ESMO Symposium “Nutrition and Cancer”

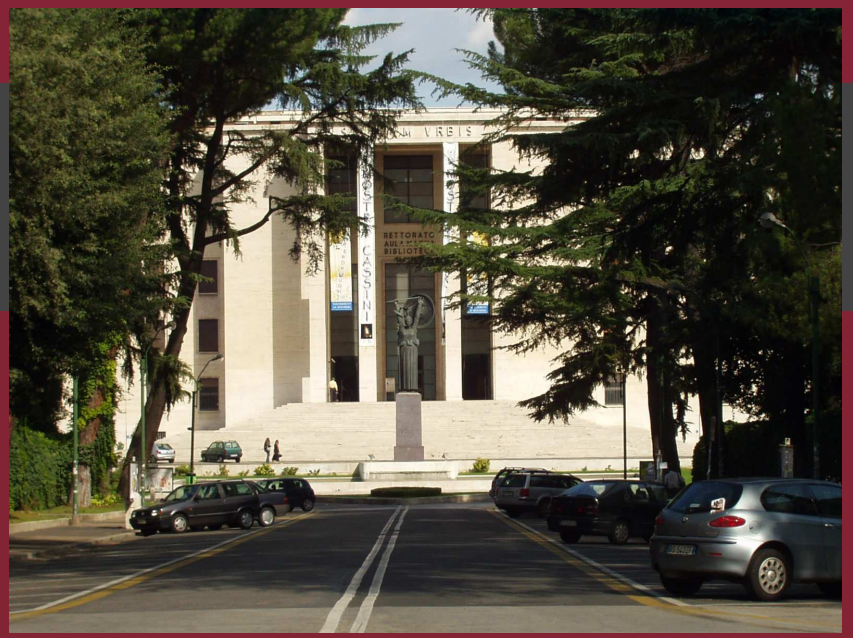
(Zurich, 20-21 March 2009)

The impact of malnutrition and overnutrition on cancer outcomes

Alessandro Laviano, MD

DIPARTIMENTO
DI MEDICINA CLINICA

SAPIENZA
UNIVERSITÀ DI ROMA



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OUTLINE

- **Malnutrition and survival**
- **Malnutrition and toxicity**
- **Fasting and treatment toxicity**
- **Does “reverse epidemiology” apply to cancer patients?**

Nutrition does make the difference …

- **From the mid-19th to mid-20th century, mortality ↓ in developed countries**
- **Search for historical evidence best explaining this phenomenon**
- **Best explaining factors: improved nutrition and immunological resistance**
- **Medicine largely irrelevant because effective interventions appeared only after mortality rates had already fallen substantially**

Mc Keown T et al. Popul Stud (Camb) 1975; 29:391-422
Birn A-E. Lancet 2005; 366:514-519

DeWys WD et al.

Prognostic effect of weight loss prior to chemotherapy in cancer patients

Am J Med 69:491-7, 1980

Effect of WL on median survival (wk)

Tumor	No WL	0-5% WL	5-10% WL	>10% WL	p
NSCL	20	17	13	11	<0.01
Prostate	46	30	18	9	<0.05
Colorectal	43	27	15	20	<0.01

Is malnutrition still a risk factor of postoperative complications in gastric cancer surgery?

"The present study suggests that weight loss and hypoalbuminemia are not associated with an increased risk of mortality and morbidity in patients who underwent surgery for gastric cancer. This study may represent a stimulus for further studies aiming at evaluating the actual role of malnutrition in the development of postoperative complications in major abdominal surgery."

Pacelli F et al. Clin Nutr 2008

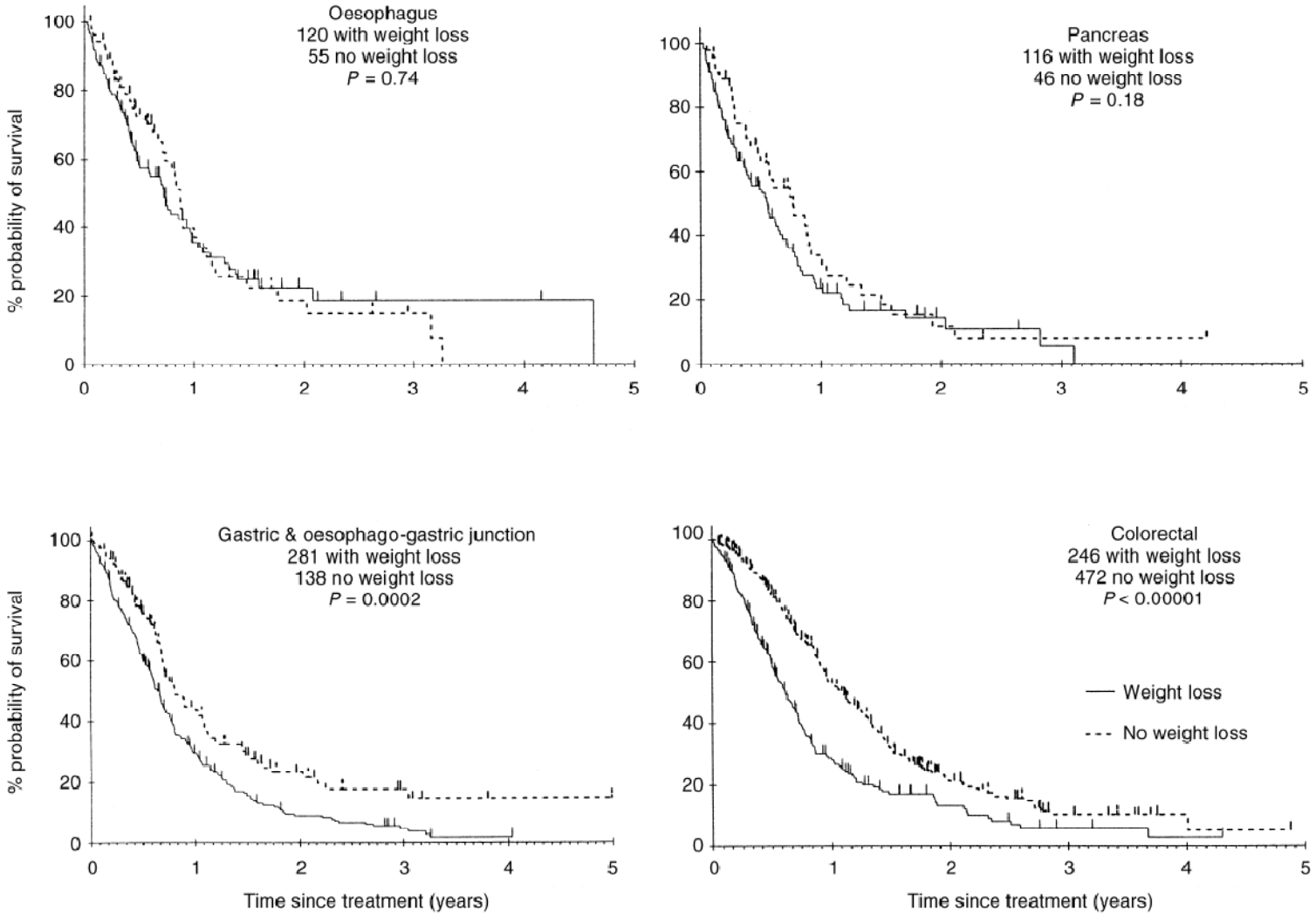


Figure 1. Effect of weight loss at presentation on overall survival.

Andreyev HJN et al. Eur J Cancer 1998

Table 2. Stomatitis induced by chemotherapy and its relationship to weight loss (missing values account for those percentages which do not add up to 100%)

	No weight loss	Weight loss	No weight loss	Weight loss	No weight loss	Weight loss	Any toxicity	Any toxicity stratified by site	Grade 0–2 compared with grade 3–4	Grade 0–2 versus 3–4 toxicity stratified by site
Grade of toxicity	0	0	1–2	1–2	3–4	3–4				
Oesophageal	44	51	48	42	4	7	$P=0.52$	$P<0.0001$	$P=0.42$	$P<0.005$
Gastric	59	44	33	43	4	9	$P=0.003$		$P=0.053$	
Pancreatic	51	39	40	50	3	9	$P=0.48$		$P=0.1$	
Colorectal	60	48	34	45	3	6	$P=0.001$		$P=0.18$	

Table 3. Plantar-Palmar syndrome induced by chemotherapy and its relationship to weight loss at presentation (missing values account for those percentages which do not add up to 100%)

	No weight loss	Weight loss	No weight loss	Weight loss	No weight loss	Weight loss	Any toxicity	For any toxicity stratified by site	Grade 0–2 compared with grade 3–4	Grade 0–2 versus 3–4 toxicity stratified by site
Grade of toxicity	0	0	1–2	1–2	3–4	3–4				
Oesophageal	65	65	27	33	5	2	$P=0.82$	$P<0.0001$	$P=0.28$	$P<0.002$
Gastric	69	53	26	41	1	3	$P=0.0007$		$P=0.27$	
Pancreatic	71	52	22	39	1	7	$P=0.0001$		$P=0.08$	
Colorectal	52	46	42	45	2	8	$P=0.065$		$P=0.002$	

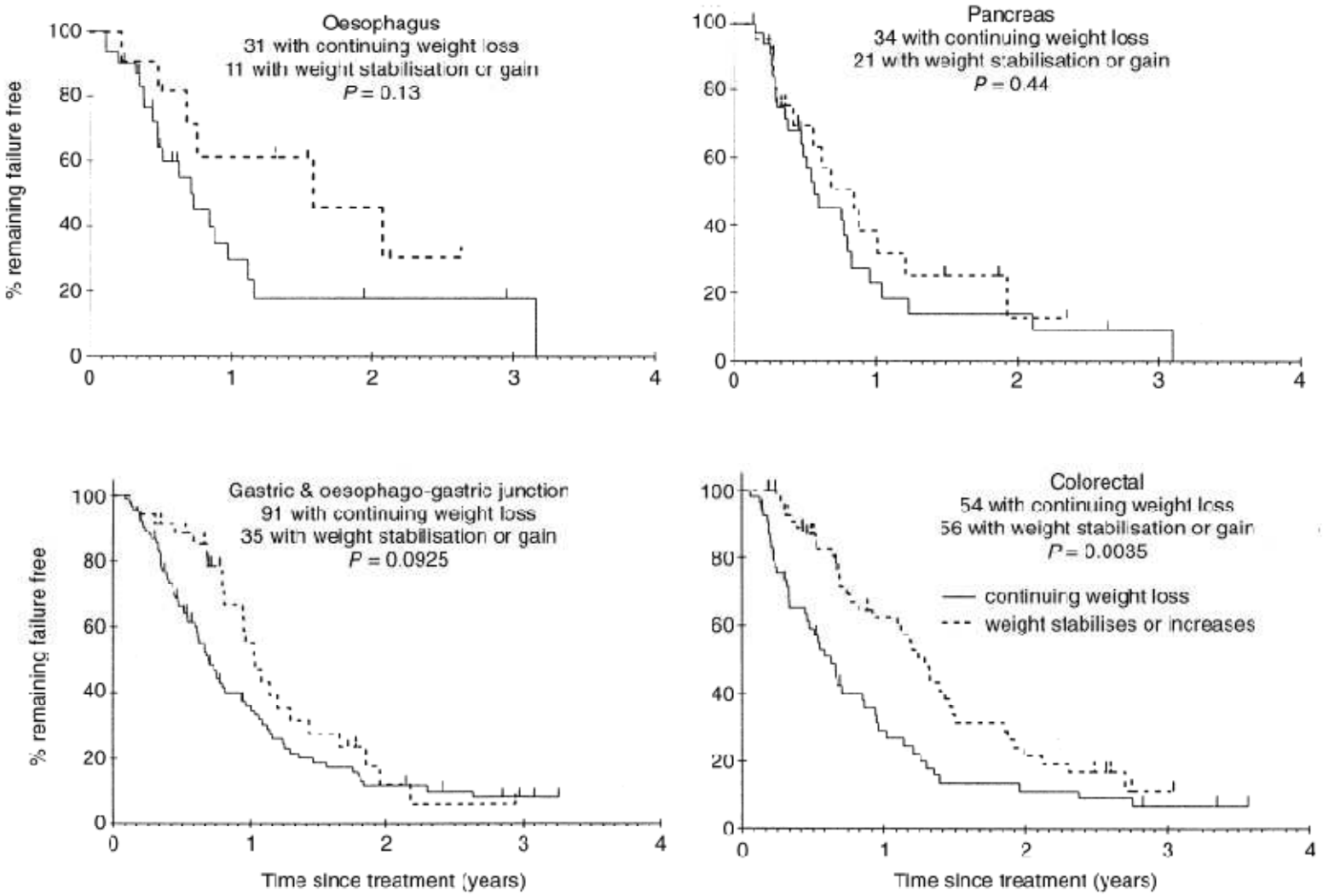


Figure 2. Effect of stabilisation of presentation weight loss over the first 120 days of treatment on failure-free survival.

Andreyev HJN et al. Eur J Cancer 1998

Nutritional status affects long term survival after lobectomy for lung cancer☆

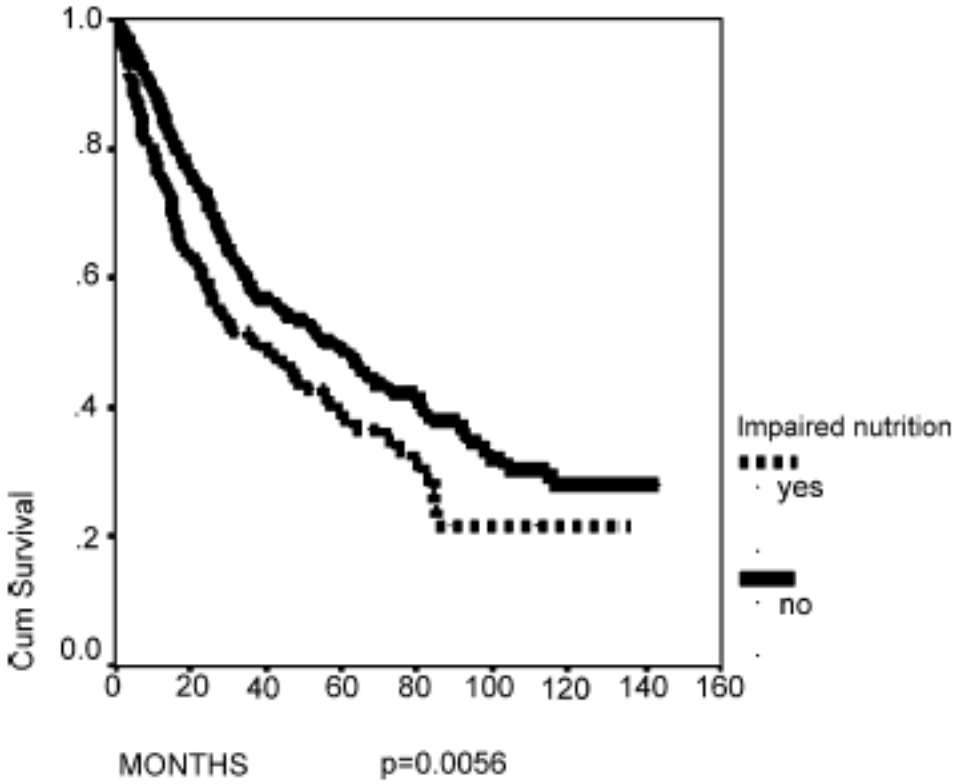
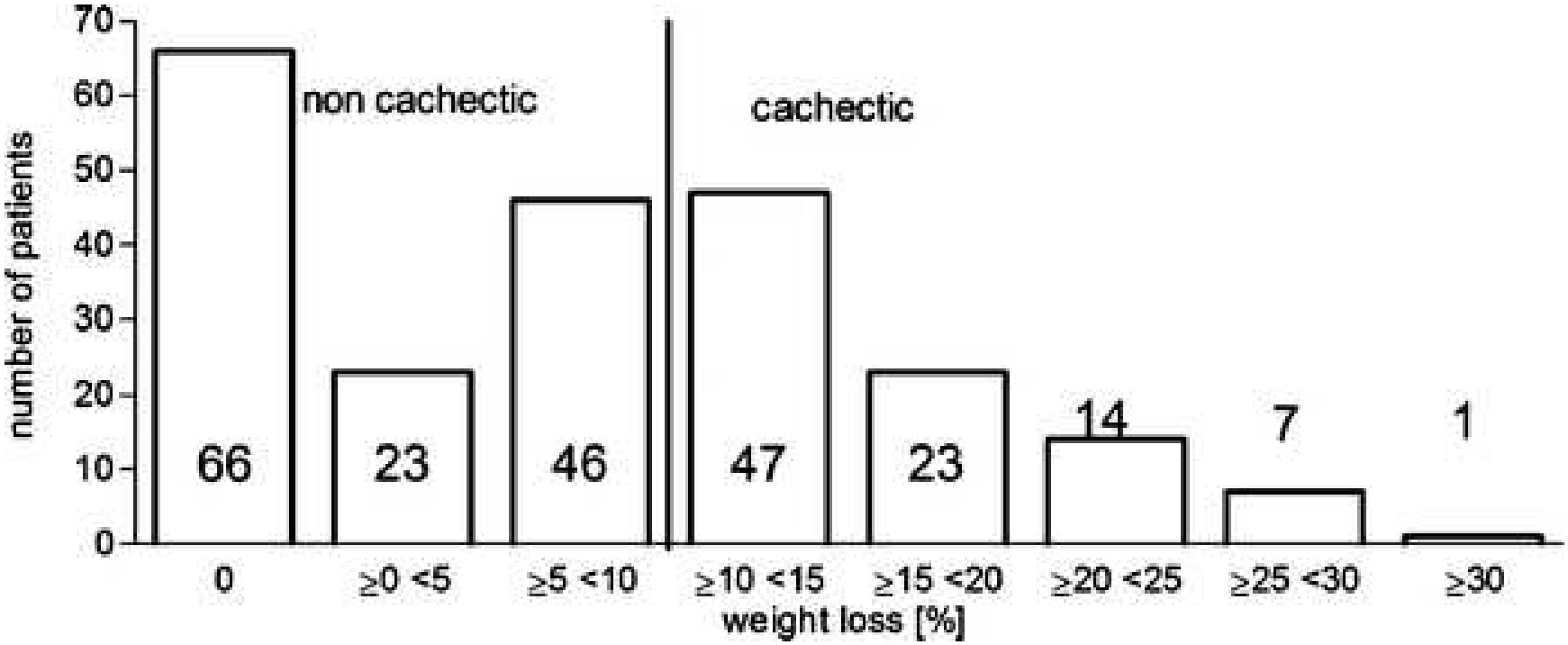


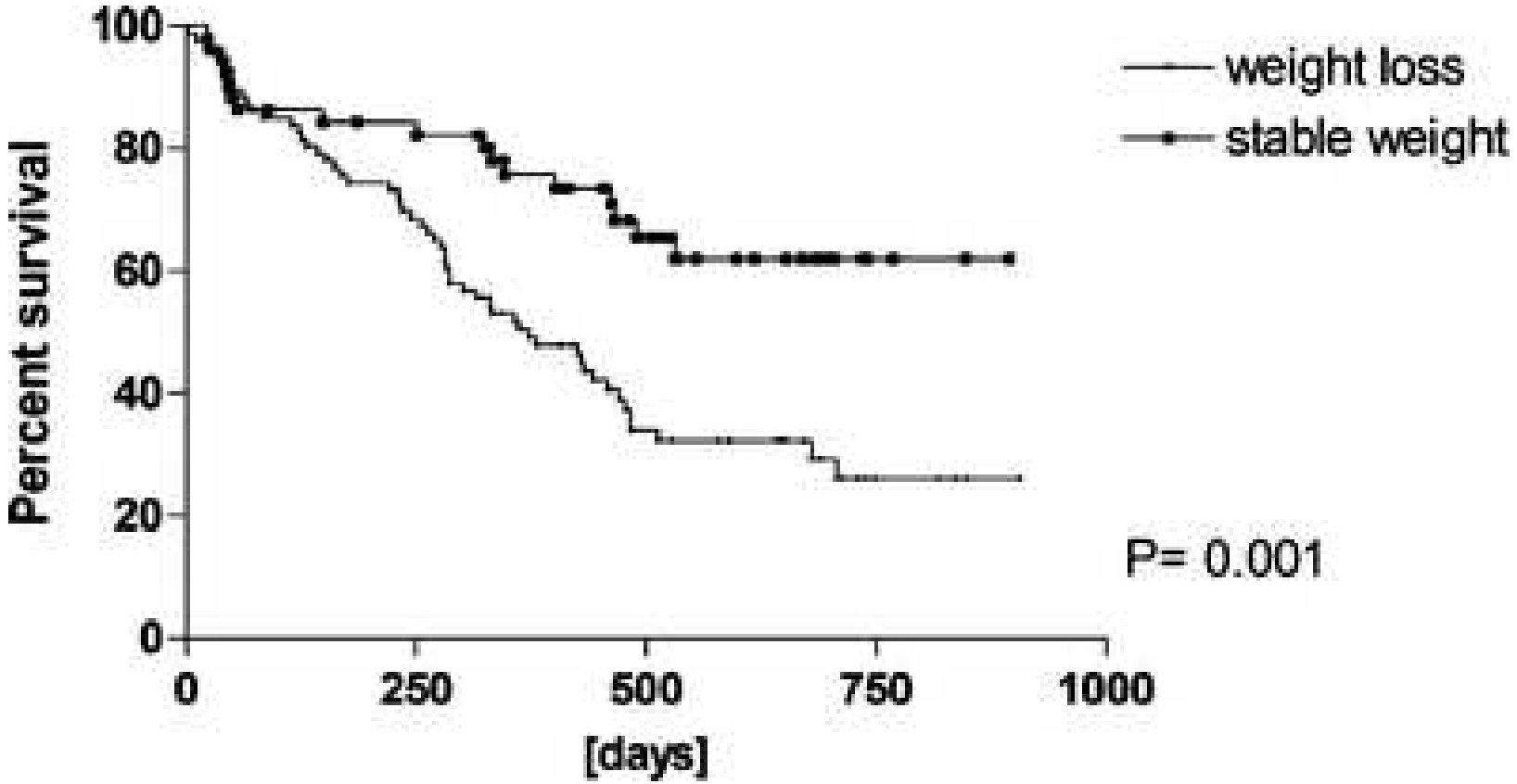
Fig. 3 Kaplan Meier survival with nutritional status.

Cachexia Worsens Prognosis in Patients with Resectable Pancreatic Cancer



Bachmann J et al. J Gastrointest Surg 2008

Cachexia Worsens Prognosis in Patients with Resectable Pancreatic Cancer



Bachmann J et al. J Gastrointest Surg 2008

Impact of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients With Stage II and III Rectal Cancer: Findings From Intergroup Trial 0114

Jeffrey A. Meyerhardt, Joel E. Tepper, Donna Niedzwiecki, Donna R. Hollis, A. David McCollum, Denise Brady, Michael J. O'Connell, Robert J. Mayer, Bernard Cummings, Christopher Willett, John S. Macdonald, Al B. Benson III, and Charles S. Fuchs

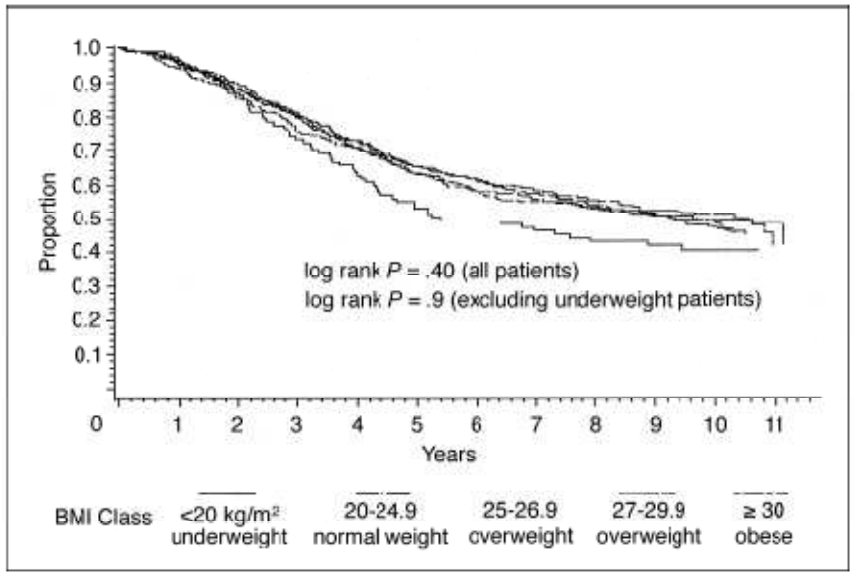


Fig 2. Overall survival by body mass index class among patients with rectal cancer.

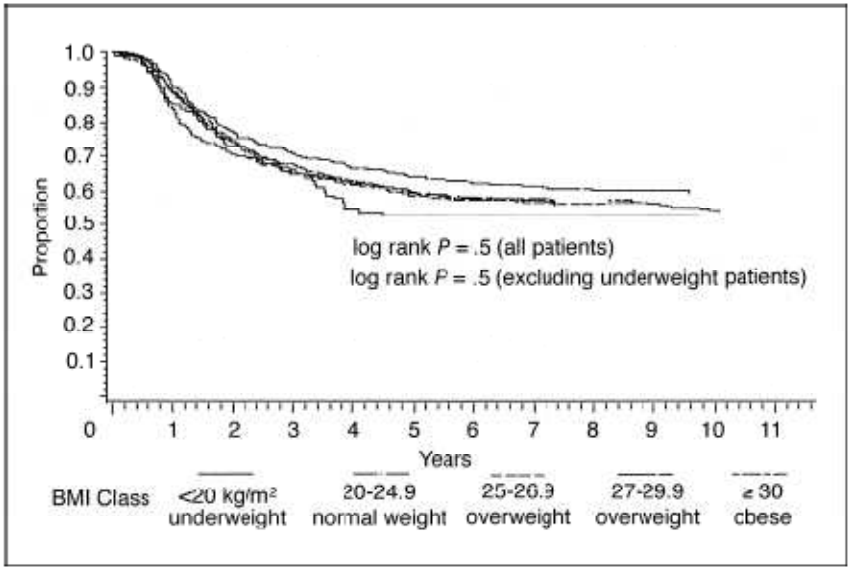


Fig 3. Recurrence-free survival by body mass index class among patients with rectal cancer.

Meyhardt JA et al. J Clin Oncol 2004

Impact of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients With Stage II and III Rectal Cancer: Findings From Intergroup Trial 0114

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Table 3. Five-Year Survival and Cancer Recurrence According to Body Mass Index Class

	BMI Class (kg/m^2)						
	< 20 kg/m^2	20-24.9	25-26.9	27-29.9	≥ 30	*P**	*P*† (≥ 20 kg/m^2)
5-year overall survival, %‡	53.1	65.5	63.5	65.2	62.9	.4	.9
Adjusted overall mortality§							
HR	1.43	Referent	0.97	0.95	1.09		.5
95% CI	1.08 to 1.89		0.80 to 1.17	0.78 to 1.15	0.90 to 1.33		
5-year disease-free survival, %‖	47.1	56.1	53.3	57.1	55.2	.6	.6
Adjusted disease-free mortality§							
HR	1.17	Referent	0.95	0.90	1.10		.5
95% CI	0.91 to 1.52		0.79 to 1.14	0.76 to 1.06	0.91 to 1.32		
5-year recurrence-free survival, %¶	52.5	59.8	58.7	64.0	59.5	.5	.5
Adjusted cancer recurrence§							
HR	1.16	Referent	1.01	0.88	1.08		.8
95% CI	0.85 to 1.58		0.81 to 1.24	0.71 to 1.09	0.87 to 1.33		
5-year local recurrence-free survival, %#	83.1	88.5	85.2	87.1	83.9	.5	.3
Adjusted local recurrence§							
HR	1.15	Referent	1.33	1.10	1.31		.17
95% CI	0.65 to 2.02		0.93 to 1.90	0.76 to 1.59	0.91 to 1.88		

Meyhardt JA et al. J Clin Oncol 2004

Impact of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients With Stage II and III Rectal Cancer: Findings From Intergroup Trial 0114

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Table 5. Major Treatment-Related Toxicity by Body Mass Index (% of patients)

	BMI Class					Unadjusted *P* Across All BMIs†	Adjusted *P**	
	< 20 kg/m²	20-24.9 kg/m²	25-26.9 kg/m²	27-29.9 kg/m²	≥ 30 kg/m²		BMI ≥ 20 kg/m²‡	BMI < 25 kg/m²§
Nausea‖	5.5	5.1	3.9	5.2	3.0	.5	.3	1.0
Emesis¶	5.5	4.6	2.2	4.1	3.3	.4	.4	.8
Diarrhea#	32.1	26.0	25.6	25.8	22.5	.4	.4	.19
Leukopenia**	32.1	28.5	26.1	23.8	20.1	.04	.01	.8
Neutropenia††	43.1	45.5	43.6	34.6	35.1	.003	.0005	.17
Stomatitis‡‡	12.2	9.8	9.6	6.7	4.7	.03	.01	.7
Any grade 3 or 4 toxicity	81.7	75.7	78.9	71.7	70.0	.02	.05	.5

Meyhardt JA et al. J Clin Oncol 2004

Prognostic Factors in Advanced Cancer Patients: Evidence-Based Clinical Recommendations—A Study by the Steering Committee of the European Association for Palliative Care

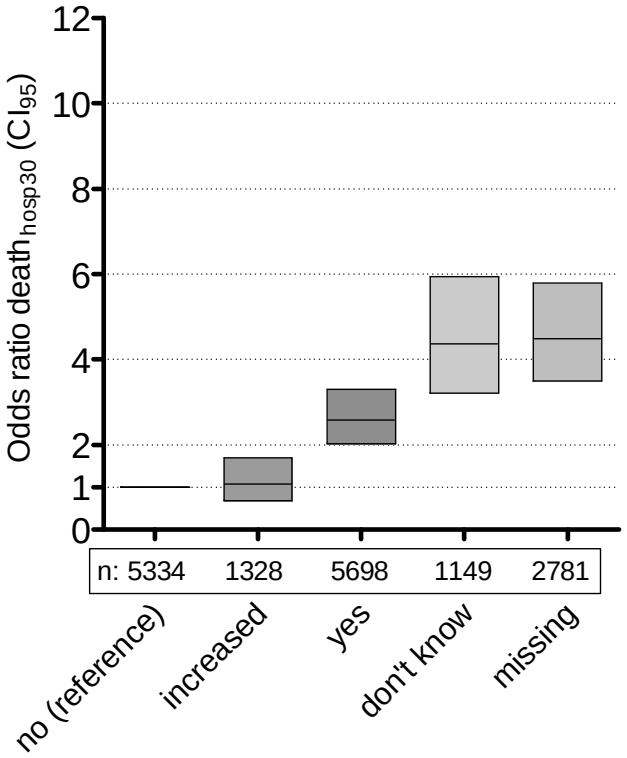
Marco Maltoni, Augusto Caraceni, Cinzia Brunelli, Bert Broeckaert, Nicholas Christakis, Steffen Eychmueller, Paul Glare, Maria Nabal, Antonio Viganò, Philip Larkin, Franco De Conno, Geoffrey Hanks, and Stein Kaasa

Table 1. Palliative Prognostic Score*

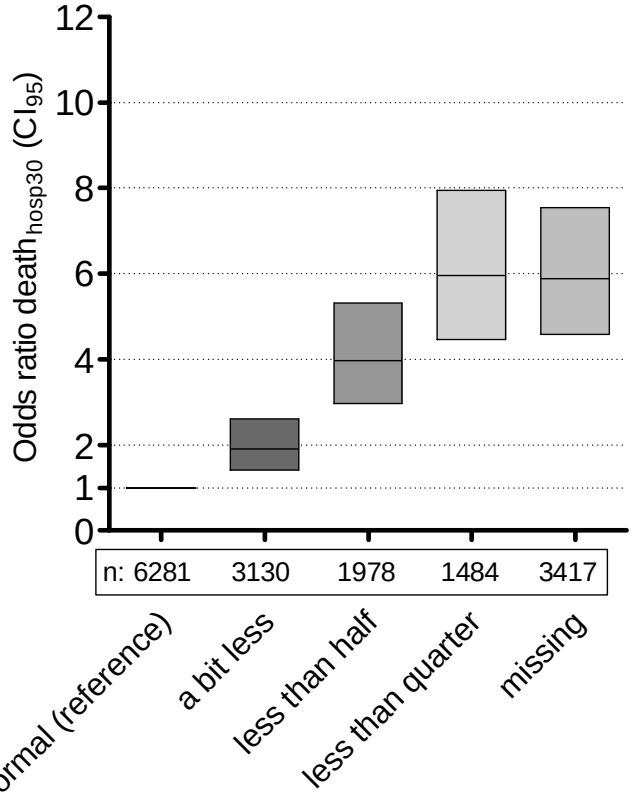
Prognostic Factor	Partial Score
Dyspnea	
Absent	0
Present	1
Anorexia	
Absent	0
Present	1.5
Karnofsky performance status	
≥ 50	0
30-40	0
10-20	2.5
Clinical prediction of survival	
> 12 weeks	0
11-12 weeks	2.0
9-10 weeks	2.5
7-8 weeks	2.5
5-6 weeks	4.5
3-4 weeks	6.0
1-2 weeks	8.5
Total WBC count (cell/mm³)	
Normal: 4,800-8,500 cells/μL	0
High: 8,501-11,000 cells/μL	0.5
Very high: > 11,000 cells/μL	1.5
Lymphocyte percentage	
Normal: 20.0%-40.0%	0
Low: 12.0%-19.9%	1.0
Very low: 0%-11.9%	2.5

nutritionDay
IN EUROPEAN HOSPITALS

Have you lost weight unintentionally within the last 3 months?

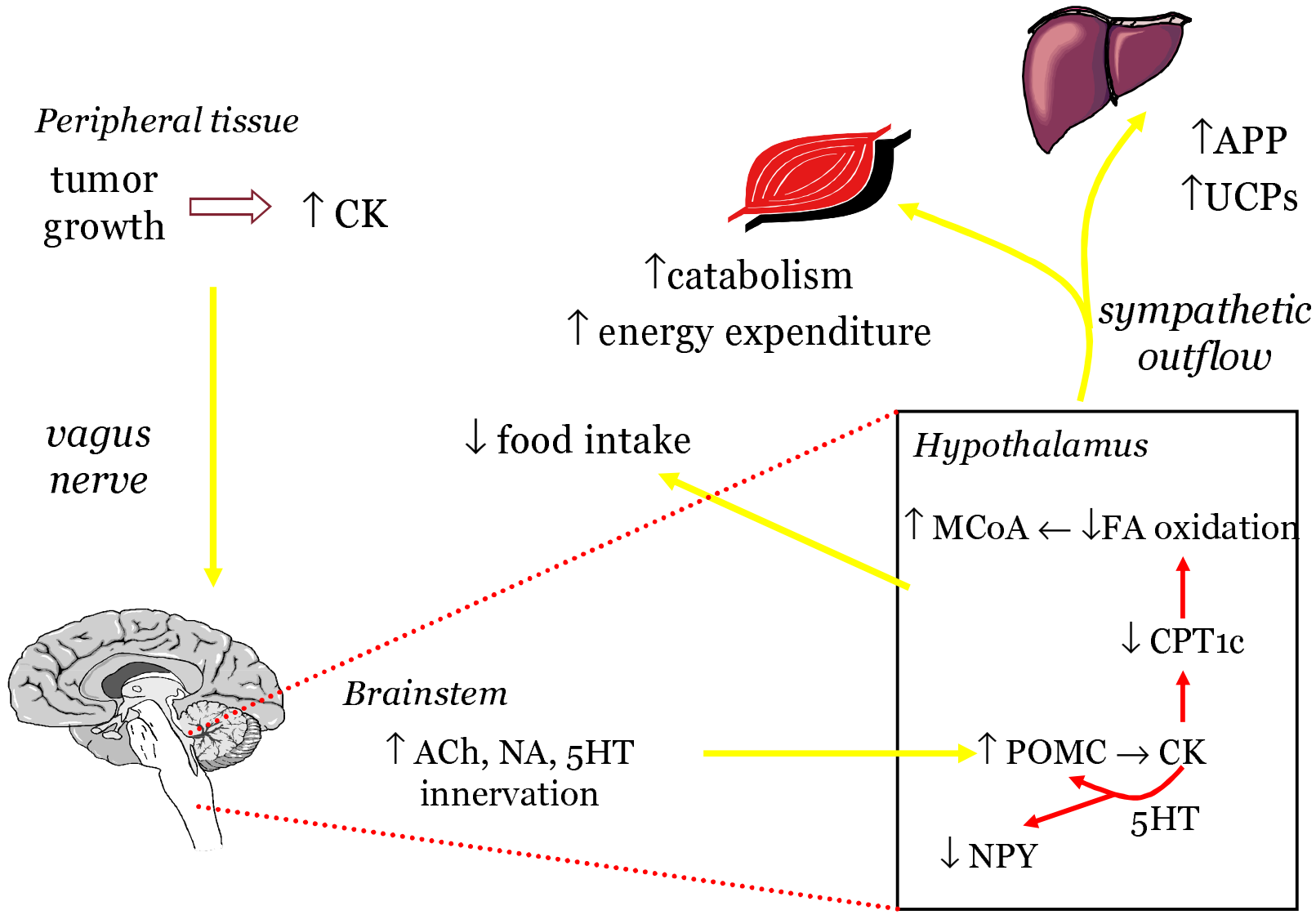


How well have you eaten during the last week?



ESPEN The European Society for Clinical Nutrition and Metabolism
MEDICAL UNIVERSITY OF VIENNA
AKE ARBEITSGEMEINSCHAFT KLINISCHE ERNÄHRUNG

Hiesmayr M et al. Lancet (submitted)



Laviano A et al. Am J Physiol Endocrinol Metab 2008

Table 4. Weight loss and quality of life

	Quality of life score			
	Patients with weight loss	Patients without weight loss	Difference between groups	All groups combined
Oesophageal	55	60	$P = 0.3$	$P < 0.0001$
Gastric	54	72	$P < 0.008$	
Pancreatic	49	63	$P < 0.0001$	
Colorectal	52	67	$P < 0.0001$	

Andreyev HJN et al. Eur J Cancer 1998

G. Reni (1575-1642)

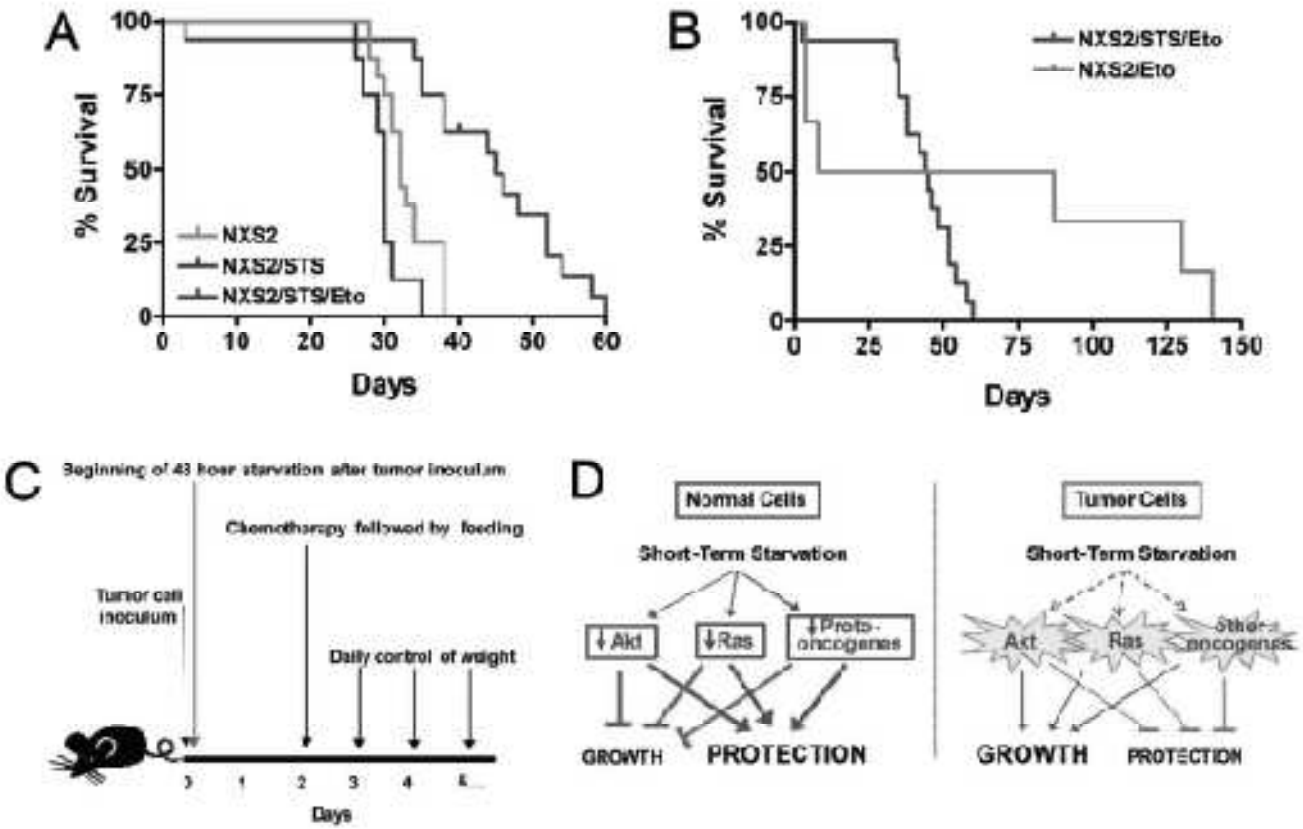
CANCER RESEARCH

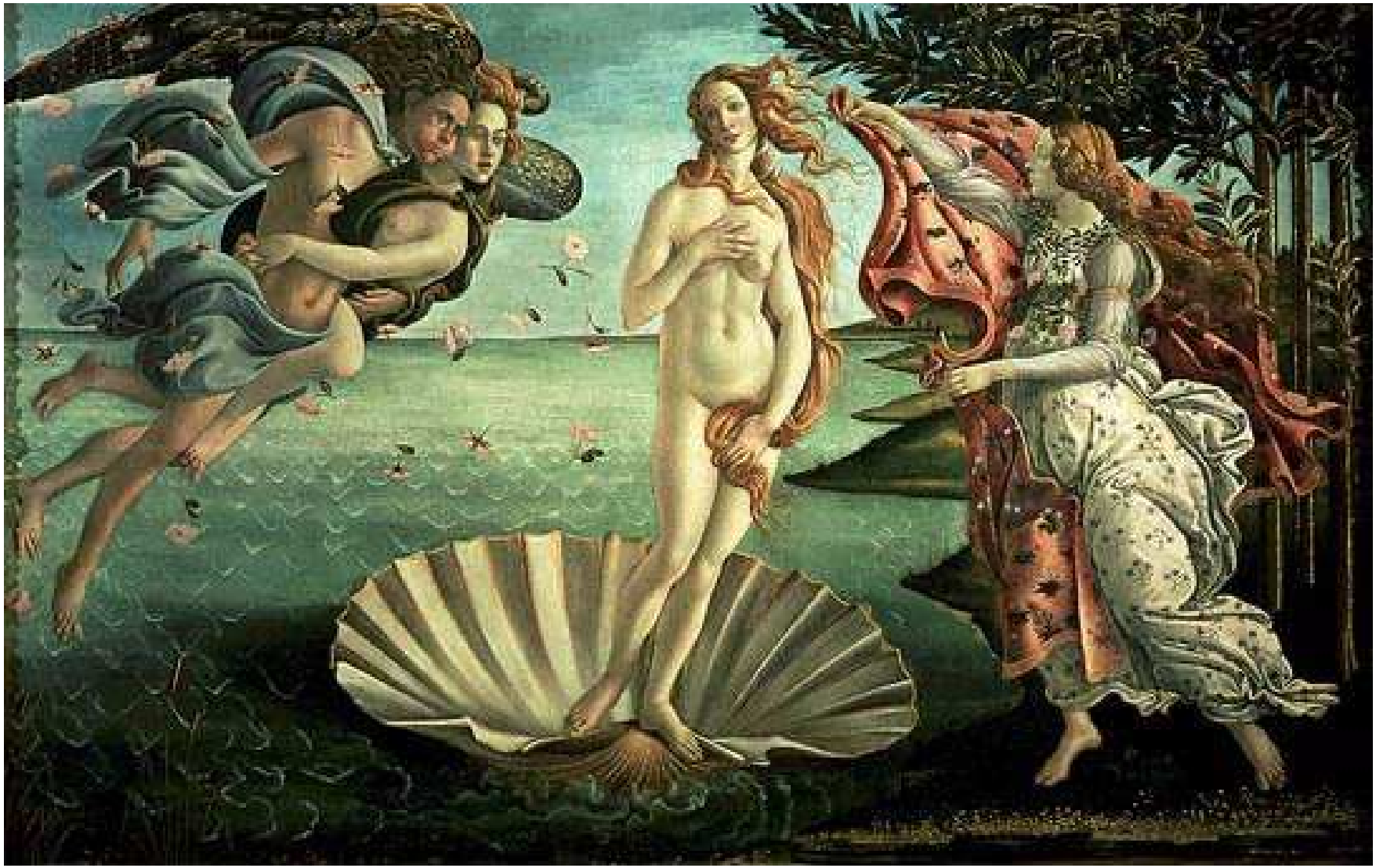
Can Fasting Blunt Chemotherapy's Debilitating Side Effects?

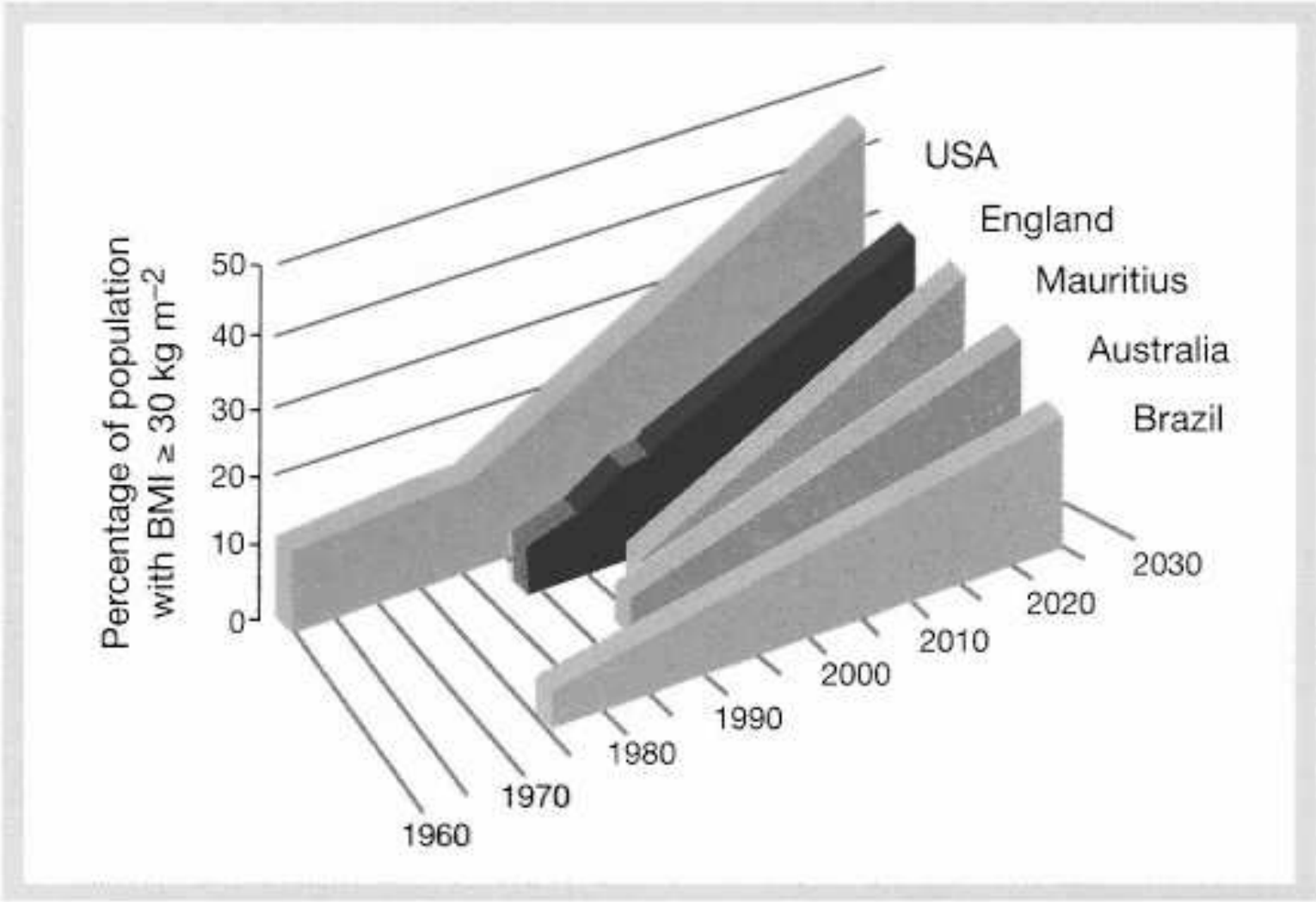
Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy

Lizzia Raffaghello*, Changhan Lee†, Fernando M. Safdie†, Min Wei†, Federica Madia†, Giovanna Bianchi*, and Valter D. Longo†‡

†Andrus Gerontology Center, Department of Biological Sciences and Norris Cancer Center, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191; and *Laboratory of Oncology, Giannina Gaslini Institute, 16147 Genova, Italy






Percentage of population with BMI ≥ 30 kg m^{-2}
0
10
20
30
40
50
1960
1970
1980
1990
2000
2010
2020
2030
USA
England
Mauritius
Australia
Brazil

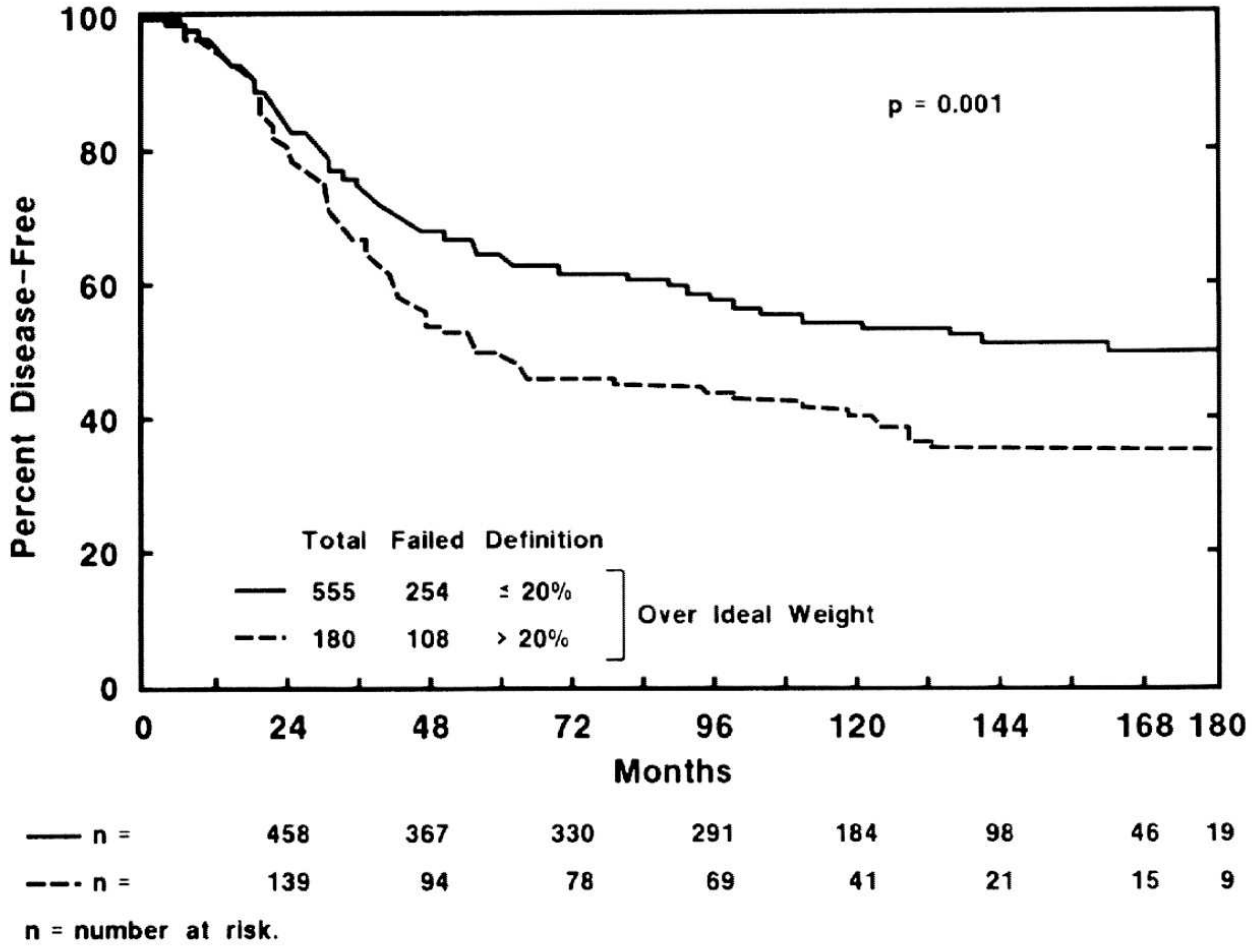

I BEAT
ANOREXIA

Effect of population trends in BMI on prostate cancer incidence and mortality in the US

- Obesity is associated with increased risk of high-grade prostate cancer and prostate cancer mortality, and it is thus likely that the increase in obesity has increased the burden of prostate cancer.
- The predicted increase in obesity prevalence since 1980 increased high-grade prostate cancer incidence by 15.5% and prostate cancer mortality by between 7.0% (under identical survival for obese and nonobese cases) and 23.0% (under different survival for obese and nonobese cases) in 2002.
- Increasing obesity prevalence since 1980 has partially obscured declines in prostate cancer mortality.

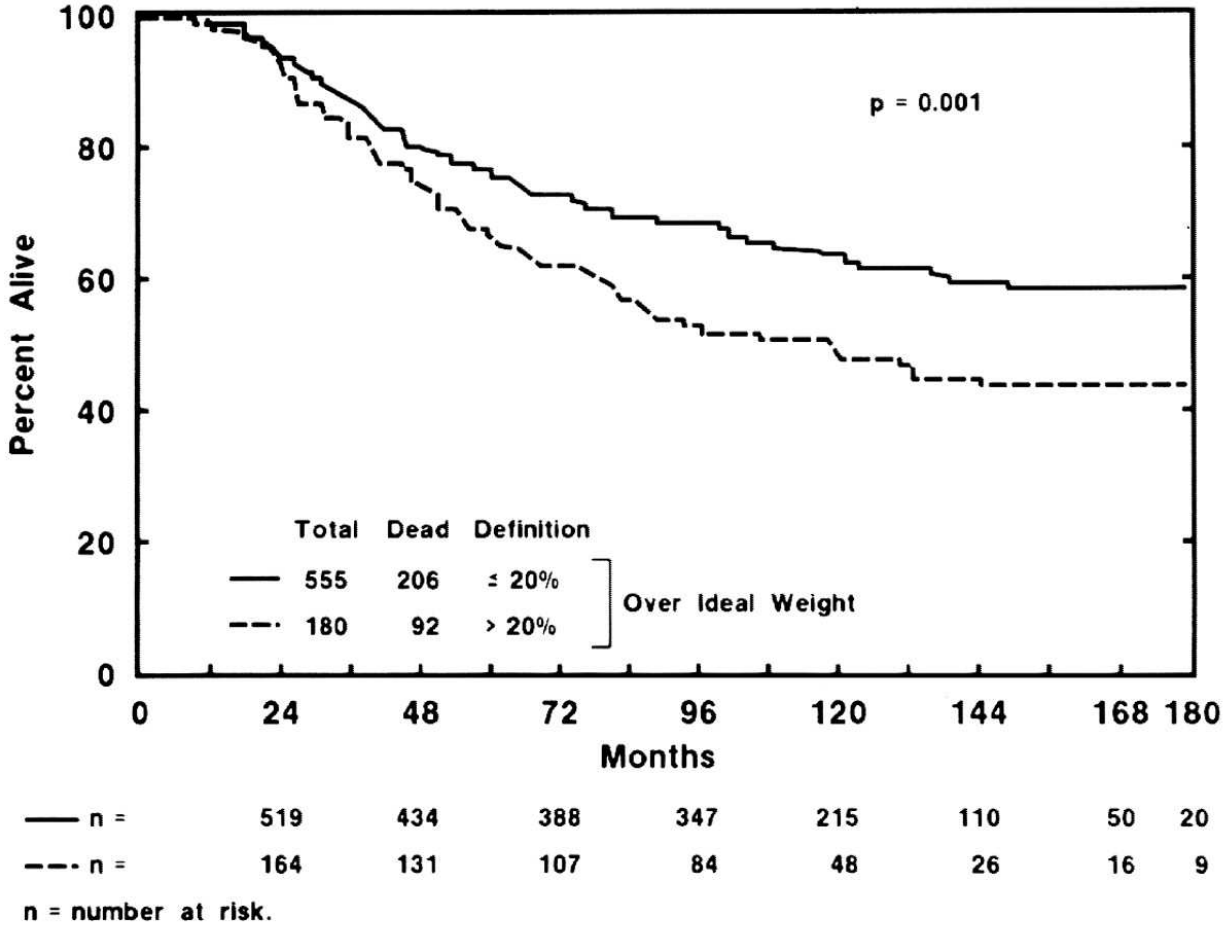
Fesinmeyer MD et al. Cancer Epidemiol Biomarkers Prev 2009

Obesity as an Adverse Prognostic Factor for Patients Receiving Adjuvant Chemotherapy for Breast Cancer



Bastarrachea J et al. Ann Intern Med 1994

Obesity as an Adverse Prognostic Factor for Patients Receiving Adjuvant Chemotherapy for Breast Cancer



Bastarrachea J et al. Ann Intern Med 1994

Influence of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients with Colon Carcinoma

TABLE 2
Survival and Recurrence for All Patients According to Body Mass Index

	BMI class (kg/m^2)					
Measure	< 21.0	21.0–24.9	25.0–27.49	27.5–29.9	≥ 30.0	*P* value
Five yr DFS (%)[a]	56.4	60.0	56.8	57.9	57.8	0.60[b]
Five yr OS (%)[c]	63.5	67.0	65.2	65.8	64.8	0.56[b]
Five yr RFS (%)[d]	63.4	65.1	61.9	62.3	61.9	0.56[b]
Unadjusted HR (95% CI)						
Overall mortality	1.10 (0.94–1.28)	1.00[e]	1.10 (0.96–1.26)	1.03 (0.88–1.21)	1.06 (0.92–1.23)	0.43[f]
Disease recurrence	1.04 (0.87–1.24)	1.00[e]	1.07 (0.92–1.24)	1.10 (0.93–1.31)	1.10 (0.94–1.29)	0.20[f]
Adjusted HR (95% CI)[g]						
Overall mortality	1.15 (0.98–1.35)	1.00[e]	1.10 (0.95–1.26)	1.05 (0.90–1.24)	1.11 (0.96–1.29)	0.20[f]
Disease recurrence	1.06 (0.88–1.27)	1.00[e]	1.06 (0.88–1.27)	1.12 (0.94–1.33)	1.11 (0.94–1.30)	0.17[f]

Meyhardt JA et al. Cancer 2003

Influence of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients with Colon Carcinoma

TABLE 3
Survival and Recurrence by Gender, Based on Body Mass Index

	BMI class (kg/m^2)					
Survival	< 21.0	21.0–24.9	25.0–27.49	27.5–29.9	≥ 30.0	*P* value
Females						
Five yr OS (%)	68.3	71.6	66.9	64.4	64.7	0.066[a]
Five yr RFS (%)	65.1	68.1	63.5	62.2	61.4	0.19[a]
Adjusted HR (95% CI)[b]						
Overall mortality	1.08 (0.87–1.35)	1.00[c]	1.18 (0.94–1.49)	1.23 (0.95–1.60)	1.34 (1.07–1.67)	0.007[d]
Disease recurrence	1.01 (0.79–1.28)	1.00[c]	1.14 (0.89–1.47)	1.20 (0.91–1.60)	1.24 (0.98–1.59)	0.061[d]
Males						
Five yr OS (%)	55.0	63.1	64.2	66.7	64.9	0.51[a]
Five yr RFS (%)	60.1	62.5	61.0	62.4	62.4	0.99[a]
Adjusted HR (95% CI)[b]						
Overall mortality	1.33 (1.05–1.67)	1.00[c]	1.03 (0.87–1.22)	0.96 (0.78–1.17)	0.94 (0.77–1.15)	0.39[d]
Disease recurrence	1.22 (0.93–1.60)	1.00[c]	1.00 (0.82–1.22)	1.05 (0.85–1.32)	0.98 (0.79–1.23)	0.93[d]

Meyhardt JA et al. Cancer 2003

Influence of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients with Colon Carcinoma

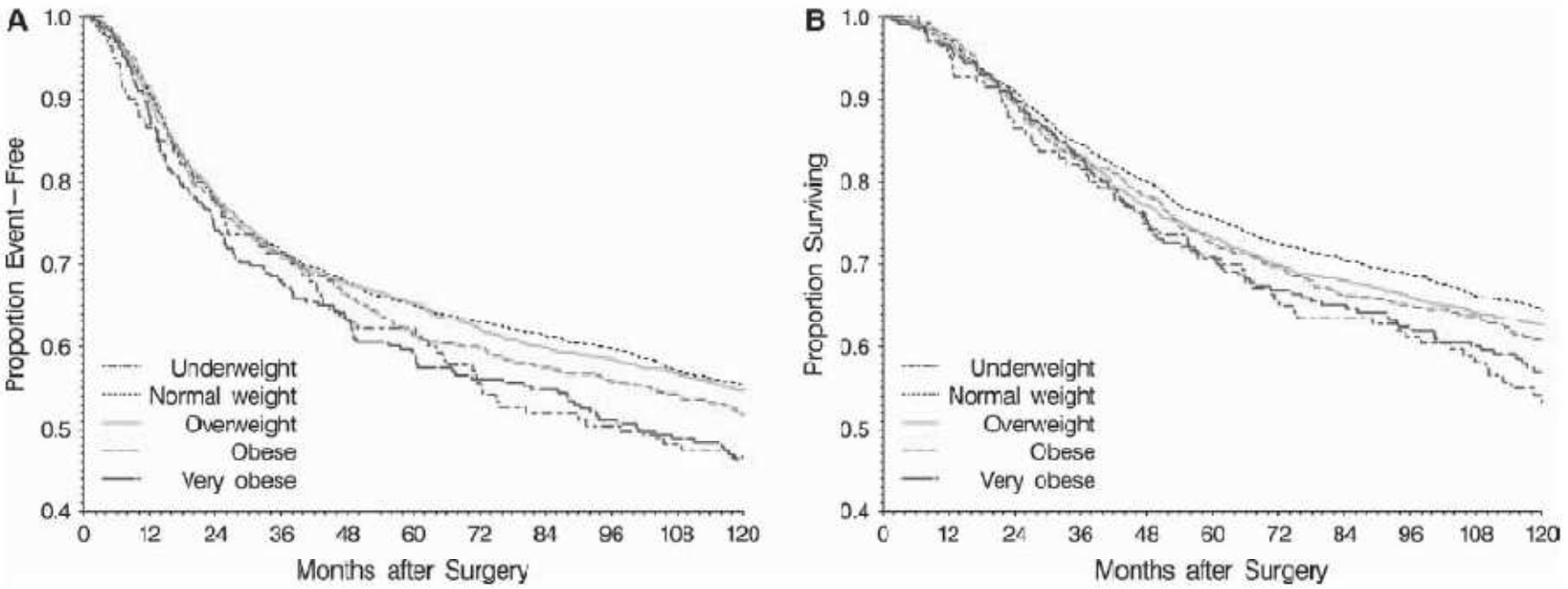
TABLE 4
Major Treatment-Related Toxicity According to Body Mass Index

	BMI class (kg/m^2)						Adjusted (kg/m^2)[b]	
Toxicity (%)	< 21.0	21.0–24.9	25.0–27.49	27.5–29.9	≥ 30.0	Unadjusted *P* across all BMIs[a]	BMI ≥ 21.0[c]	BMI < 25.0[d]
Nausea[e]	8.1	4.6	4.7	4.3	4.6	0.027	0.84	0.016
Emesis[f]	4.2	3.2	3.0	3.0	4.3	0.57	0.20	0.66
Diarrhea[g]	21.3	21.3	20.6	20.6	21.2	1.0	0.43	0.94
Leukopenia[h]	10.8	11.7	8.6	9.1	6.1	0.0036	0.0097	0.54
Stomatitis[i]	15.0	11.9	11.8	10.4	9.7	0.089	0.39	0.21
Any Grade 3–4 toxicity	53.4	53.2	51.3	51.8	45.8	0.044	0.020	0.66
Treatment-related death	1.0	1.3	1.1	1.3	1.4	0.99	0.99	0.85

Meyhardt JA et al. Cancer 2003

Body Mass Index and Outcomes in Patients Who Receive Adjuvant Chemotherapy for Colon Cancer

James J. Dignam, Blase N. Polite, Greg Yothers, Peter Raich, Linda Colangelo, Michael J. O'Connell, Norman Wolmark



J Natl Cancer Inst 2006

Body Mass Index and Outcomes in Patients Who Receive Adjuvant Chemotherapy for Colon Cancer

James J. Dignam, Blase N. Polite, Greg Yothers, Peter Raich, Linda Colangelo, Michael J. O'Connell, Norman Wolmark

Table 2. Relative hazards for events comprising disease-free survival by body mass index (BMI)*

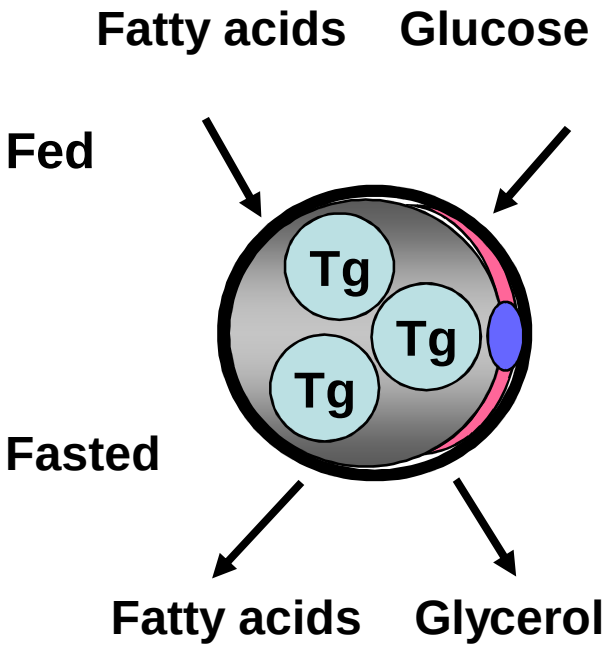
Category	Disease-free survival (2074 events)	Colon cancer events (1286 events)	Second primary cancer (453 events)	Prior deaths† (335 events)
BMI‡				
Underweight	1.42 (1.14 to 1.78)	1.14 (0.84 to 1.55)	1.96 (1.27 to 3.04)	2.11 (1.26 to 3.52)
Normal weight	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Overweight	0.96 (0.87 to 1.06)	1.08 (0.95 to 1.23)	0.80 (0.64 to 0.99)	0.81 (0.63 to 1.04)
Obese	1.06 (0.93 to 1.21)	1.04 (0.88 to 1.24)	1.05 (0.79 to 1.40)	1.29 (0.93 to 1.77)
Very obese	1.27 (1.05 to 1.53)	1.38 (1.10 to 1.73)	0.97 (0.61 to 1.53)	1.51 (0.93 to 2.45)
P: BMI§	<.001	.004	.11	.018

Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma

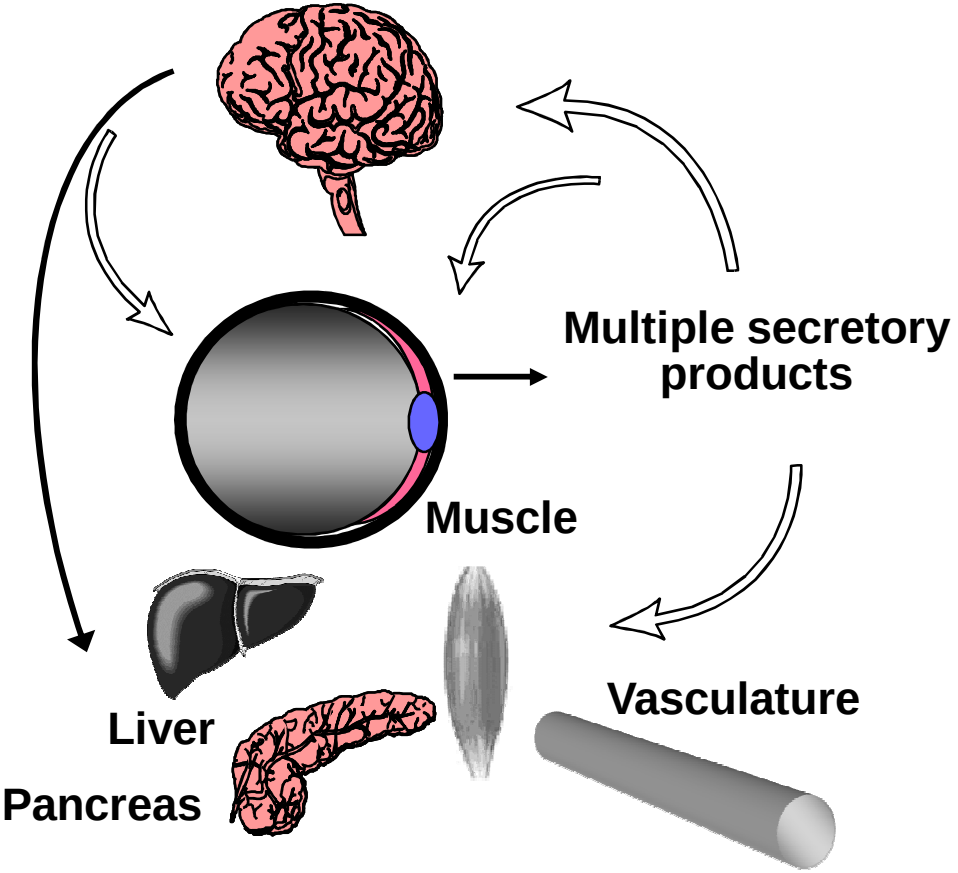
- Two hundred eighty-five consecutive patients with data available for BMI calculation who underwent potentially curative pancreas resection to treat adenocarcinoma from January 1, 1999, to October 31, 2006.
- Influence of BMI and other known prognostic variables on the incidence of lymph node metastasis and disease-free and overall survival.
- Obese patients (BMI >35) were at 12-fold risk of lymph node metastasis compared with nonobese patients (BMI < or =35). The estimated disease-free and overall survival rates were decreased in the obese patients, and the risk of cancer recurrence and death after pancreatectomy was nearly twice that in nonobese patients.
- Data suggest that the negative influence of BMI of more than 35 on cancer-related end points is unrelated to the potential complexity of performing major oncologic surgery in obese patients.

Fleming JB et al. Arch Surg 2009

Old View: inert storage depot

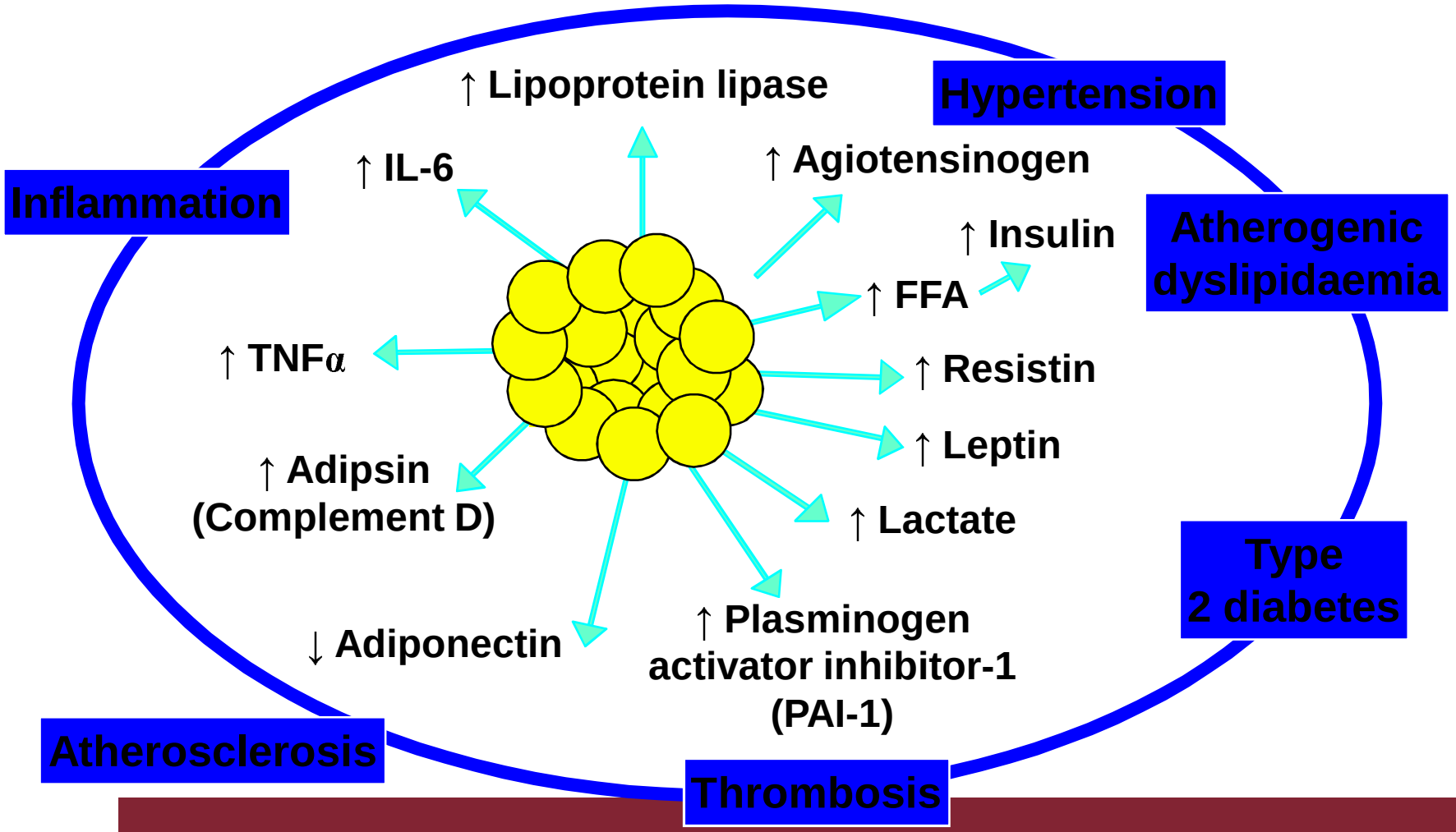


Current View: secretory/endocrine organ



Lyon CJ et al 2003

Adverse metabolic effects of products of adipocytes



Lyon 2003; Trayhurn et al 2004; Eckel et al 2005

Conclusions

- Malnutrition remains a negative prognostic factor for cancer patients
- The increasing prevalence of obesity has offset in part the reduction of cancer mortality.
- Limited “reverse epidemiology” for obese cancer patients
- The mechanisms by which malnutrition and overnutrition impact on cancer outcomes are many, including reduced tolerance/response to therapy and corroboration of cancer-induced metabolic alterations.