Prediction of toxicity of cancer treatments : metabolic factors

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Background

Drug toxicity in the elderly

Clinical Trials and Drug Toxicity in the Elderly

The Experience of the Eastern Cooperative Oncology Group

COLIN B. BEGG, PHD,* AND PAUL P. CARBONE, MD†

Nineteen studies of advanced cancer in 8 disease sites have been examined using data from the Eastern Cooperative Oncology Group. The purpose of the investigation was to determine susceptibility of elderly patients (≥70 years of age) to cancer chemotherapy and to compare the results with corresponding figures in control patients (<70 years of age). The results indicate that in general, the elderly patients have identical rates of severe toxicity as their younger counterparts. The only exception is for hematologic reactions in a few of the sites studied. On closer examination, the agents that appear to be responsible for these especially adverse effects are methotrexate and methyl-CCNU. It is demonstrated that the elderly patients have similar response rates and survival expectancy to the nonelderly patients. Consequently, it is concluded that the apparent discrimination in not treating elderly patients as aggressively as younger patients, and in excluding elderly patients from protocols, does not appear to be justified. Exclusions should be based on physiologic functional parameters, such as measures of renal, liver and marrow function, or performance status, rather than on an arbitrary age limit. Exceptions should only be made for agents which have a clearly demonstrated adverse effect on the elderly.

***Cancer* 52:1986–1992, 1983.**

There has long been interest in ways to predict and reduce the toxicity of chemotherapy, and more recently of targeted therapies or immune checkpoints inhibitors in the elderly.

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Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology

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Can we avoid the toxicity of chemotherapy in elderly cancer patients?

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Major Issues in geriatric oncology

Anticancer treatment feasibility

- Older patients are heterogeneous

- Tailoring cancer treatment to the individual requires weighing risks against benefits in the context of frailty

- Narrow therapeutic margin of anti-tumor treatments :

  - Over-treatment: increased risk of toxicities and acute complications

  - Under-treatment: risk of non-optimal treatment due to excess of caution

Tools Available for Predicting Treatment Toxicity in Older Adults With Cancer

ECOG PS: *these 1-item assessment do not capture the depth or complexity of health issues faced by older patients with cancer.*

Screening tools

Hematologic Toxicity Predictors	Point Score
Diastolic blood pressure >72 mm Hg	1
IADL score 10–25	1
Lactate dehydrogenase >459 U/L	2
Chemotherapy toxicity*	
0.45–0.57	1
>0.57	2
Nonhematologic Toxicity Predictors	**Point Score**
ECOG PS score	
1–2	1
3–4	2
Mini-Mental Health Status <30	2
Mini-Nutritional Assessment <28	2
Chemotherapy toxicity*	
0.45–0.57	1
>0.57	2
Chemotherapy Risk Category	**Total Point Scores**
Low	0–3
Medium low	4–6
Medium high	7–9
High	>9

*Based on individual chemotherapy regimen types: http://moffitt.org/media/4831.max2-score.xlsx.

CRASH tool

Risk Characteristics	Point Scores
Age ≥72 y	2
Gastrointestinal or genitourinary malignancy	2
Standard chemotherapy dose	2
Polychemotherapy	2
Hemoglobin: <11 g/dL (male), or <10 g/dL (female)	3
Creatinine clearance (Jelliffe, ideal weight) <34 mL/min	3
Hearing: fair or worse	2
Falls: ≥1 in past 6 mo	3
IADL: taking medications with some help/unable	1
MOS: walking 1 block, somewhat limited/limited a lot	2
MOS: decrease social activity from physical/emotional health, limited at least sometimes	1
Chemotherapy Risk Category (Incidence of Grade 3–5 Toxicity)	**Total Point Scores**
Low (30%)	0–5
Intermediate (52%)	6–9
High (83%)	10–19

MOS indicates Medical Outcomes Study.

CARG toxicity calculator

Extermann M. *et al* Cancer 2012; Hurria A. *et al* JCO 2011

~~Tools Available for Predicting Treatment Toxicity in Older Adults With Cancer~~

Comprehensive Geriatric Assessment:

functional status,
mobility,
nutritional status,
comorbidities,
cognition,
polypharmacy,
emotional status,
geriatric syndromes,
social support.

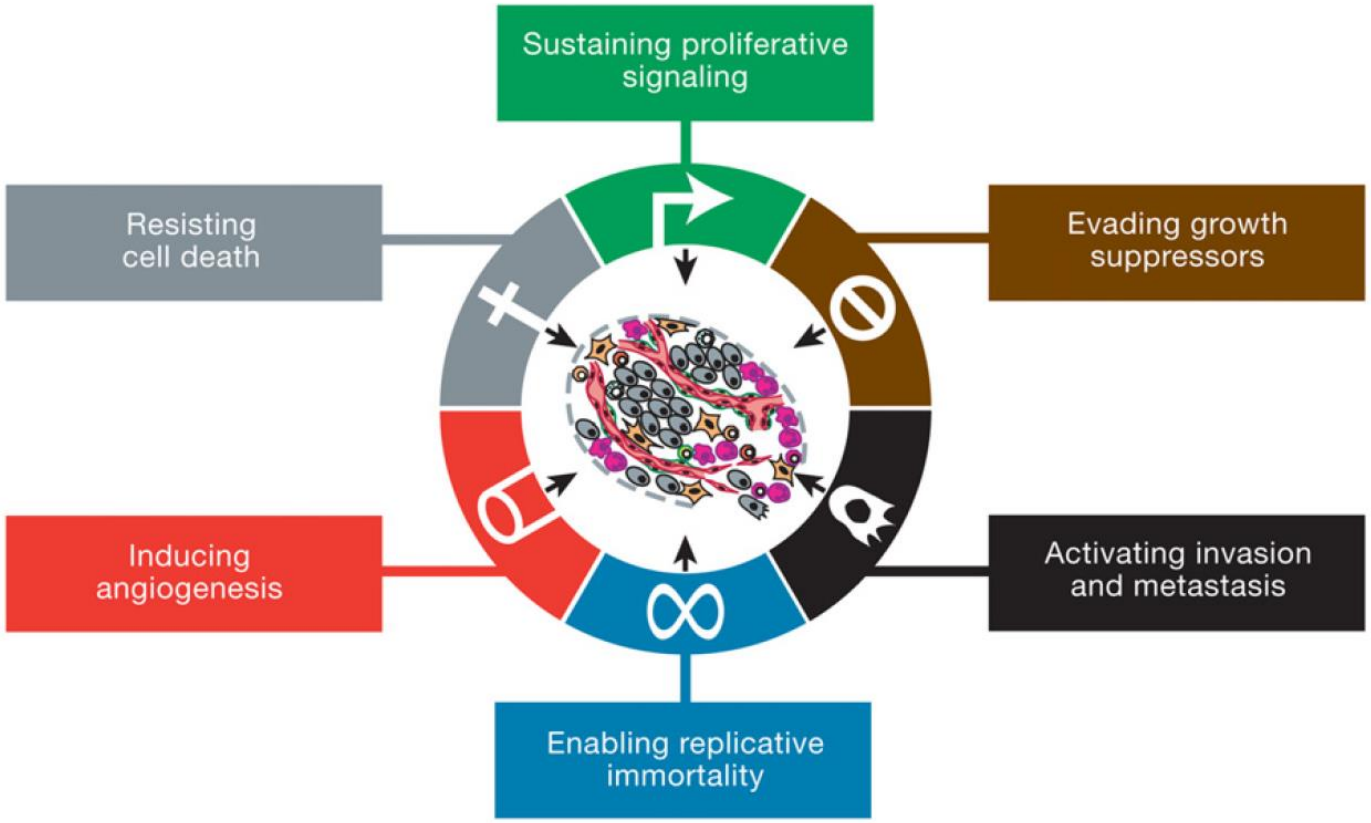
Mohile SG *et al.* JCO **2018** Aug 1;36(22):2326-2347; Koh W.J et al. Cancer **2020**, 126, 2416–2423
Extermann M *et al.* Crit. Rev. Oncol. Hematol. **2005**, 55, 241–252

Prospective studies of geriatric assessment to predict chemotherapy tolerance

	Geriatric assessment domain encompassed										
Study	N	Cancer	ADL IADL	Physical Performance	Comorbidities	Cognition	Medications	Depression	Geriatric syndromes	Social support	Nutrition
Marinello, R. 2009	110	Breast, lung or colo rectal	●		●	●					●
Aaldricks, A.A. 2011	202	Various				●			●		●
Hurria, A. 2011, 2016	750	Various	●	●	●	●	●	●	●	●	●
Extermann, M. 2012	518	Various	●		●	●	●	●			●
Luciani, A. 2015	648	Various	●		●	●	●			●	●
Retornaz, F. 2020	97	Colo rectal	●								

The emerging key role of energy metabolism

Hallmarks of cancer

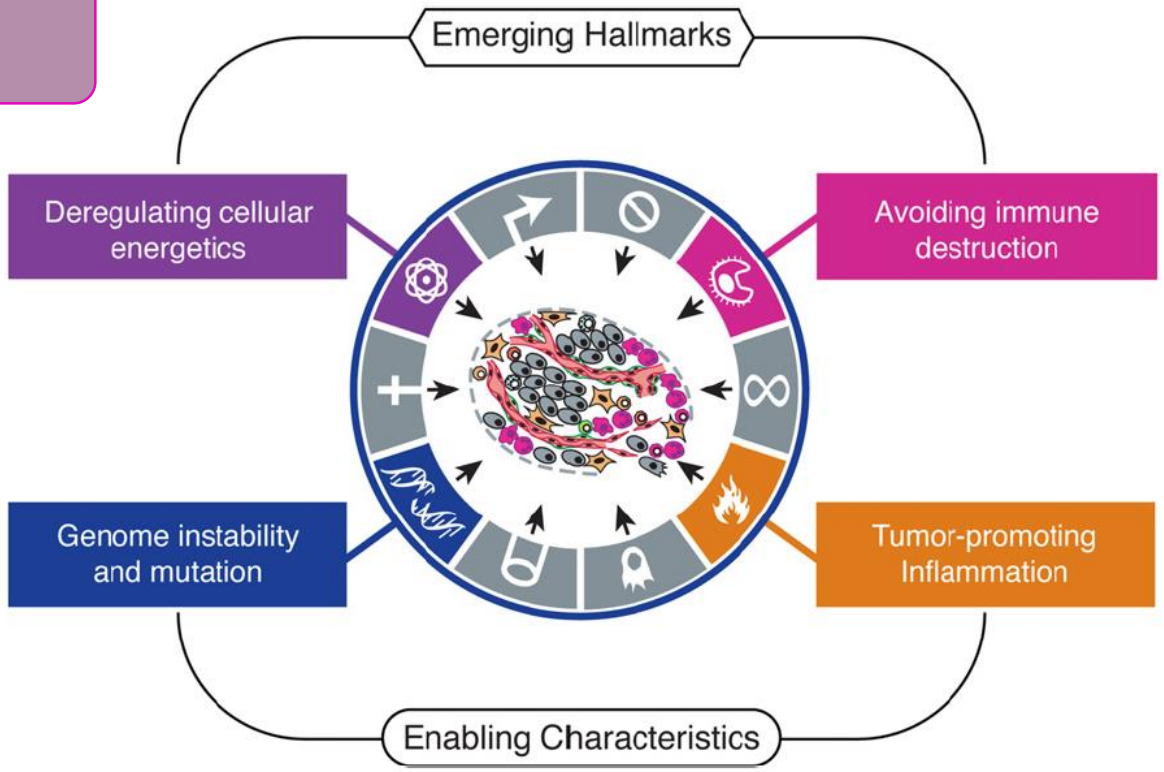


Hanahan D, Weinberg RA. Cell. 2000 Jan 7;100(1):57-70

The emerging key role of energy metabolism

Hallmarks of cancer

HOST



In 2011, "dysregulation of cellular energy metabolism" emerges as a key mechanism involved in cancer

(at the same time is identified "immune system escape")

Hanahan D and Weinberg RA. Cell. 2011 Mar 4;144(5):646-74.

Resting energy expenditure

Total Energy Expenditure

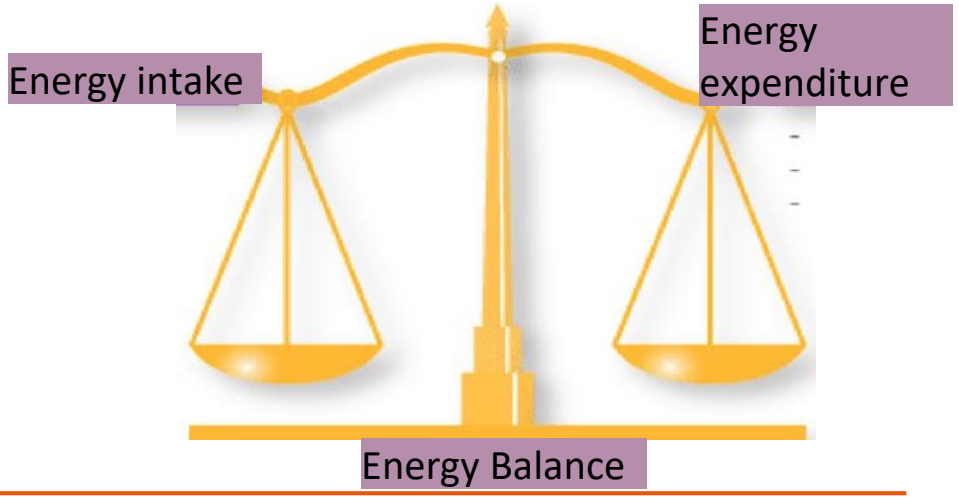
REE	+	Physical Activity	+	Thermogenesis
60-75%		15-30%		10%

REE varies according to :

- Age, sex, mass, genetics, feeding mode (energy availability)

Transient situations:

- physiological (growth, pregnancy)
  pathological (burn, infection, cancer)



Butte NF *et al*. Public Health Nutr 2005

Resting energy expenditure

Resting energy expenditure (REE) is the amount of energy expended in 24 hours by the body at rest.

It can be measurement :

- by direct or indirect **calorimetry** or
- calculated by formulas based on age, weight, height and sex, which are the major

basal energy expenditure predicted (pREE) by the revised **Harris-Benedict formula** :

male: pREE = 88.362 + 13.397 × weight + 479.9 × height − 5677 × age in years

female: pREE = 447.593 + 9247 × weight + 309.8 × height − 4.33 × age in years

Harris JA, Benedict FG. Natl Acad Sci USA. 1918;4(12):370–3.

Resting energy expenditure

Boothby and Sandiford have shown that 85% of the healthy population has an REE between 90% and 110% of the pREE predicted by the Harris and Benedict equation.

REE estimated by equations is within clinically acceptable limits when analyzed in a group.

However, in the cancer population, these equations fail to reflect the large variation in REE related to muscle mass, cancer type, dietary intake, medications, genetics…

Boothby WM, Sandiford RB. Boston Med Surg J. 1921;185:337–354

Resting Energy Expenditure measure

Based on the ratio of mREE to pREE (predicted by the revised Harris-Benedict formula), patients are classified according to the standards of *Boothby et al.* as :

- **hypo-metabolic** (mREE<90% pREE),
- **normo-metabolic** (90< mREE <110% pREE)
- **hyper-metabolic** (>110% pREE).

Roza AM, Am J Clin Nutr Jul; 40(1):168-82

Resting energy expenditure AND cancer

Abnormal metabolism is **frequent** among cancer patients

Hypermetabolism is an early determinant of cancer **cachexia**

Vazeille C *et al*. Am J Clin Nutr 2017 ;
Fearon K et al, Lancet Oncol 2011

HM was associated with negative energy balance, weight loss, systemic inflammation, alteration of performance status in a cohort of 390 adult cancer patients before chemotherapy initiation

Hypermetabolism

Hypermetabolism is associated with poor response and **poor survival** in cancer patients

Bosaeus I *et al*. J Nutr 2002
Vazeille C *et al*. Am J Clin Nutr 2017
Jouinot A *et al*. Clin Nutr 2019
Boudou-Rouquette P *et al.* E Biomedicine 2021

Hypermetabolism is associated associated with anticancer **treatment toxicity in adult cancer patients**

Jouinot A *et al*. Clin Nutr 2018

Resting energy expenditure AND older patients

Energy metabolism

Tendency to **hypo** metabolism

Pannemans DL *et al*. Br J Nutr 1995 ; **Rothenberg EM** *et al*. Br J Nutr 2000 ; **Lührmann PM** *et al*. Eur J Clin Nutr 2009

↘ REE : associated with greater frailty

Abizanda P *et al*. J Gerontol A Biol Sci Med Sci 2016

↘ Activity related expenditure: associated with greater mortality

Manini TM *et al*. JAMA 2006

Resting energy expenditure in older cancer patients

ELCAPA 25 study

Inclusion criteria

- Patients included in the ELCAPA cohort
- Between December 2014 and October 2018 at Cochin Hospital
- Age > 70 years old
- Geriatric assessment performed
- Referred for pre-treatment EGA
- Measurement of REE by IC
- Systemic treatment with toxicity monitoring

Data collected prospectively

- Tumor characteristics
- EGA
- Clinical factors
- Biological factors
- Basal metabolism (mREE, pREE, changes in metabolism expressed in %)

Data collected retrospectively

- Anti-tumor treatment performed
- Acute limiting toxicities over 3 months (hospitalization, delay or reduction or discontinuation of treatment)
- Calculation of predictive CARG and CRASH scores

Resting energy expenditure in older patients

Inclusion criteria	Data collected prospectively	Data collected retrospectively

Primary objective : assess the association between elevated REE and early limiting toxicities in older patients with cancer.

Secondary objectives : assess the discriminant ability of a predictive model including REE (relative to the CARG and CRASH scores) and the prognostic value of elevated REE.

Resting Energy Expenditure measure

REE (mREE, Kcal/d) was measured by a portable indirect calorimeter (IC) using a face mask system (Fitmate VM®, COSMED).

Under standard resting conditions (after a 6 h fasting, complete bed rest for 15 min, in a thermoneutral environment).

No smoking within 2h before examination.

During the IC test, the patients remained silent and awake.

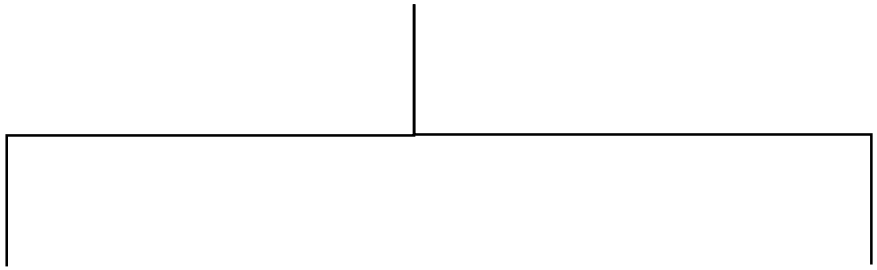
A first 5 min measurement was performed to reach the steady state which was defined by an average oxygen consumption (VO2) variation less than 10% and was then followed by a 10 min measurement for REE assessment.

The modified Weir equation was used to calculate REE.

de Weir JB. J Physiol. 1949;109:1–9.

Flow chart of patients study

*253 Patients were **assessed for eligibility** between December 2014 and October 2018*
- *Aged 70 or over*
- *With solid cancer*
- *Geriatric assessment performed*
- *Measurement of Resting Energy Expenditure by indirect calorimetry*
- *Systemic treatment with toxicity monitoring*



*179 Were **included** in ELCAPA METABO study*

*74 Were **excluded***
- *58 Did not receive systemic treatment*
- *11 Had uninterpretable calorimetry data*
- *5 Had missing toxicity data*

121 Received chemotherapy
21 Received targeted therapy (Tyrosine Kinase Inhibitors)
37 Received hormone therapy

The median age was 80 [IQ range: 76-84] years,
37% of the patients were female
81.8% had metastatic disease

Results : resting energy expenditure

	Overall population (N=242)	Patients who received systemic anti tumor therapy with toxicity assessment at 3 months (N=179)
measured REE (kcal/d) - median (IQ3)	1406 (1191 ; 1672)	1405 (1184 ; 1641)
predicted REE (kcal/d) - median (IQ3)	1279 (1129 ; 1426)	1317 (1149 ; 1465)
mREE/pREE - N (%)		
Hypometabolism (<90%)	39 **(16,1%)**	34 (17,7)
Normometabolism (90-110%)	77 **(31,8%)**	67 (34,9)
Hypermetabolism (>110%)	126 **(52,1%)**	91 (47,4)

Mean underestimation of DER by 88kcal/d
Difference between measured and predicted REE from -711kcal/d to +691kcal/d (ratio mREE/pREE varying from 46% to 200%)

Results : association between energy metabolism and CGA

CGA parameters	Metabolism (mREE/pREE)			p-value
	Hypometabolism (N=39) N (%)	Normometabolism (N=77) N (%)	Hypermetabolism (N=126) N (%)	
Patient living alone	9 (11,7)	29 (37,7)	39 (50,7)	0,276
ADL impaired (<6/6)	3 (6,5)	15 (32,6)	28 (60,9)	0,119
IADL impaired (<8/8)	17 (13,5)	39 (31,0)	70 (55,6)	0,346
Polypharmacy (≥5/d)	24 (15,6)	51 (33,1)	79 (51,3)	0,732
TGUG altered (>20s)	4 (10,3)	11 (28,2)	24 (61,5)	0,320
MNA altered (<24)	14 (12,2)	33 (28,7)	68 (59,1)	**0,028**
MMSE altered (<24)	4 (9,5)	15 (35,7)	23 (54,8)	0,405
Mini-GDS altered (≥1)	14 (18,0)	22 (28,2)	42 (53,9)	0,736
History of falls	11 (20,8)	12 (22,6)	30 (56,6)	0,216

Results : association between energy metabolism and nutritional and inflammatory parameters

Paramètres	Metabolism (mREE/pREE) Normo/Hypometabolism N (%)	Hypermétabolism N (%)	p
BMI (kg/m2)			0,361
21 to <25	42 (36,2)	47 (38,2)	
<21)	12 (10,3)	20 (16,6)	
25 to <30)	43 (37,1)	43 (35)	
Obesity (≥30)	19 (16,4)	13 (10,6)	
Weight loos			**0,011**
0-5%	85 (75,2)	74 (59,7)	
>5 à <10%	21 (18,6)	28 (22,6)	
≥10%	7 (6,2)	22 (17,7)	
Albumin <35g/L	16 (14)	33 (26,6)	**0,017**
CRP ≥10mg/L	35 (31,5)	51 (41,1)	0,127
GPS			**0,041**
0	69 (62,7)	66 (53,2)	
1	31 (28,2)	32 (25,8)	
2	10 (9,1)	26 (21)	
LDH >N	48 (44,9)	54 (45,8)	0,892

Results : early limiting toxicities description of patient's study

- A total of 38 different anticancer regimens and schedules were recorded.
- Sixty of the 179 patients (**33.5%**; 95%CI = [26.7-40.9]) experienced ELT within 3 months of treatment initiation.
- ELT was more frequent in patients treated with tyrosine kinase inhibitors (12 out of 21; **57.1**%) than those treated with intravenous cytotoxic chemotherapy (42 out of 121; **34.7**%) or with hormone therapy (6 out of 37; **16.2**%).

Predictive factors of toxicity at 3 months : univariate and multivariate analysis

Variables	P (univariate)
Age	0,281
Primary cancer	**0,019**
Cancer stage	0,910
Performance status	0,336
Comorbidities	**0,023**
Polypharmacy	0,247
BMI (kg/m²)	0,063
Weight loss (within last 6 months)	0,612
Social activities	0,091
ADL	0,752
IADL	0,138
TGUG	0,682
MMSE	0,365
mini-GDS	0,078
Depression	**0,012**
Antitumoral treatment	**0,014**
Dose	0,061
Albumin (g/L)	0,862
CRP (mg/L)	0,230
LDH (U/L)	**0,033**
mREE/pREE	**0,029**

Predictive factors of toxicity at 3 months : univariate and multivariate analysis

Variables		OR (IC95)	P (multivariate)
Primary cancer	Digestive	1,00 (ref.)	**0,037**
	Gynecological/breast	1,29 (0,24-6,87)	
	Prostate	4,82 (0,79-29,3)	
	Urinary tract	11,3 (2,04-62,6)	
	Lung	2,53 (0,54-11,8)	
	Other	1,71 (0,33-8,89)	
Comorbidities	>1 G3-4 (defined by CIRS-G)	2,26 (0,93-5,5)	0,073
Depression	Clinical judgment	3,09 (1,27-7,50)	**0,013**
Treatment	Hormone therapy	1,00 (ref.)	0,176
	Monochemotherapy	4,62 (1,06-20,1)	
	Polychemotherapy	5,96 (1,00-35,6)	
	Targeted therapy	8,58 (1,07-68,9)	
LDH (U/L)	≥N+100	1,81 (1,1-2,97)	**0,020**
mREE/pREE	Normometabolism (90-110)	1,00 (ref.)	**0,012**
	Hypometabolism (<90)	0,32 (0,07-1,44)	
	Hypermetabolism (>110)	2,44 (1,02-5,80)	

The discriminant ability of the multivariate model including REE and adjusted factors

	PREDICTIVE SCORES OF TOXICITIES RELATED TO CHEMOTHERAPY		
	Score CARG	Score CRASH	Elcapa Metabo composite score (including mREE/pREE)
C-index [IC95]	**0,57** [0,45-0,68]	**0,51** [0,40-0,62]	**0,82** [0,73-0,91]

Conclusion

- Poor accuracy of predictive equations for REE in older cancer patients
- Frequent abnormal metabolism
- Hypermetabolism: risk factor for toxicity of anti-tumor treatments
- Poor performance of predictive chemotoxicity scores (CRASH and CARG)
- Failure of these tests in other cohorts as well :

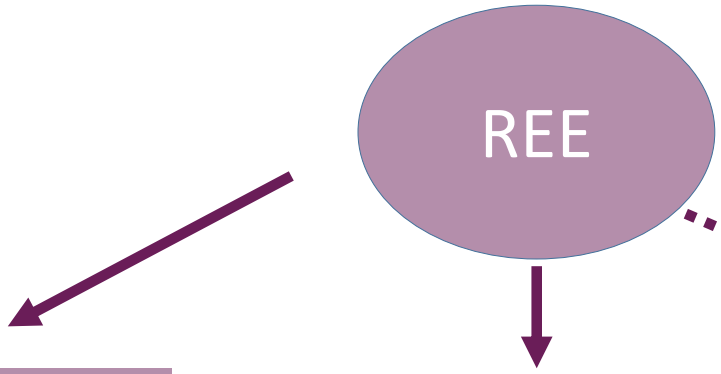
  Alibhai SMH et al. J Geriat Oncol 2017;

  Moth EB et al. J Geriat Oncol 2019 ;

  Frelaut M et al. ASCO 2020

Conclusion

- Independent early informative variable in patients (elderly or not) with cancer
- Measurement method adapted to current practice: portable indirect calorimetry
- Additional clinically significant tool to be integrated into the overall management



Routine clinical application

- Early identification of patients at risk of malnutrition
- Adaptation of energy intake to the measured REE

Clinical application in the future ?

- Use of REE to adjust the benefit-risk balance
- Adaptation of the prescription of anti-tumor treatments

Research

- Therapeutic target: metabolism-regulating treatments under study
- Correct hypermetabolism

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Merci de votre attention !

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Results : early limiting toxicities description of patient's study

Early Limiting Toxicities in the first three months	no.	%
Unplanned hospitalization	21	11.7
Emergency unit admission	15	8.4
Treatment delay >7 days	25	14.0
Dose reduction	22	12.3
Treatment discontinuation	32	17.9
Acute limiting haematological toxicity	17	9.5
Neutropenia	5	2.8
Febrile neutropenia	5	2.8
Thrombocytopenia	6	3.4
Anemia	5	2.8
Acute limiting non haematological toxicity	33	18.4
Altered general condition attributable to treatment	23	12.8
Infection without neutropenia	11	6.1
Renal toxicity	3	1.7
Digestive toxicity	12	6.7
Liver toxicity	3	1.7
Cardiovascular toxicity	6	3.4
Arterial hypertension	1	0.1
Skin toxicity	1	0.1