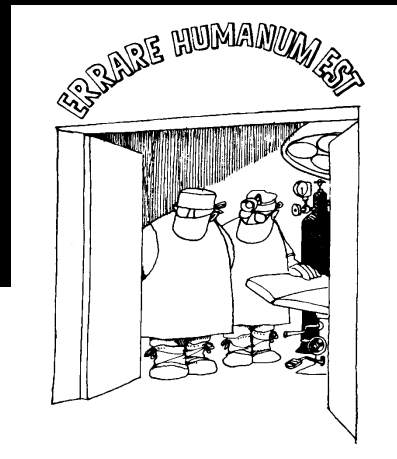
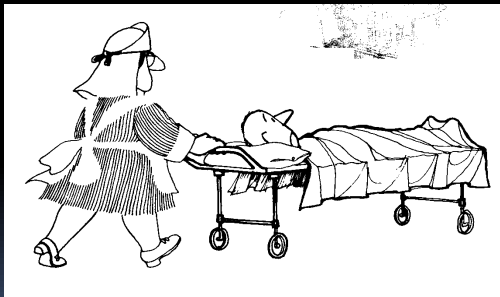


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CAN TOLERANCE TO TREATMENT IN OLDER CANCER PATIENTS BE PREDICTED?



PACE and 30 days morbidity

Morbidity	Yes (64)	No (149)	<i>p</i>
Co-morbidity	Median 2	Median 1	0.024
ECOG 0	46.9%	81.9%	<0.0001
ADL dep	59.4%	26.9%	0.005
IADL dep	40.6%	23.5%	0.043
GDS	Median 3	Median 2	0.018
ASA 1,2	45.1%	49%	NS
MMS, BFI	28/2.2	28/1.2	NS

Ramesh *Clin Interv Aging* 2006;1:221-7

PACE and post-op complications

No. altered variables	Risk of complications
0	18%
1	30%
2	50%
3	60%

Ramesh *Clin Interv Aging* 2006;1:221-7

Colorectal cancer surgery

- 178 patients 70+ yo
- Preoperative CGA

	FIT	FRAIL
	All of the following criteria	One or more of the following criteria
PADL	>18	<19
IADL	>43	
CIRS	No co-morbidity > grade 2	Any grade 4 co-morbidity
	<3 co-morbidities grade 2	>2 co-morbidities grade 3
Polypharmacy	<5 daily medications	>7 daily medications
MNA	≥24	<17
MMSE	>26	<24
GDS		>13

Patients who were neither "fit" nor "frail" were classified as intermediate.

30 days severe complications

	Any complication	<i>p</i> -Value (χ^2)	Complications grade II or above	<i>p</i> -Value (χ^2)
CGA classification				
Fit (<i>n</i> = 21)	10 (48%)		7 (33%)	
Intermediate (<i>n</i> = 81)	39 (48%)	.001	29 (36%)	.002
Frail (<i>n</i> = 76)	58 (76%)		47 (62%)	
Tumor location				
Colon (<i>n</i> = 126)	67 (53%)		49 (39%)	
Rectum (<i>n</i> = 52)	40 (77%)	.004	34 (65%)	.002
Type of surgery				
Open (<i>n</i> = 118)	78 (66%)		63 (53%)	
Laparoscopic (<i>n</i> = 52)	24 (46%)	.049	16 (31%)	.023
Converted (<i>n</i> = 8)	5 (63%)		4 (50%)	

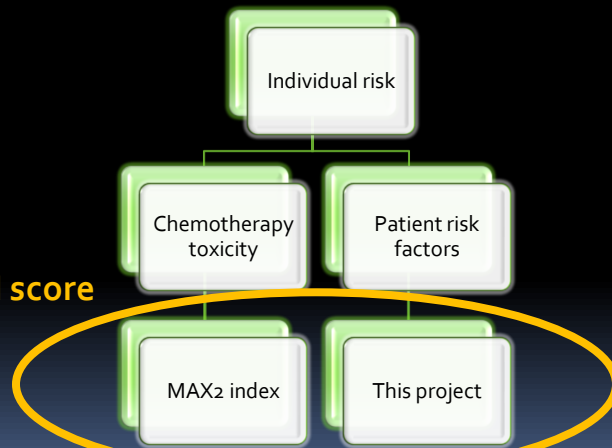
ASA score, age, stage, sex = NS

Kristjansson et al., 2011



Project framework

The CRASH score



Extermann et al., EJC 2002, 2004

The MAX2 index

Most frequent G₄ hem. tox + most frequent G₃₊₄ non-hem. tox

2

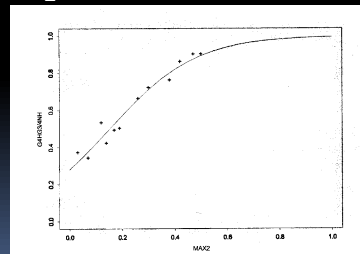
Example

25% grade 4 neutropenia
13% grade 3+4 diarrhea

$$\text{MAX2} = \frac{0.25 + 0.13}{2} = 0.19$$

Validation

4 ECOG trials
12 treatment arms
2526 patients



Extermann et al., EJC 2002, 2004

Extermann et al., EJC 2002

Methods

- Prospective multicentric study
- Prospective evaluation of toxicity
- Weekly CBC
- Regimen free, but published
- Management free
- 24 potential predictors
- G₄H or G₃₋₄ NH toxicity (CTCAE 3.0)

Results: Profile

- 585 eligible, 518 evaluable patients
- 337 Moffitt, 181 affiliates. Very similar baseline characteristics.
- Median age 76 (70-92)
- 23 tumor types
- 121 chemotherapy regimens (!)

End-points

- G₄H 32%
- G₃₋₄NH 56%
- Combined 64%
- Median time to 1st toxicity: 22 days
- Interquartile: 9-51 days

Global chemotoxicity prediction

- Hemoglobin and CrCl associated
- All models had poor fit (Nagelke $R^2 < 0.05$)
- From parallel work, increasing impression that G₄H & G₃₋₄NH have different predictors.
- We assessed a two subscores approach

Univariate predictors*

- **Heme**
 - Diastolic blood pressure
 - LDH
 - IADL
 - AST
 - Lymphocytes
- **Non-heme**
 - ECOG PS
 - Hemoglobin
 - Creatinine Clearance
 - Albumin
 - MMS
 - Self-rated health
 - MNA

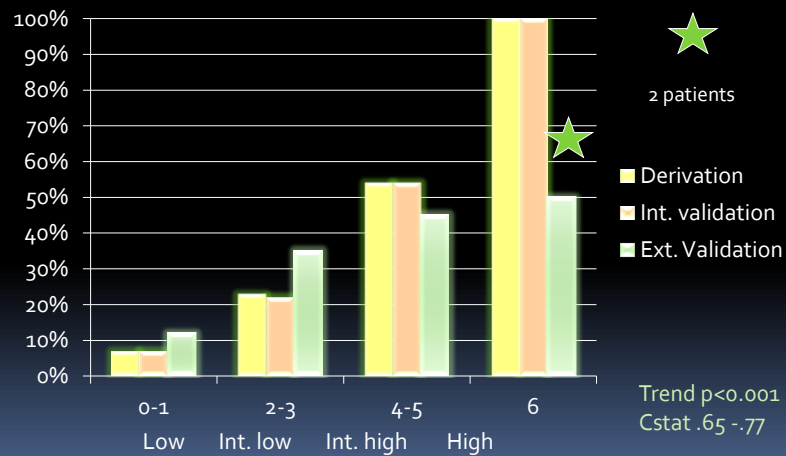
*adjusted for chemotox

Heme model

Item	0	1	2 points
DBP	≤ 72	> 72	
IADL	26-29	10-25	
LDH*	0-459		> 459
Chemotox	0-0.44	0.45-0.57	> 0.57

*ULN = 618

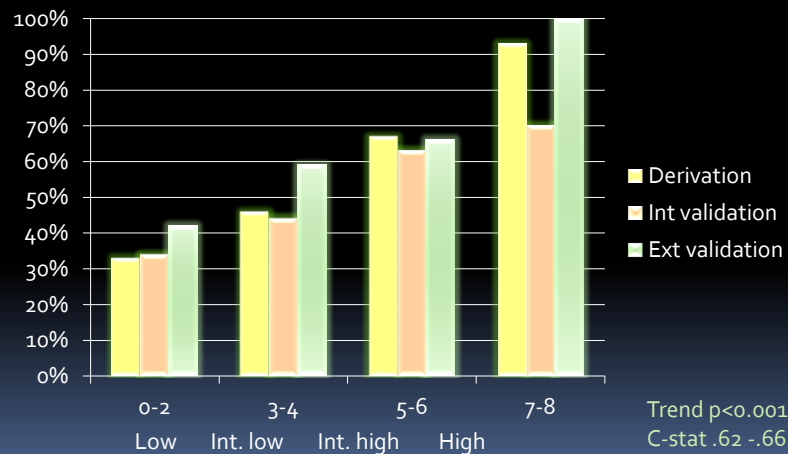
Heme model



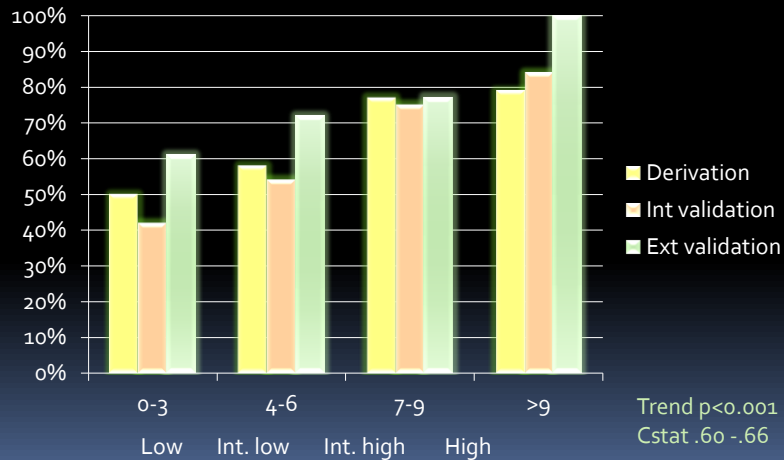
Non-heme model

Item	0	1	2 points
ECOG PS	0	1-2	3-4
MMS	30		<30
MNA	28-30		<28
Chemotox	0-0.44	0.45-0.57	>0.57

Non-heme model



Combined model



Conclusions I

- Validated model
- The split model is better than the unified model
- Geriatric instruments are helpful in oncology
- Splits are high on the geriatric instruments, so key impairments might be captured by shorter screens

Conclusions II

- Formal validation should be done for patients under 70.
- A global approach is sound given the striking number of chemo regimens we give to older cancer patients.
- Rating package available:
- www.moffitt.org/saoptools
- In press: Cancer 2011

Hurria et al. (model 2)

- | | |
|--------------------------------------|-------|
| ▪ Age >73 | 2 pts |
| ▪ GI/GU cancer | 3 pts |
| ▪ Standard dose chemo | 3 pts |
| ▪ Polychemo | 2 pts |
| ▪ Hb <11 in males, <10 in females | 3 pts |
| ▪ Creat cl <34 | 3 pts |
| ▪ Falls in last 6 months | 3 pts |
| ▪ Hearing impairment (fair or worse) | 2 pts |
| ▪ Limited in walking 1 block (MOS) | 2 pts |
| ▪ Needs help with meds (IADL) | 1 pt |
| ▪ Decreased social activity (MOS) | 1 pt |

ASCO 2010, abstr. 9001

Results

- Low: 0-5 27%
- Mid: 6-11 53%
- High: 12-25 83%
- ROC 0.72
- Internal validation: range 0.62-0.84

Chemo risk scores: Comparison

	CRASH	Hurria
Tox end-point	G4H + G3-4 NH	G3-5
Age	70+	65+
Chemo adjustment	MAX2	Tumor type, standard dose, poly/mono
Validation	Int. + external	Internal
ROC/c-stat	0.65-0.77H/0.62-0.66NH/0.64-0.65C	Mod I: 0.54-0.80 Mod II: 0.62-0.84
Simplicity	Full scales	items

Ability to complete chemo

- 202 patients 70+ receiving chemotherapy

Baseline test results in 192 subjects, comparing patients who received less than four cycles to patients who received four or more cycles of chemotherapy.

Test	Score	Number of cycles				p-Value
		<4 (n=74)		≥4 (n=118)		
		n	%	n	%	
MNA	Well nourished	37	51	86	75	0.001
	Risk of malnutrition/malnourished	35	49	29	25	
	Missings	2		3		
IQCODE	≥3.3	14	20	15	13	0.20
	<3.3	55	80	99	87	
	Missings	5		4		
GFI	<4	42	57	79	67	0.15
	≥4	32	43	39	33	
MMSE	>24	64	89	113	97	0.04
	≤24	8	11	4	3	
	Missings	2		1		

Aldricks et al., CROH 2011

Low risk of neutropenia

- 223 patients 70+ receiving chemotherapy
- Weekly CBCs
- Is there a subgroup that would not need them after the first cycle?

Janssen-Heijnen et al., CROH 2011

G4 neutropenia cycles 2+

Grade 4 neutropenia during subsequent cycles				
MAX2-score < 0.20		MAX2-score 0.20+		
%	P-value	%	P-value	
<i>Grade of hematological toxicity during first cycle</i>				
<i>Neutropenia 1st</i>				
0	4.6	0.0005	23	0.02
1	21		38	
2	18		50	
3	38		29	
4	46		64	

Febrile neutropenia if Go 1st cycle = 1.5%

Janssen-Heijnen et al., CROH 2011

