 7 (3%)	0·99	3 (1%) vs 11 (5%)	0·03
Vomiting								
Grade ≥2	5 (5%)	13 (12%)	12 (11%)	21 (19%)	17 (8%) vs 34 (16%)	0·01	18 (8%) vs 33 (15%)	0·03
Grade ≥3	1 (1%)	2 (2%)	3 (3%)	3 (3%)	4 (2%) vs 5 (2%)	0·73	3 (1%) vs 6 (3%)	0·33
Anorexia								
Grade ≥2	12 (11%)	15 (14%)	19 (17%)	26 (24%)	31 (14%) vs 41 (19%)	0·18	27 (12%) vs 45 (20%)	0·03
Grade ≥3	3 (3%)	3 (3%)	6 (5%)	4 (4%)	9 (4%) vs 7 (3%)	0·62	6 (3%) vs 10 (5%)	0·33
Stomatitis								
Grade ≥2	12 (11%)	13 (12%)	6 (5%)	12 (11%)	18 (8%) vs 25 (11%)	0·25	25 (12%) vs 18 (8%)	0·24
Grade ≥3	2 (2%)	3 (3%)	1 (1%)	2 (2%)	3 (1%) vs 5 (2%)	0·47	5 (2%) vs 3 (1%)	0·46
Diarrhoea								
Grade ≥2	20 (18%)	21 (19%)	23 (21%)	38 (35%)	43 (20%) vs 59 (27%)	0·06	41 (19%) vs 61 (28%)	0·03
Grade ≥3	5 (5%)	7 (6%)	10 (9%)	20 (18%)	15 (7%) vs 27 (12%)	0·05	12 (6%) vs 30 (14%)	0·003
Lethargy								
Grade ≥2	41 (38%)	46 (42%)	40 (36%)	47 (43%)	81 (37%) vs 93 (43%)	0·21	89 (40%) vs 87 (39%)	0·88
Grade ≥3	8 (7%)	10 (9%)	15 (13%)	16 (15%)	23 (10%) vs 26 (12%)	0·63	18 (8%) vs 31 (14%)	0·06
Pain								
Grade ≥2	17 (16%)	18 (17%)	24 (21%)	20 (18%)	41 (19%) vs 38 (17%)	0·74	35 (16%) vs 44 (20%)	0·30
Grade ≥3	9 (8%)	5 (5%)	11 (10%)	6 (5%)	20 (9%) vs 11 (5%)	0·10	14 (6%) vs 17 (8%)	0·61
Neurosensory								
Grade ≥2	2 (2%)	10 (9%)	4 (4%)	15 (14%)	6 (3%) vs 25 (11%)	0·0005	12 (6%) vs 19 (9%)	0·21
Grade ≥3	0 (0%)	1 (1%)	0 (0%)	4 (4%)	0 (0%) vs 5 (2%)	0·02	1 (1%) vs 4 (2%)	0·18
HFS								
Grade ≥2	1 (1%)	2 (2%)	24 (21%)	13 (12%)	25 (11%) vs 15 (7%)	0·10	3 (1%) vs 37 (17%)	<0·0001
Grade ≥3	0 (0%)	0 (0%)	11 (10%)	2 (2%)	11 (5%) vs 2 (1%)	0·01	0 (0%) vs 13 (6%)	0·0001
Platelets								
Grade ≥2	0 (0%)	2 (2%)	1 (1%)	2 (2%)	1 (0·5%) vs 4 (2%)	0·17	2 (1%) vs 3 (1%)	0·67
Grade ≥3	0 (0%)	1 (1%)	1 (1%)	1 (1%)	1 (0·5%) vs 2 (1%)	0·56	1 (0·5%) vs 2 (1%)	0·57
Anaemia								
Grade ≥2	20 (18%)	21 (19%)	14 (13%)	18 (16%)	34 (15%) vs 39 (18%)	0·49	41 (19%) vs 32 (14%)	0·22
Grade ≥3	3 (3%)	3 (3%)	1 (1%)	2 (2%)	4 (2%) vs 5 (2%)	0·73	6 (3%) vs 3 (1%)	0·30
Neutropenia								
Grade ≥2	6 (6%)	11 (10%)	3 (3%)	10 (9%)	9 (4%) vs 21 (10%)	0·02	17 (8%) vs 13 (6%)	0·42
Grade ≥3	3 (3%)	6 (6%)	2 (2%)	2 (2%)	5 (2%) vs 8 (4%)	0·39	9 (4%) vs 4 (2%)	0·15

D'Andre, Clin Colorectal Cancer, 2005; Feliu, JCO, 2005; Seymour, Lancet, 2011

COLON CANCER – ADVANCED STAGE

- **Oxaliplatin**
  - **FOLFOX** is just as effective and well tolerated in fit older patients enrolled in clinical trials, although slightly higher rates of side effects
  - In less fit patients enrolled in **MRC FOCUS2** trial:
    - FOLFOX produces higher ORR (38% versus 11%) and DCR (71% versus 46%)
    - Trend toward longer mPFS (5.8 versus 3.5 months) and OS (10.7 versus 10.1 months) with FOLFOX
    - Higher G3+ toxicities (33% versus 27%) (diarrhoea, neurosensory toxicity, nausea, vomiting and neutropenia) with oxaliplatin
  - **XELOX** is an effective alternative in fit older patients
- **Irinotecan**
  - Higher response rates with FOLFIRI versus 5FU alone (42% versus 21%) but no better PFS/OS and higher G3+ adverse events (76% versus 52%)
  - No differences in toxicity, PFS and OS in patients <70 versus ≥70 years on FOLFIRI
  - Infusional 5FU safer than bolus 5FU
- No age-specific data published about **TAS-102**



Sastre, Crit Rev Oncol Hematol, 2009; Arkenau, Clin Colorectal Cancer, 2008; Seymour, Lancet, 2011; Folprecht, JCO, 2006 (abs #3578); Jackson, Cancer, 2009; Aparicio, Ann Oncol, 2016

COLON CANCER – TARGETED AGENTS

- **Anti-EGFR MoAbs** – RAS and BRAF wild-type disease:
  - Comparable efficacy and no safety concerns on **Cetuximab** or **Panitumumab** in older adults versus younger individuals
  - **Single-agent Panitumumab** may be a well tolerated option in frail patients (mPFS 7.9 months and no G4 toxicities)
- **Bevacizumab**:
  - Similar efficacy in older versus younger adults
  - Higher rates of AEs in older patients enrolled in trials of bevacizumab versus no bevacizumab – PRODIGE 20: arterial hypertension 14% vs 6%
  - **AVEX study (Capecitabine +/- Bevacizumab)**:
    - Better mPFS: 9.1 versus 5.1 months
    - Trend toward longer mOS: 21 versus 17 months
    - Higher discontinuation rates (25% versus 15%), hypertension (19% versus 5%) and VTE (12% versus 5%)
- **Aflibercept, Regorafenib:** no age-specific toxicity data

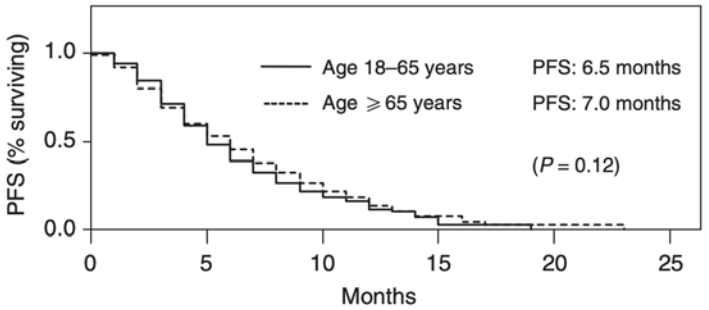
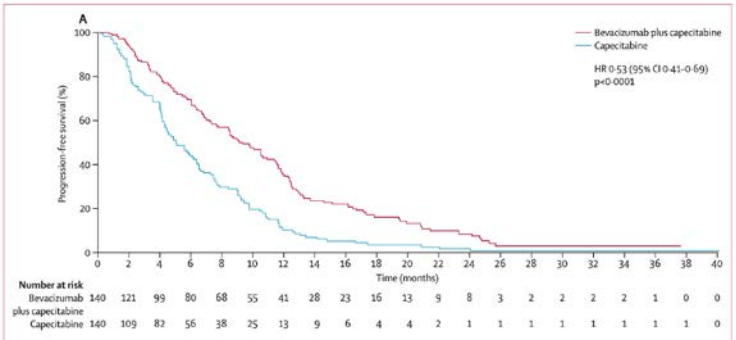
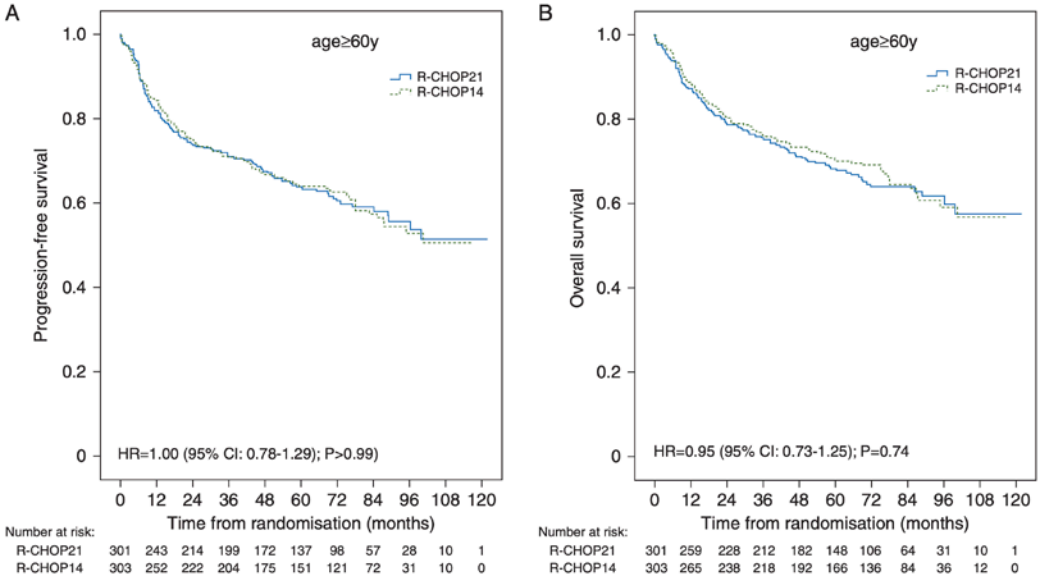


Figure 2 Progression-free survival of pts in age groups 18–65 years *vs* ⩾65 years clearly showing no difference between both patient subsets.



Jehn, Br J Cancer, 2012; Sastre, Oncologist, 2012; Sastre, EJC, 2015; Cassidy, J Cancer Res Clin Oncol, 2010; Cunningham, Lancet Oncol, 2013

DLBCL



- 5y-OS 69% (95% CI 65-73%)
- ≥98% median planned doses for all agents

Table 2. Most common grade ≥3 toxicities and cause of treatment-related deaths

	R-CHOP-21 (*N*=301)		R-CHOP-14 (*N*=303)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
All toxicities	292 (97%)	216 (72%)	299 (99%)	182 (60%)
Neutropenia	224 (74%)	185 (61%)	138 (46%)	109 (36%)
Thrombocytopenia	73 (24%)	22 (7%)	112 (37%)	37 (12%)
Anemia	60 (20%)	6 (2%)	95 (31%)	14 (5%)
Infection	145 (48%)	71 (24%)	146 (48%)	71 (23%)
Fever	70 (23%)	16 (5%)	56 (18%)	16 (5%)
Mucositis	143 (48%)	4 (1%)	167 (55%)	8 (3%)
Nausea	188 (62%)	7 (2%)	151 (50%)	12 (4%)
Vomiting	98 (33%)	7 (2%)	82 (27%)	9 (3%)
Diarrhoea	109 (36%)	12 (4%)	113 (37%)	16 (5%)
Constipation	185 (61%)	7 (2%)	160 (53%)	8 (3%)
Neurological	167 (55%)	23 (8%)	183 (60%)	36 (12%)
Fatigue	240 (80%)	31 (10%)	252 (83%)	40 (13%)
Bone pain	68 (23%)	7 (2%)	102 (34%)	6 (2%)
Cardiac	29 (10%)	2 (1%)	29 (10%)	9 (3%)

Table 3. Response to treatment

End of treatment response	**R-CHOP-21 (*N*=274) *n* (%)**	**R-CHOP-14 (*N*=274) *n* (%)**
Complete response (CR)	145 (53)	119 (43)
Unconfirmed complete response (CRu)	39 (14)	50 (18)
Partial response	64 (23)	80 (29)
Stable disease	16 (6)	16 (6)
Progressive disease or relapse	10 (4)	9 (3)
CR/Cru	184 (67)	169 (62)
Overall response rate	248 (91)	249 (91)

Fields, Br J Haematol, 2012; Kuhnl, Ann Oncol, 2017

DLBCL

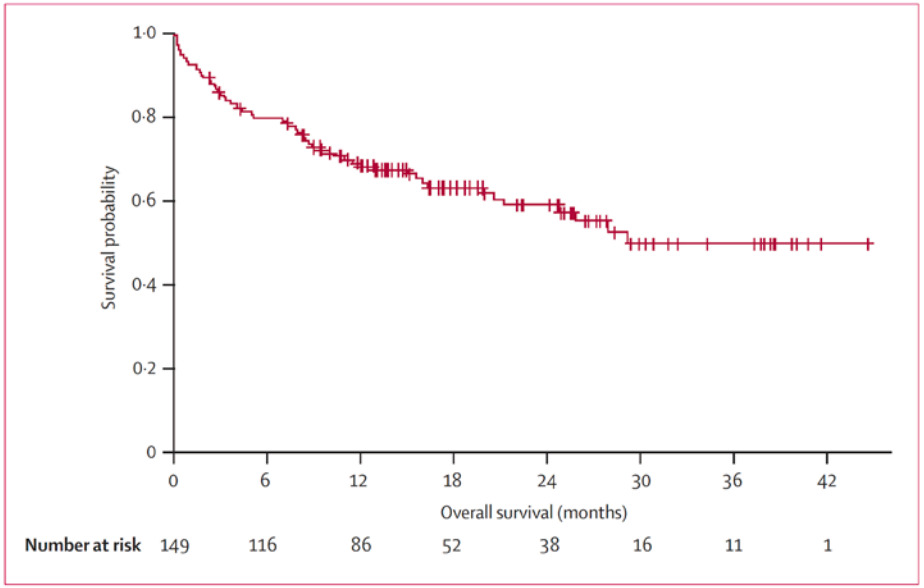


Figure 2: Overall survival

- **R-mini-CHOP** appropriate if concerns about R-CHOP21
  - G3+ neutropenia 39%, G3+ thrombocytopaenia 7%, febrile neutropenia 7%
  - ORR 74% (CR 63%)
  - 2y-OS 59% - 2y-PFS 47%

	Patients (n=149)
Men	51 (34%)
Age (years)	83 (80–95)
Performance status	
0	27 (18%)
1	72 (48%)
2	50 (34%)
Ann Arbor stage	
I	13 (9%)
II	24 (16%)
III	35 (23%)
IV	77 (52%)
Tumour mass ≥10 cm	30 (20%)
>1 extranodal sites	55 (37%)
LDH concentration >618 U/L	102 (68%)
B symptoms*	49 (33%)
β2-microglobulin ≥3 mg/L	82/112 (73%)
Serum albumin <35 g/L	69/137 (50%)
IPI	
0–1	13 (9%)
2	31 (21%)
3	46 (31%)
4–5	59 (40%)
Age-adjusted IPI	
0	15 (10%)
1	36 (24%)
2	66 (44%)
3	32 (21%)
IADL scale†	
Without limitation (score 4)	63 (47%)
With limitation (score <4)	72 (53%)

Data are number (%) or median (range). LDH=lactate dehydrogenase. IPI=international prognostic index. IADL=instrumental activities of daily living. Percentages do not add up to 100% in some cases because of rounding. *fever, night sweats, and weight loss. †Completed by 135 patients.

Table 1: Patient characteristics

Peyrade, Lancet Oncol, 2011

HODGKIN'S LYMPHOMA

- **ABVD** is standard of care
  - 60+ patients: CR 80%, 5y-OS 67%; G3+ toxicity 43% (lung 26%; hematologic 10%; infection 3%)
- **Bleomycin should not be routinely omitted or dose-reduced upfront** in order not to compromise cure
  - Pulmonary function tests after cycle 2 – omit B **in case of lung toxicity or in case of PET score 1, 2, 3**
  - Reasonably omitted in 80+ or very frail patients, if CrCl ≤5mL/min and in active smokers and/or in case of underlying pulmonary disease
- **Brentuximab vedotin + AVD?**
  - Single agent BV in older patients (median age 78 years):
    - ORR 92% - CR 73%
    - mPFS 10 months - mOS not reached
    - Peripheral neuropathy: 78%

Stamatoullas, Br J Haematol, 2015; Behringer, Lancet, 2015; Böll, Blood, 2016; Kumar, Blood, 2016; Forero-Torres, Blood, 2015; Evens, Hematol Oncol, 2015 (abs #089)

OUTLINE

- Introduction
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- Specific malignancies
  - Breast cancer
  - Non-small cell lung cancer
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  - Lymphoma
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OLDER ADULTS ARE HETEROGENEOUS

Cancer
Health behaviours
Access to healthcare
Geographical location
Social engagement and support
Comorbidities

FIT — **FRAIL**

Life expectancy

Comorbidities

Functional status

Polypharmacy

Organ reserve

Toxicities risk

Focus on survival

Focus on QOL

COMPREHENSIVE GERIATRIC ASSESSMENT: APPLYING GENERAL GERIATRICS TO ONCOLOGY

- Predicting **complications and side effects** from treatment
- Estimating **survival**
- Assisting in cancer **treatment decisions**
- Detecting **problems not found by routine evaluations**
- Identification and management of **new problems during follow-up**
- Improving **mental health and well being**
- Improving **pain control**

Tool by Domain	Time to Administer (min)	Abnormal Score
Demographic and social status		
Conditions of living, marital status, educational level, financial resources, social activities, family support	10	
Identification of the caregiver and burden (Zarit Burden Interview)	15-20	> 20
Comorbidity		
Charlson comorbidity index[11]	2	
CIRS[12]		
CIRS-G[13]		
Physical Health Section (subscale of OARS)[8]		
Simplified comorbidity score[14]		
Polypharmacy		
Beers criteria[15]		
STOPP and START criteria[16]		
Functional status		
ADL (Katz index)[17]		< 6
IADL (Lawton scale)[18]		< 8
Visual and/or hearing impairment, regardless of use of glasses or hearing aids		
Mobility problem (requiring help or use of walking aid)		
Timed Get Up and Go[19]		
Hand grip strength		≥ 14s
Walking problems, gait assessment, and gait speed[20,21]		< 1m·s^{-1}
Self-reported No. of falls (within different time frames)		
Cognition		
Mini-Mental State Examination[22,23]	10-15	< 24
Montreal Cognitive Assessment[24,25]		< 26
Clock-drawing test[26]		< 5
Blessed Orientation-Memory-Concentration Test[23]		> 4
Mini-Cog[27,28]		< 4

Tool by Domain	Time to Administer (min)	Abnormal Score
Mood		
GDS (Mini-GDS, GDS-15, GDS-30)[29,30]	15	Mini-GDS: < 1; GDS-15: > 5; GDS-30: > 10
Hospital Anxiety and Depression Scale[31,32]		> 7
Distress thermometer		
Nutrition		
Body-mass index (weight and height)		< 23
Weight loss (unintentional loss in 3 or 6 months)		
Mini-Nutritional Assessment[33,34]		< 24
Dentition		
Fatigue		
MOB-T[35]		
Geriatric syndrome[36]		
Dementia		
Delirium		
Incontinence (fecal and/or urinary)		
Osteoporosis or spontaneous fractures		
Neglect or abuse		
Failure to thrive		
Pressure ulcer		
Sarcopenia		

Abbreviations: ADL, activity of daily living; CIRS, Cumulative Illness Rating Scale; CIRS-G, Cumulative Illness Rating Scale-Geriatrics; GDS, Geriatric Depression Scale; IADL, instrumental activity of daily living; MOB-T, Mobility Tiredness Test; OARS, Older Americans Resources and Services; PS, performance status; START, Screening Tool to Alert Doctors to Right Treatment; STOPP, Screening Tool of Older Person's Prescriptions.

Wildiers, JCO, 2014; Loh, J Oncol Practice, 2018

PRE-CGA SCREENING TOOLS

Tool	No. of Items	Score Range	Time to Perform (min)	Abnormal Score	Sensitivity for Abnormal CGA (%)	Specificity for Abnormal CGA (%)	PPV (%)	NPV (%)	Positive Screen (%)
G8[56,58,59]	8	0-17	4.4	≤ 14	65-92	3-75	44-86	8-78	64-94
VES-13[60]	13	0-10	5.7	≥ 3	39-88	62-100	60-100	18-88	29-60
TRST[61]	5	0-6	2	≥ 1	91-92	42-50	81-87	63	74-82
GFI[59,62]	15	0-15	N/A	≥ 4	30-66	47-87	86-94	40-59	64-79
Abbreviated CGA[63]	15	–	4	≥ 1	51	97	97	48	68
Fried frailty criteria[63]	5	–	5	≥ 3	37-87	49-86	77-95	16-66	66-88
SAOP2[64]	27	–	N/A	≥ 1	100	40	90	100	84

Abbreviations: CGA, comprehensive geriatric assessment; G8, Geriatric 8; GFI, Groningen Frailty Index; NPV, negative predictive value; PPV, positive predictive value; SAOP2, Senior Adult Oncology Program 2; TRST, Triage Risk Screening Tool; VES-13, Vulnerable Elders Survey-13.

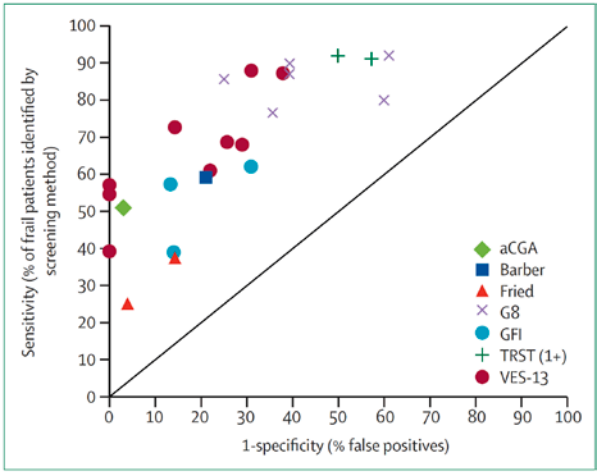


Figure 2: **Sensitivity and 1-specificity of screening methods for predicting outcome of comprehensive geriatric assessment**
aCGA=abbreviated comprehensive geriatric assessment. G8=Geriatric 8. GFI=Groningen Frailty Index. TRST=triage risk screening tool. VES-13=Vulnerable Elders' Survey-13.

- Recommended in a busy practice to **identify patients requiring full GA**
- **Limited power to predict outcomes of a CGA**
- If abnormal, **to be followed by GA and guided multidisciplinary interventions**

Decoster, Ann Oncol, 2014; Hamaker, Lancet Oncol, 2012; Loh, J Oncol Practice, 2018

CHEMOTHERAPY RISK ASSESSMENT SCALE FOR HIGH AGE (CRASH) SCORE

	Points		
Predictors	**0**	**1**	**2**
Hematologic score[a]			
Diastolic BP	≤72	>72	
IADL	26-29	10-25	
LDH (if ULN 618 U/L; otherwise, 0.74 /L*ULN)	0-459		>459
Chemotox[b]	0-0.44	0.45- 0.57	>0.57
Nonhematologic score[a]			
ECOG PS	0	1-2	3-4
MMS	30		<30
MNA	28-30		<28
Chemotox[b]	0-0.44	0.45-0.57	>0.57

Abbreviations: BP, blood pressure; Chemotox, toxicity of the chemotherapy regimen (for details, see text); ECOG PS, Eastern Cooperative Oncology Group performance status; IALD, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MMS, Mini Mental Health Status; MNA, Mini Nutritional Assessment; ULN, upper limit of normal.

[a] For the combined score, add the points from the hematologic and nonhematologic score, counting Chemotox only once.

[b] For examples of Chemotox values for specific regimens, see Table 6.

CRASH Points[b]

0	1	2
Capecitabine 2g	Capecitabine 2.5 g	5-FU/LV (Roswell-Park)
Cisplatin/pemetrexed	Carboplatin/gemcitabine AUC 4-6/1 g d1,d8	5-FU/LV (Mayo)
Dacarbazine	Carboplatin/pemetrexed	5-FU/LV and bevacizumab
Docetaxel weekly	Carboplatin/paclitaxel q3w	CAF
FOLFIRI	Cisplatin/gemcitabine d1,d8	Carboplatin/docetaxel q3w
Gemcitabine 1 g 3/4 wk	ECF	CHOP
Gemcitabine 1.25 g 3/4 wk	Fludarabine	Cisplatin/docetaxel 75/75
Paclitaxel weekly	FOLFOX 85 mg	Cisplatin/etoposide
Pemetrexed	Gemcitabine 7/8 wk then 3/4 wk	Cisplatin/gemcitabine d1,d8,d15
	Gemcitabine/irinotecan	Cisplatin/paclitaxel 135-24 h q3w
	PEG doxorubicin 50 mg q4w	CMF classic
	Topotecan weekly	Doxorubicin q3w
	XELOX	FOLFOX 100-130 mg
		Gemcitabine/pemetrexed d8
		Irinotecan q3w
		Paclitaxel q3w
		Docetaxel q3w
		Topotecan monthly

	CRASH score (points / % with severe toxicity)			
Sample	**Heme subscore**	**Non-Heme subscore**	**Combined score**	**Risk Category**
Derivation (n=347)	0-1: 7%	0-2: 33%	0-3: 50%	Low
	2-3: 23%	3-4: 46%	4-6: 58%	Int-Low
	4-5: 54%	5-6: 67%	7-9: 77%	Int-High
	Greater than 5: 100%	Greater than 6: 93%	Greater than 9: 79%	High
Validation	0-1: 12%	0-2: 42%	0-3: 61%	
	2-3: 35%	3-4: 59%	4-6: 72%	
	4-5: 45%	5-6: 66%	7-9: 77%	
	Greater than 5: 50%	Greater than 6: 100%	Greater than 9: 100%	

https://moffitt.org/for-healthcare-providers/clinical-programs-and-services/senior-adult-oncology-program/senior-adult-oncology-program-tools/

Extermann, Cancer, 2012

CANCER AND AGING RESEARCH GROUP MODEL

Table 5. Predictive Model

Risk Factor	Prevalence No.	Prevalence %	Grades 3 to 5 Toxicity No.	Grades 3 to 5 Toxicity %	OR	95% CI	Score
Age ≥ 72 years	270	54	163	60	1.85	1.22 to 2.82	2
Cancer type GI or GU	185	37	120	65	2.13	1.39 to 3.24	2
Chemotherapy dosing, standard dose	380	76	204	54	2.13	1.29 to 3.52	2
No. of chemotherapy drugs, polychemotherapy	351	70	192	55	1.69	1.08 to 2.65	2
Hemoglobin < 11 g/dL (male), < 10 g/dL (female)	62	12	46	74	2.31	1.15 to 4.64	3
Creatinine clearance (Jelliffe, ideal weight) < 34 mL/min	44	9	34	77	2.46	1.11 to 5.44	3
Hearing, fair or worse	123	25	76	62	1.67	1.04 to 2.69	2
No. of falls in last 6 months, 1 or more	91	18	61	67	2.47	1.43 to 4.27	3
IADL: Taking medications, with some help/unable	39	8	28	72	1.50	0.66 to 3.38	1
MOS: Walking 1 block, somewhat limited/limited a lot	109	22	69	63	1.71	1.02 to 2.86	2
MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	218	44	126	58	1.36	0.90 to 2.06	1

Abbreviations: GU, genitourinary; IADL, instrumental activities of daily living; MOS, Medical Outcomes Study; OR, odds ratio.

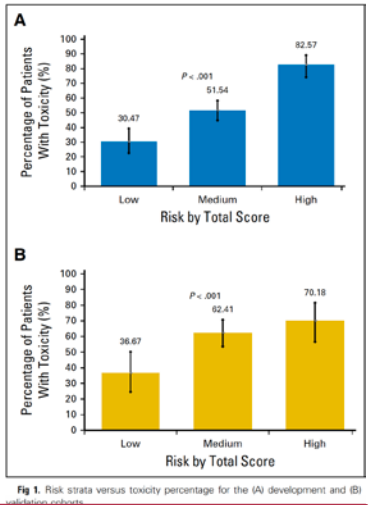
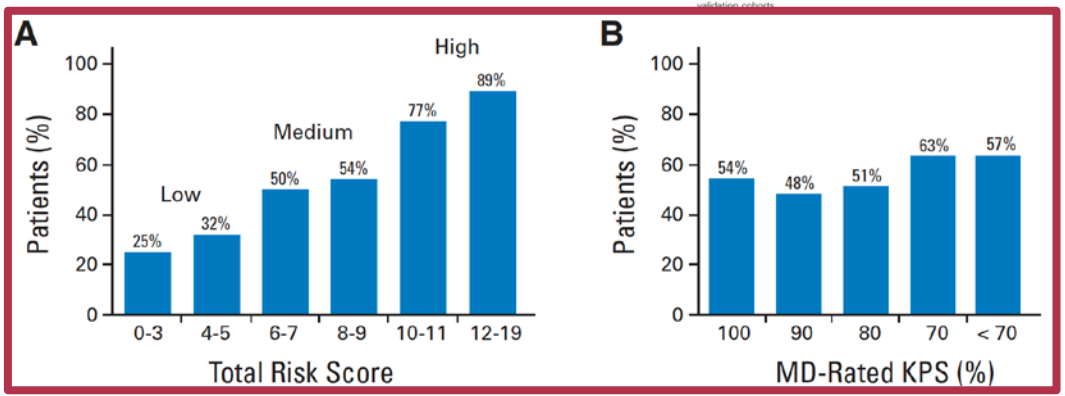


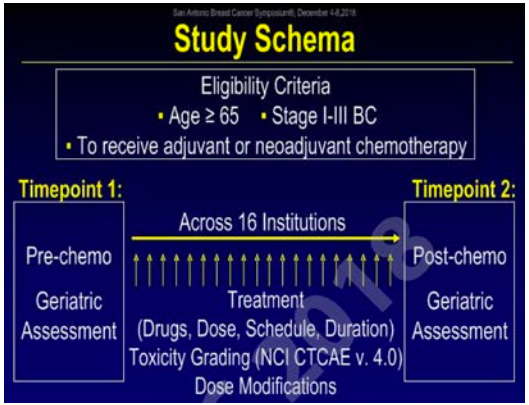
Fig 1. Risk strata versus toxicity percentage for the (A) development and (B) validation cohorts



http://www.mycarg.org/Chemo_Toxicity_Calculator

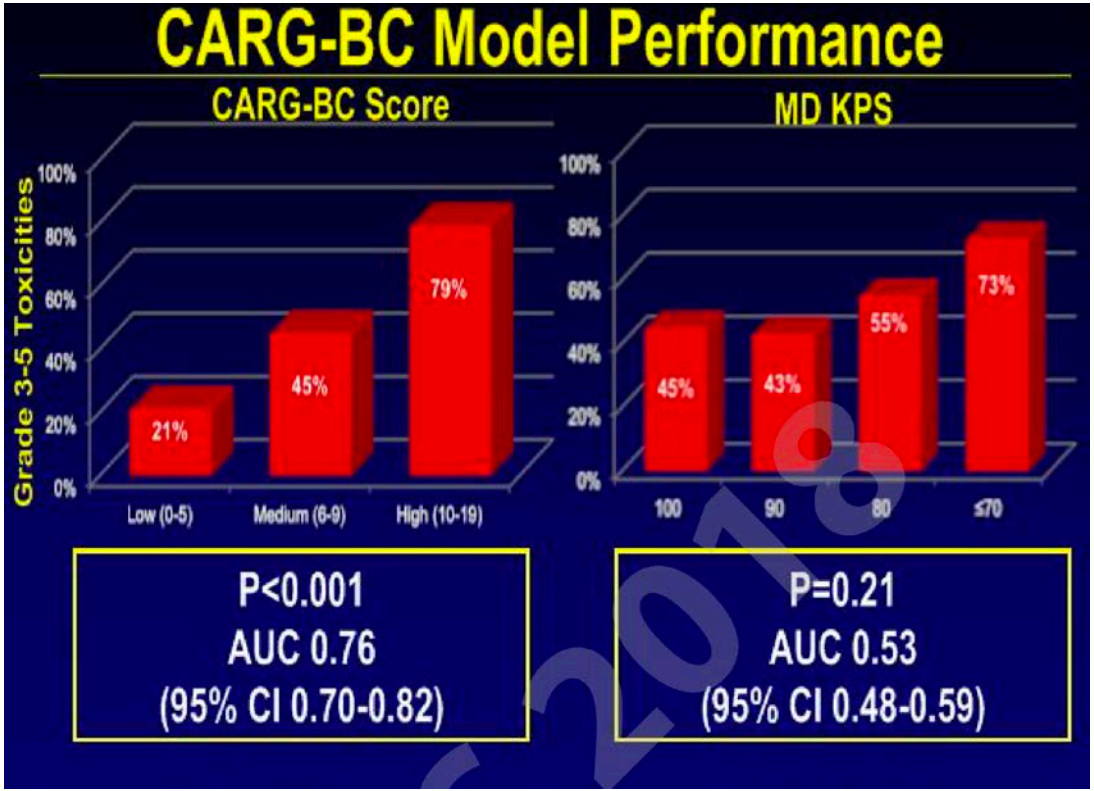
Hurria, JCO, 2011; Hurria, JCO, 2016

CARG-BC MODEL



CARG-BC Risk Score

Risk factors for Gr. 3-5 Toxicity	OR (95% CI)	Score
CARG Score: Medium Risk High Risk	2.47 (1.35-4.51) 2.26 (0.70-7.35)	3
Anthracycline	1.37 (0.65-2.85)	1
Stage II/III	1.79 (1.00-3.23)	2
Duration of tx > 3 months	2.98 (1.46-6.09)	4
Abnormal liver function	2.21 (0.90-5.47)	3
Limited in walking a mile	2.22 (1.21-4.05)	3
Lack of someone to provide advice	2.34 (0.99-5.58)	3



Magnuson, SABCS, 2018

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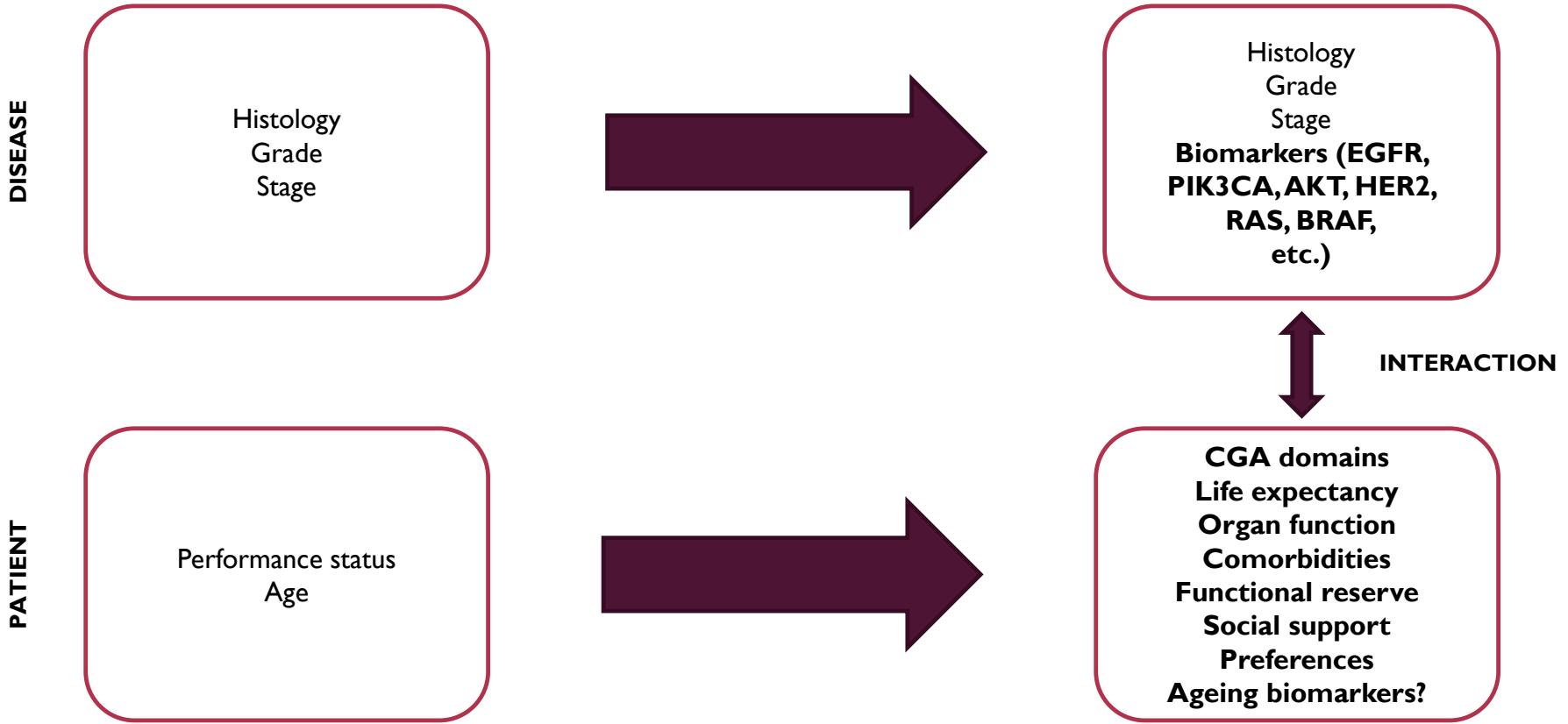
TOWARDS A NEW TREATMENT PARADIGM



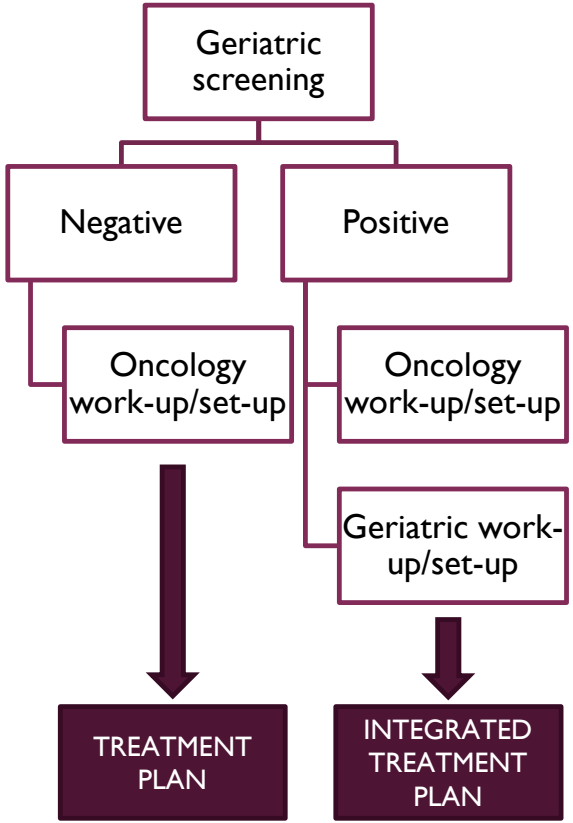
Adapted from a slide courtesy of Martine Extermann

MANY DIFFERENT MODELS FOR THE SAME GOAL

STEP 1: EVALUATE

STEP 2: INTEGRATE

STEP 3: ACTION



Adapted from a slide courtesy of Martine Extermann

TOOLS AND RESOURCES

- International Society of Geriatric Oncology http://www.siog.org/ @SIOGorg @YoungSIOG
- Cancer and Aging Research Group http://www.mycarg.org/ @myCARG
- British Geriatrics Society https://www.bgs.org.uk/ @GeriSoc
- Moffitt Cancer Center Senior Adult Oncology Program tools https://moffitt.org/for-healthcare-providers/clinical-programs-and-services/senior-adult-oncology-program/senior-adult-oncology-program-tools/
- Journal of Geriatric Oncology https://www.geriatriconcology.net/ @JGeriOnc
- #gerionc #gerihem

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