Does peri-operative nutritional support improve the outcome in GI cancer patients?

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Disclosures

- B. Braun and Nutricia

Slide withheld at speaker’s request

Malnutrition

"A state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue/ body structure and function and clinical outcome."

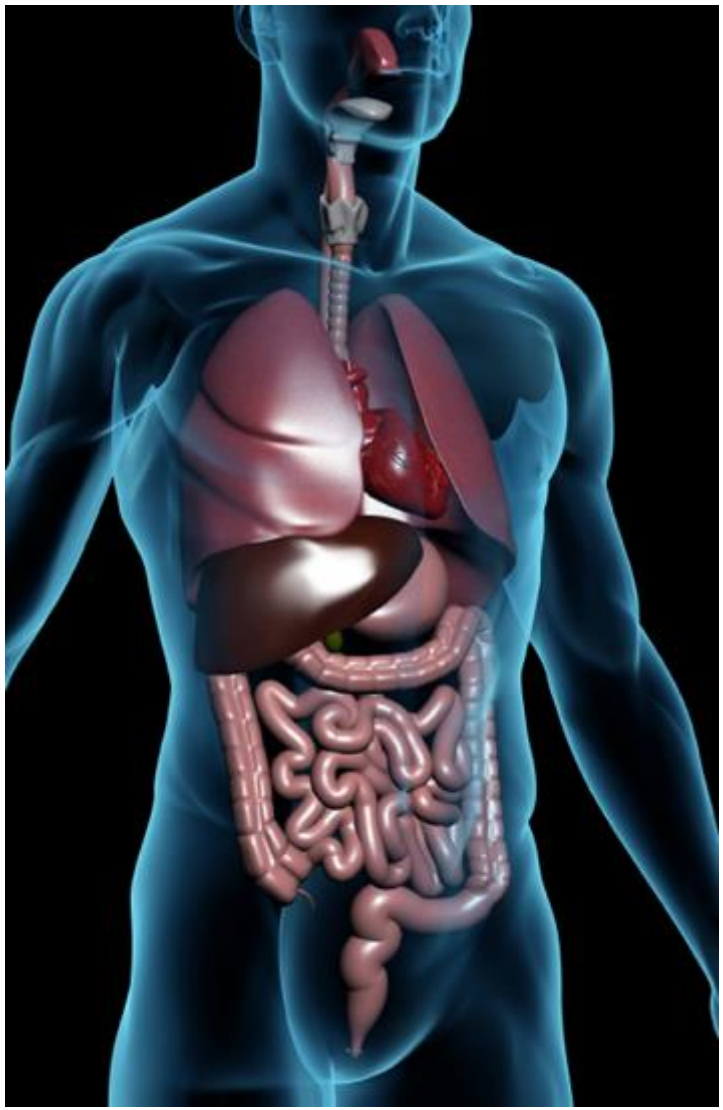
Causes of Undernutrition

↓ Consciousness
Depression
Anorexia

Disease burden

Liver processing
Jaundice

Effects of treatment



Poor diet – age, poverty, alcohol, drugs

Dysphagia

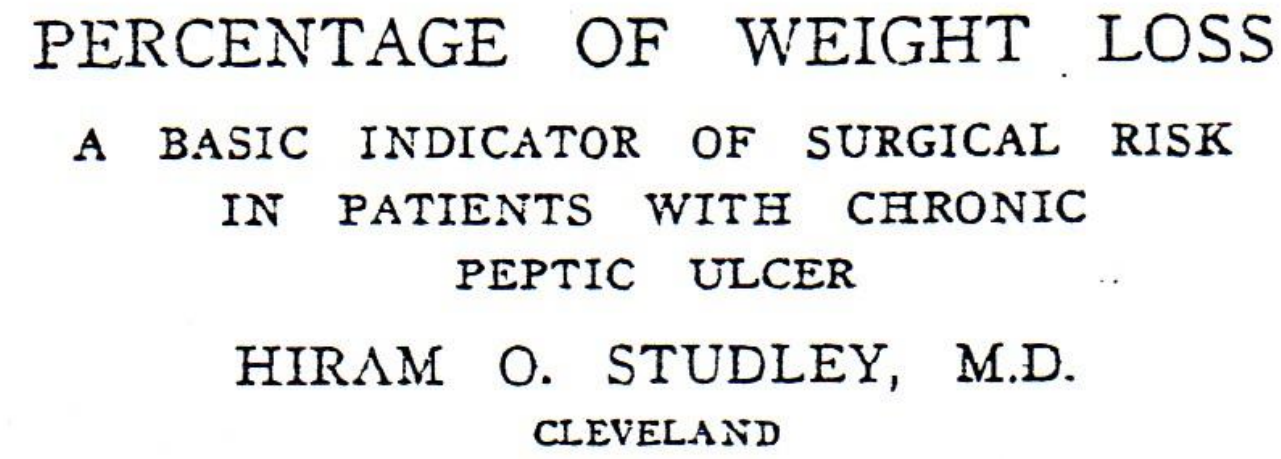
Obstruction
Vomiting

Pancreatic insufficiency

Malabsorption

Increased metabolic demands (e.g. inflammation, infection, injury)

Effects of Malnutrition on Surgical Outcome



PERCENTAGE OF WEIGHT LOSS

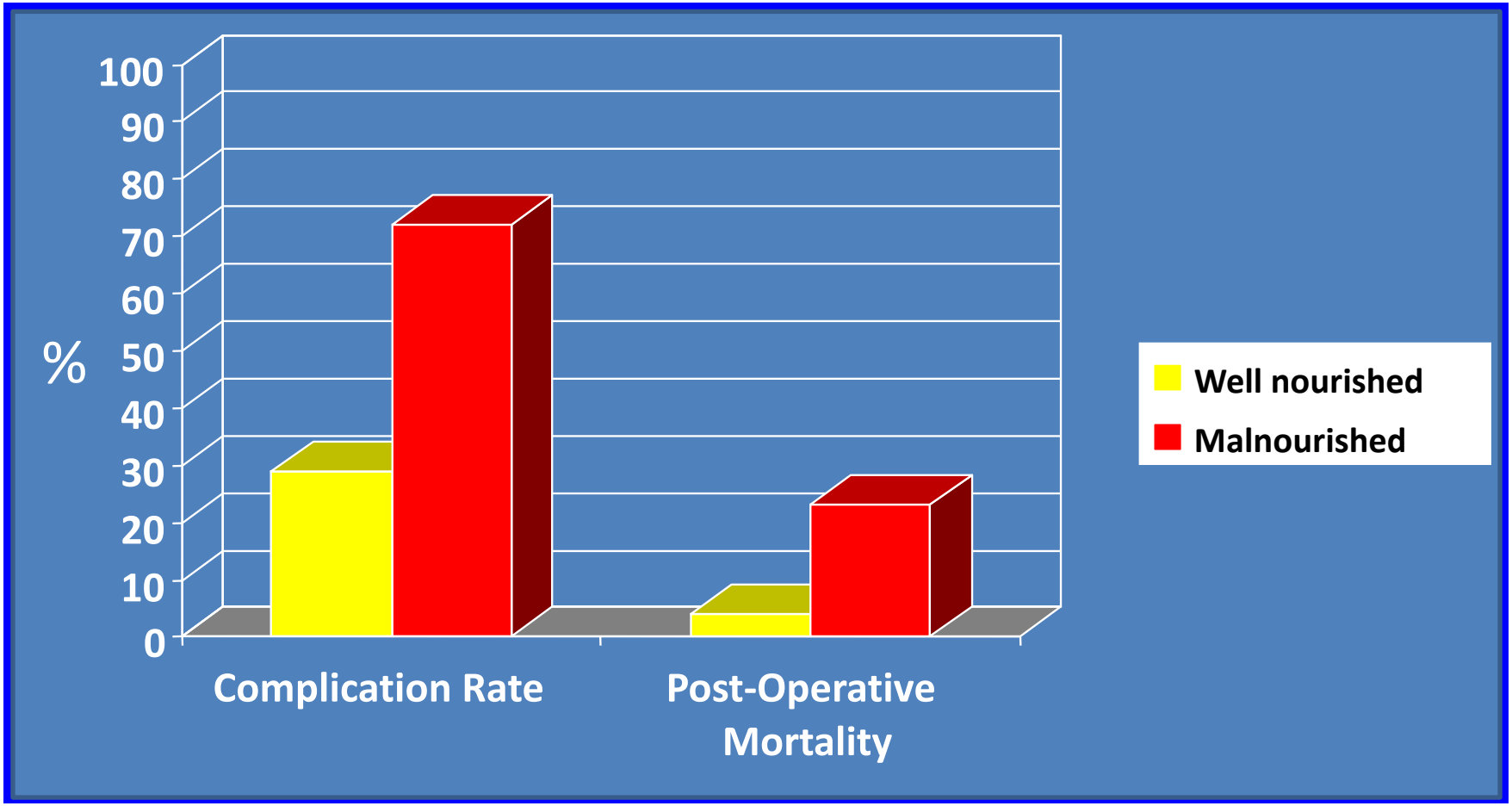
A BASIC INDICATOR OF SURGICAL RISK IN PATIENTS WITH CHRONIC PEPTIC ULCER

HIRAM O. STUDLEY, M.D.

CLEVELAND

Preop. weight loss	Postop. mortality
<20%	3.5%
>20%	33%

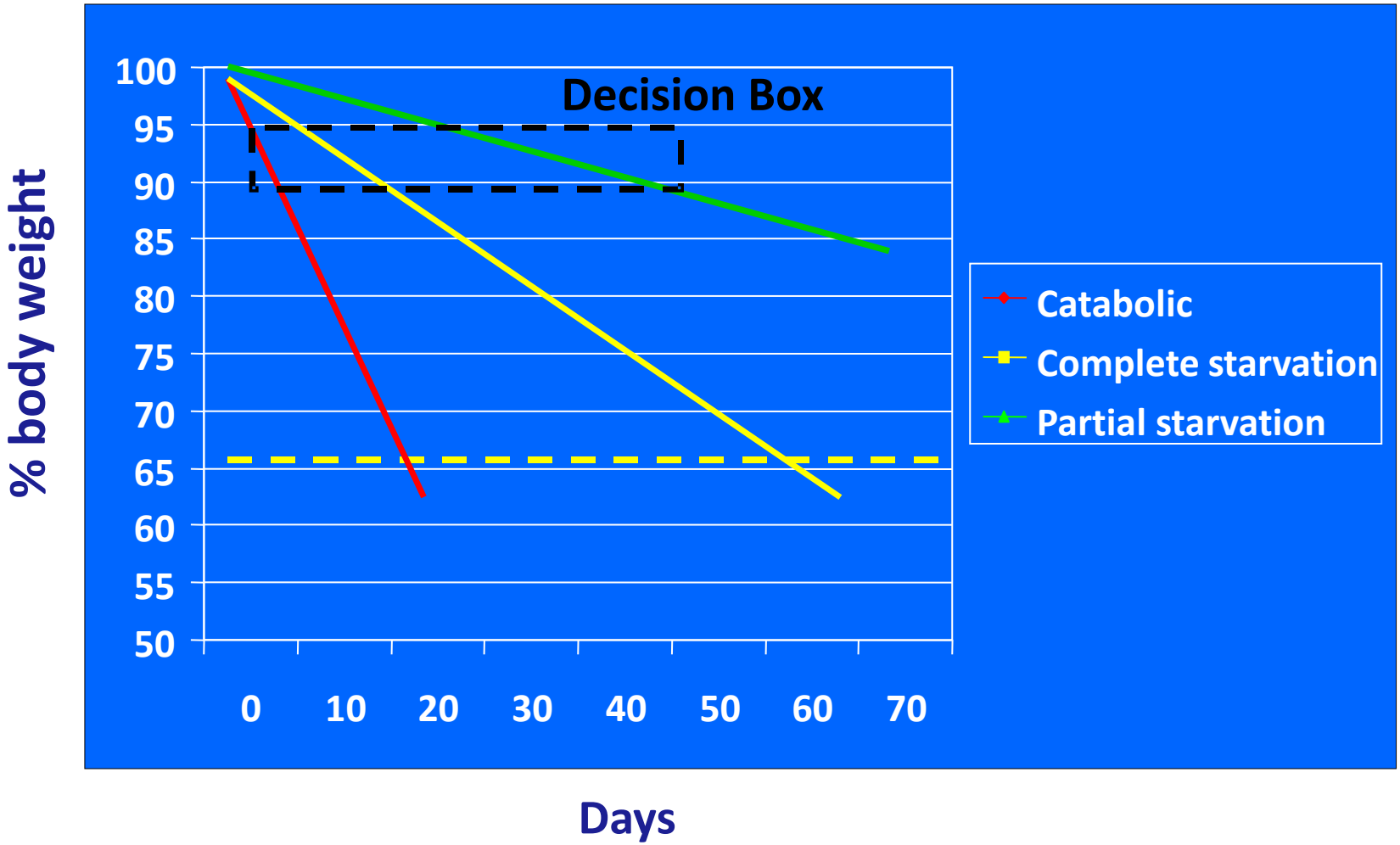
Studley HO, JAMA 1936



Meguid M, et al, Am J Surg 1988

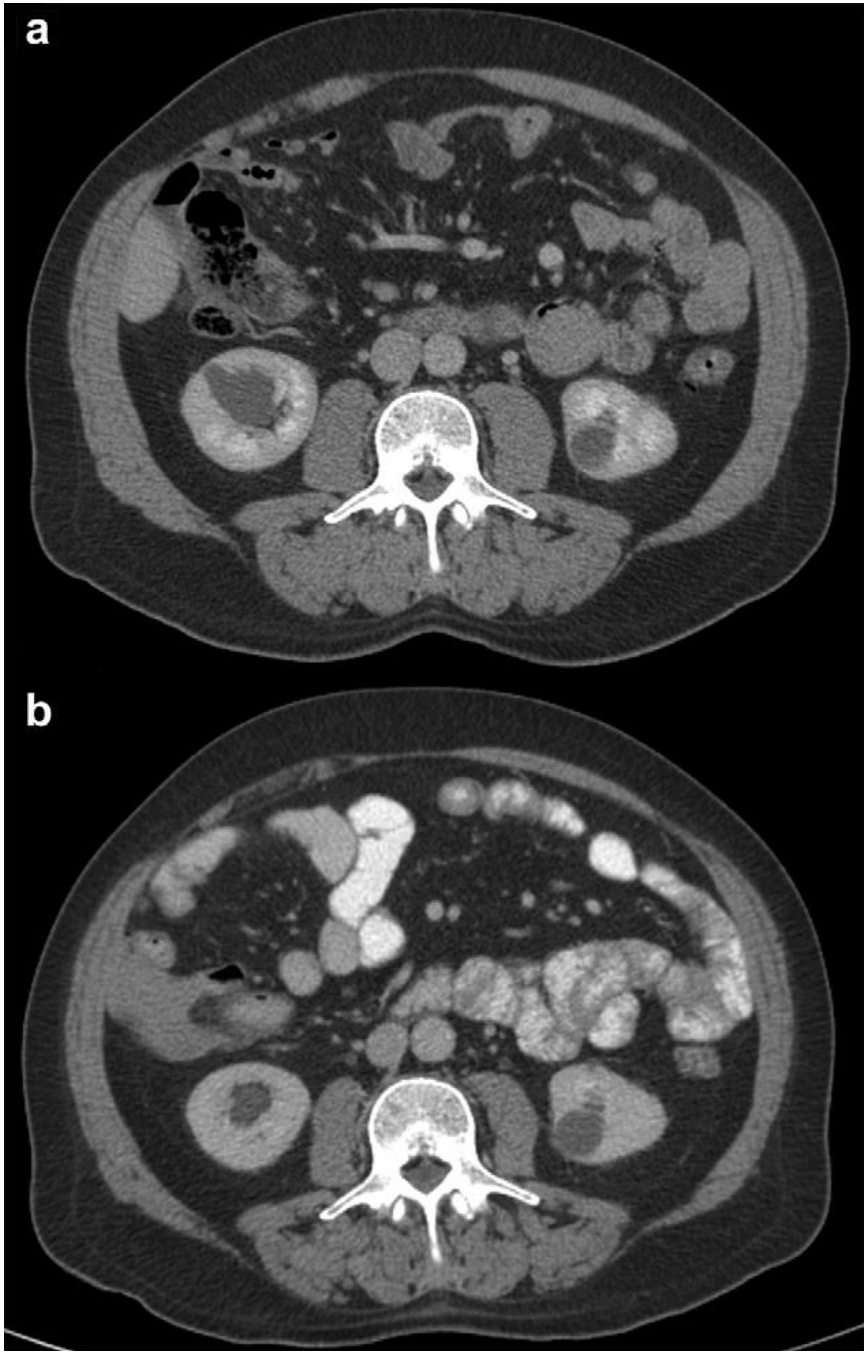
Starvation & Weight loss

(After Allison)

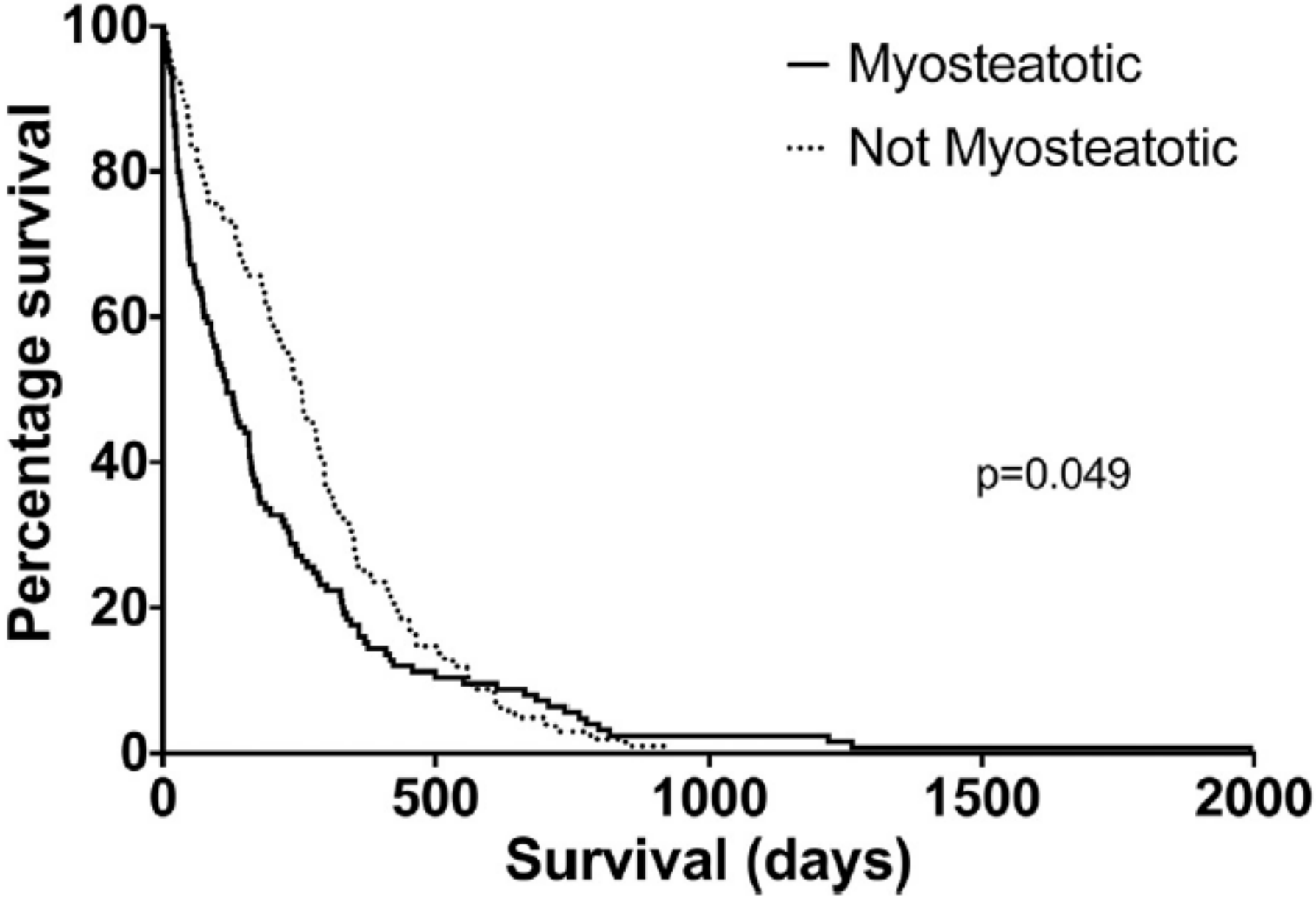


Sarcopenia

- Reduced quantity of skeletal muscle
- Absolute muscle mass >2 SD below that typical of healthy adults
- Muscle loss may be masked by weight stability
- Muscle loss with fat gain – sarcopenic obesity



Awad S, et al, Clin Nutr 2012

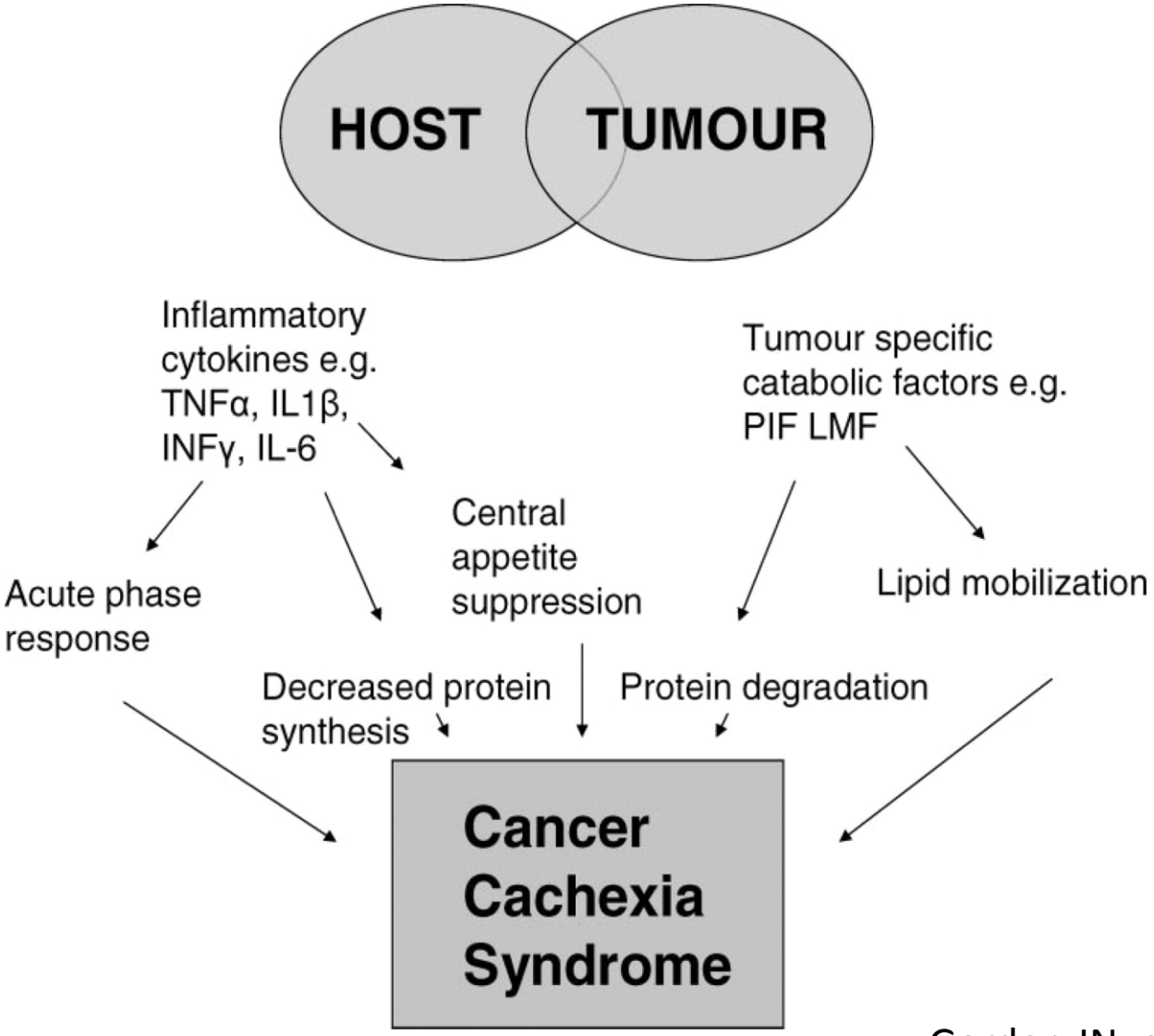


Rollins K, et al, Clin Nutr 2016

Cachexia

- Complex metabolic syndrome associated with underlying illness characterised by
  - Loss of muscle with or without loss of fat mass
  - Anorexia
  - Inflammation
  - Insulin resistance
  - Increased muscle protein breakdown

Cancer Cachexia



Gordon JN, et al, QJM 2005

Prevalence of Cachexia

Malignancy	Patients with cachexia
Oesophagogastric cancer	85%
Pancreatic cancer	83%
Non-small cell lung cancer	61%
Small cell lung cancer	57%
Prostate cancer	56%
Colon cancer	54%
Non-Hodgkin's lymphoma (unfavourable)	48%
Sarcoma	40%
Acute non-lymphocytic lymphoma	39%
Breast cancer	36%
Non-Hodgkin's lymphoma (favourable)	31%

Skipworth RJ, et al, Clin Med 2006

Undernutrition and the Cancer Patient

- More intensive treatment
- High dependency nursing
- Increased hospital stay
- Higher cost of care
- Increased morbidity and mortality
- Reduced quality of life

Outcome

- Malnutrition impairs outcome
- But, does nutritional support improve it??
- If so, how should we approach the problem in practice?

Integrated Nutrition 1

- Nutrition cannot be considered in isolation

- It will not compensate for inadequacies in other aspects of management

Integrated Nutrition 2

- It interacts with other treatments, e.g. drugs, fluid balance, which influence gastrointestinal function

- It must, therefore, be integrated into an overall protocol of care, e.g. ERAS programme

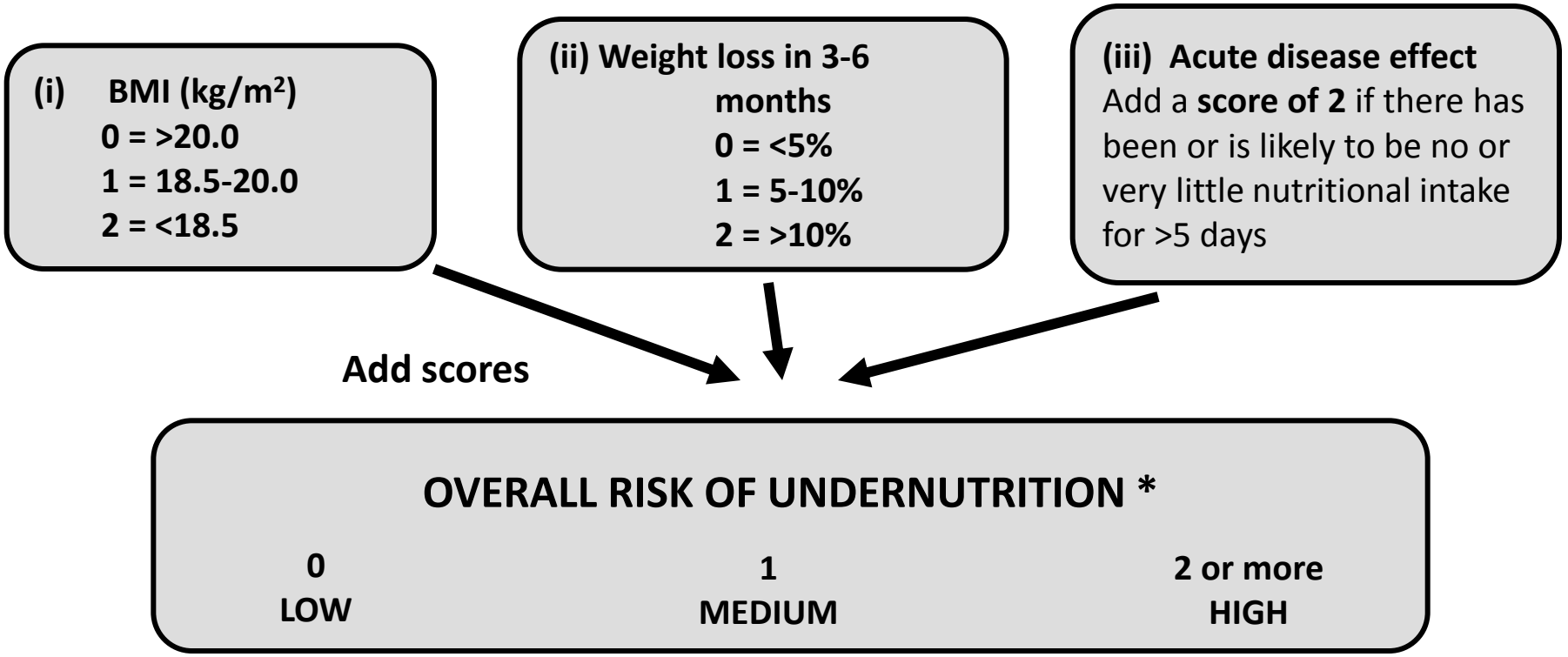
- It must be delivered by a team trained adequately in nutritional care as well as other aspects of perioperative management

Goals of Nutritional Therapy

- Acute/Short-term
  - Recognise risk of malnutrition
  - Preserve function
  - Minimise complications
  - Avoid nutrient overload
  - Correct mineral, micronutrient and electrolyte balance
- Medium to Long-term
  - Restore function
  - Improve quality of life

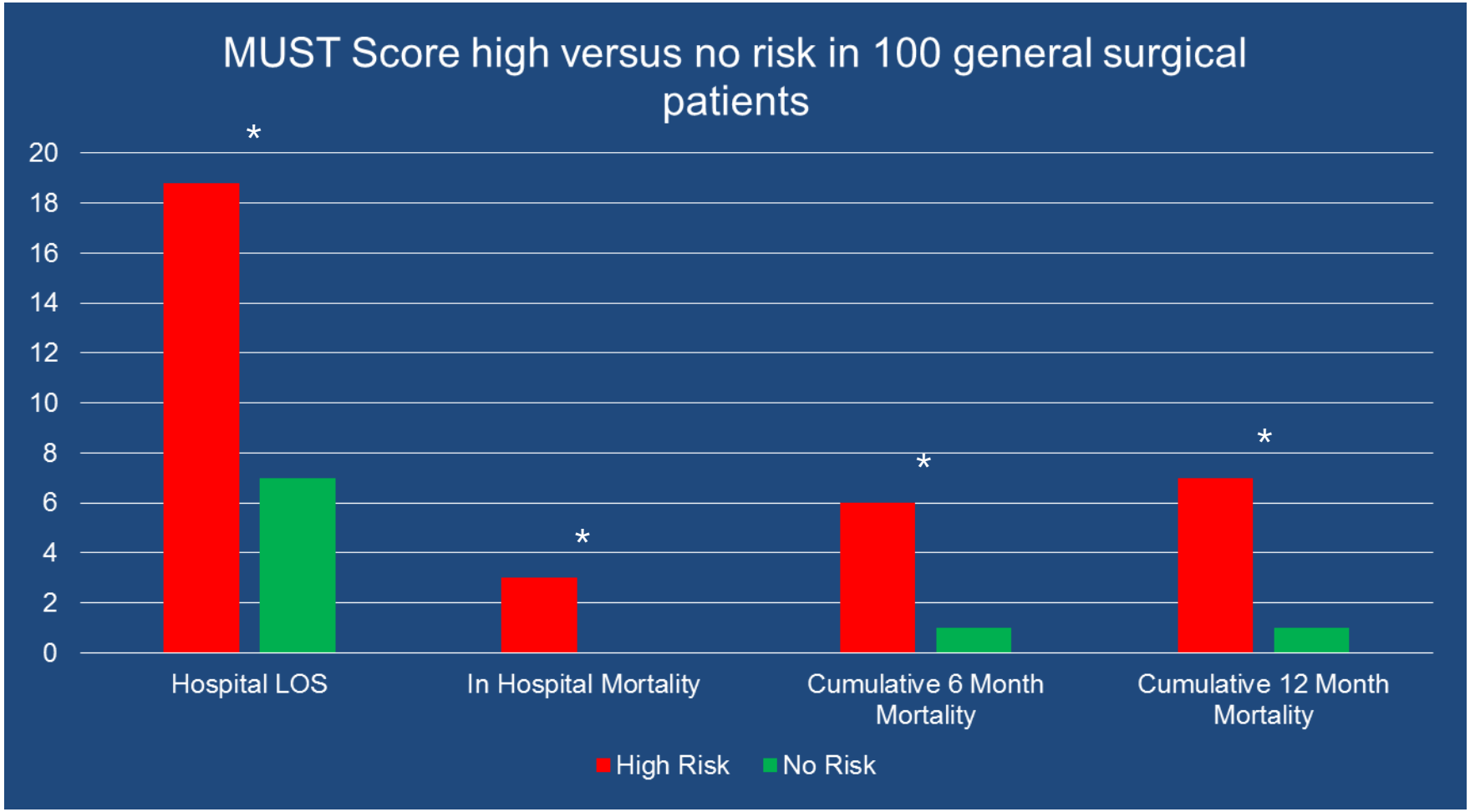
Nutrition Screening:

The Malnutrition Universal Screening Tool



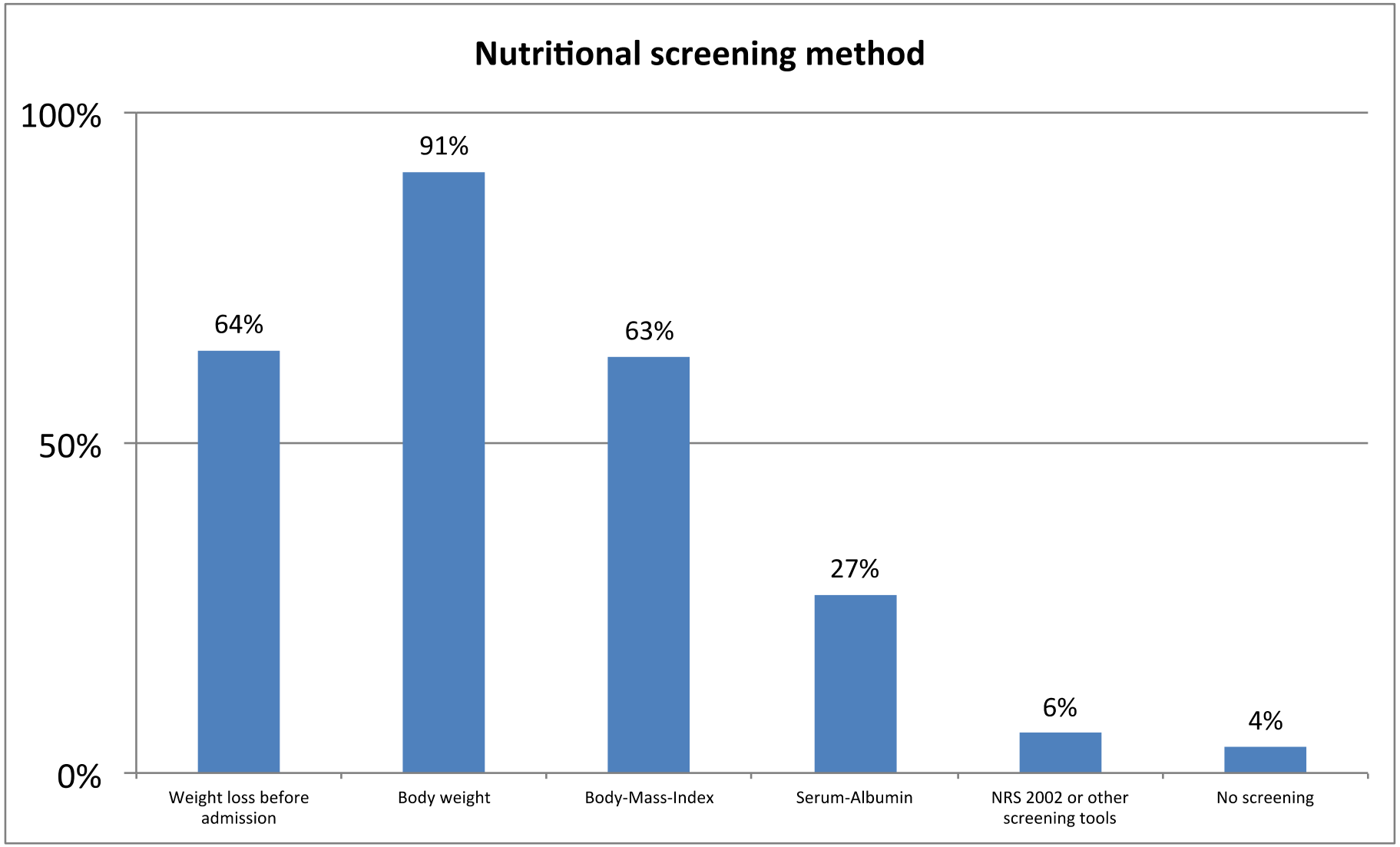
Disease Related Malnutrition
Stratton, Green & Elia, 2003

MUST Score and Clinical Outcomes



Ben-Ishay et al, Gastro Res Prac 2011

The Real World

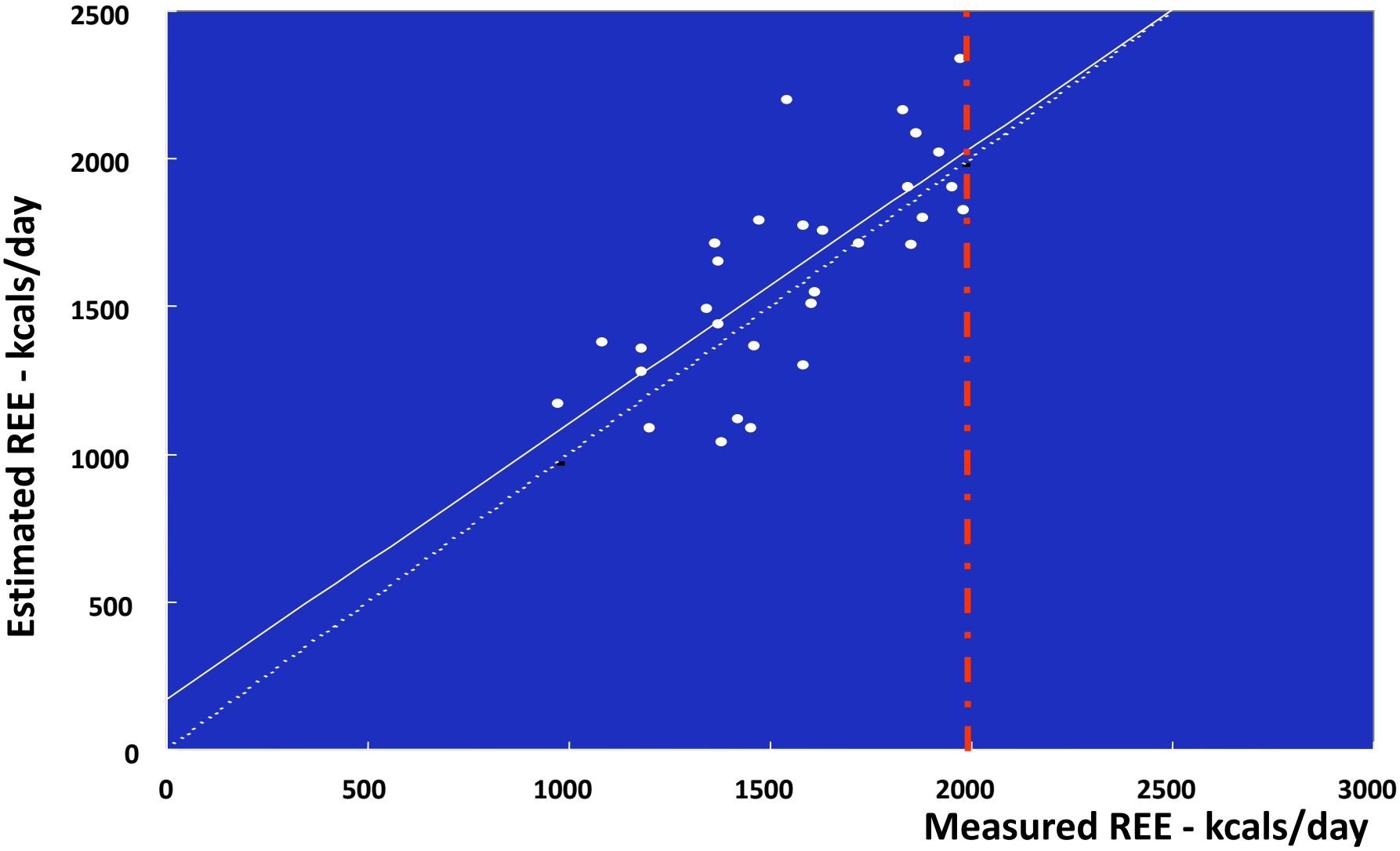


Breuer JP, et al, Zentralbl Chir 2013

How Much is Needed?

- Give 1.0 – 1.3 × RMR
  - Most patients need 30-35 Cal/kg/day
  - 50% non-protein energy requirement from fat and 50% from carbohydrate.
  - Protein requirements range from 1.2-1.5 g/kg/day.
- Permissive underfeeding?
  - 20 Cal with 1 g protein/kg/day.

Energy Expenditure in Patients



Enteral Nutrition

- Pro
  - Gut regulation of absorption
  - Liver activation
  - Protection of gut integrity & immunity
  - Decreased cytokine and acute phase responses
  - Relatively simple and cheap
- Con
  - Access – insertion, misplacement, "fall out“
  - Aspiration
  - Poor absorption
  - Diarrhoea
  - Metabolic upset

Parenteral Nutrition

- Pro
  - Intestinal failure
  - Severe acute pancreatitis
  - Guaranteed delivery
- Con
  - Access related complications
  - Line occlusion, misplacement, displacement
  - Infections
  - Metabolic complications
  - Expense

EN *vs.* PN

- If the gut works use it
- If intakes are inadequate or GI tolerance in doubt, supplement with PN
- PN and EN are not mutually exclusive, they are complementary

Perioperative Management – Aims

- Improved function
- Improved survival and outcome
- Reduced complications
- Enhanced rate of recovery
- Reduced hospital stay and costs
- Early return to normal life

Perioperative Nutrition

- 2-3 weeks: Preoperative assessment
- 7-14 days: Preoperative nutrition
- 12 h preoperatively: Prolonged starvation not necessary
- During operation and immediate recovery
- Postoperatively until discharge from hospital
- Post discharge

What to Give?

- Macronutrients
  - Protein, CHO, Fat
- Micronutrients
  - Fat soluble vitamins: A, D, E & K
  - Water soluble vitamins: B group, C, etc.
- Electrolytes
  - Na, K, Ca, Mg, PO_4
- Elements
  - Fe, Zn, Cu, Se, Mn

Problems of Overfeeding Energy

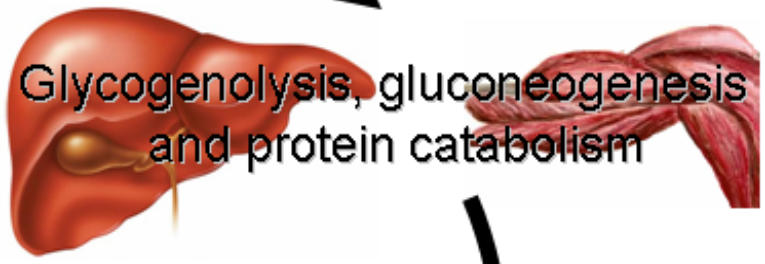
- Ventilatory demands - O_2 and CO_2
- Lipid
  - Liver dysfunction
  - Immunosuppression
- Carbohydrate
  - Re-feeding syndrome
  - Wernicke Korsakoff
  - Hyperglycaemia

What is the Refeeding Syndrome?

- A potentially lethal condition characterised by severe fluid and electrolyte shifts associated with metabolic abnormalities in malnourished patients undergoing oral, enteral or parenteral refeeding.

Crook MA, et al, Nutrition 2001

Starvation / Malnutrition



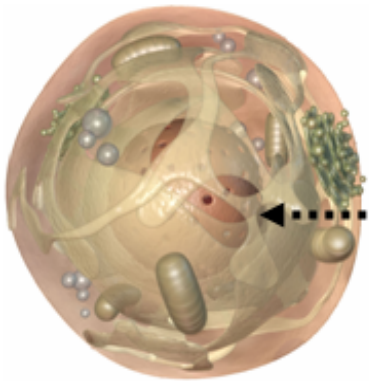
Protein, fat, mineral, electrolyte and vitamin depletion – salt and water intolerance

Refeeding (switch to anabolism)

Fluid, salt, nutrients
(CHO major energy source)

Insulin secretion

↑ Glucose uptake
↑ Utilization of thiamine
↑ Uptake of K^+, Mg^{2+} & PO_4^{2-}



↑ Protein and glycogen synthesis

Hypokalaemia
Hypomagnesaemia
Hypophosphataemia
Thiamine deficiency
Salt and water
retention - oedema

Refeeding syndrome

Stanga et al, Eur J Clin Nutr 2008

Interventions for Cachexia

Drug	Mode of action	Effect	Side-effects
Steroids Megesterol acetate Medroxyprogesterone	Anabolic effects Appetite stimulants	Total weight gain due to increased fat mass and fluid retention. No increase in lean body mass. Increased sense of well-being	Diabetes Osteoporosis Mood swings Thromboembolism
NSAIDs	Inhibits prostaglandin production. Reduces REE and acute phase response	Total weight gain, reduced need for alternative analgesics, improved quality of life. No increase in lean body mass. Prolonged survival in one study	GI upset/haemorrhage
Cannabinoids	Appetite stimulant	Ineffective	Nausea/vomiting
Eicosapentaenoic acid (EPA) Fish oils	Inhibits NFκB Inhibits PIF Reduces pro-inflammatory cytokines	Increased lean body mass in pilot studies. Overall ineffective at increasing weight in large RCTs—possibly due to inability of patients to achieve target dose	Nausea, fishy taste/odour, GI upset
Pentoxifylline	Inhibits TNFα	Ineffective	
Thalidomide	Inhibits TNFα, Effect Th1 to Th2 shift. Inhibit NFκB	Weight stabilization. Attenuated loss of lean body mass. Trend towards prolonged survival	Rash, peripheral neuropathy, daytime somnolence, constipation

Gordon JN, et al, QJM 2005

Multidisciplinary Approach

Multidimensional Assessment
- Medical & treatment history
- Nutritional history
- Symptoms: physical & psychological
- Physical examination
- Laboratory tests
- Anthropometry/body composition

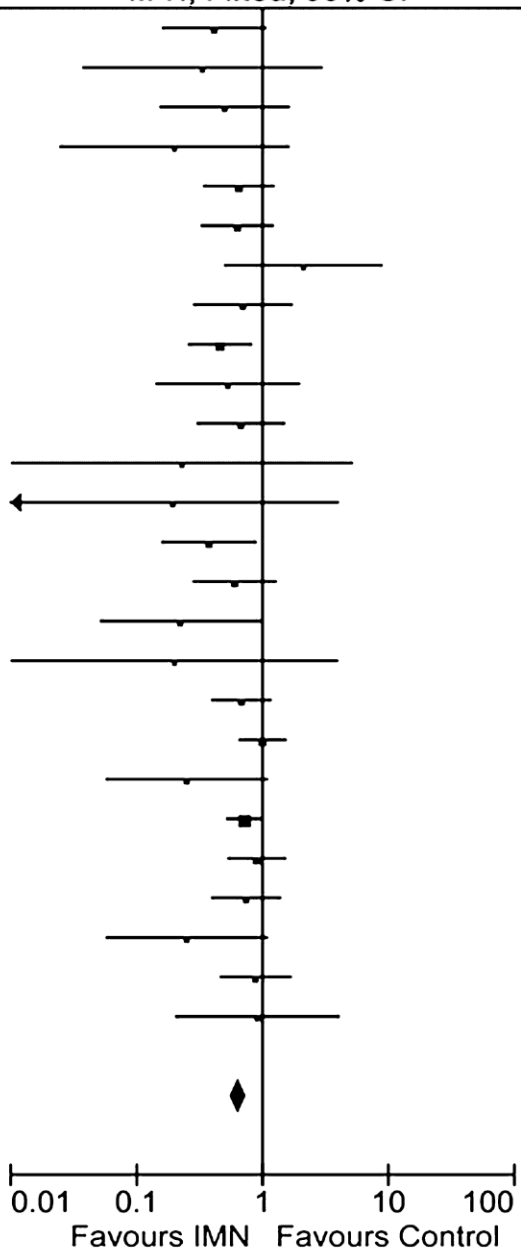
Decision Making Process
- Individualised goals
- Define realistic outcomes
- Determine prognosis and antineoplastic treatment
- Discuss future challenges
- Consider patient & family attitudes
- Consider costs

Individualised Treatment Plan
- Manage treatable causes
- Nutritional counselling
- Artificial nutrition if appropriate
- Pharmacological support
- Physical therapy/exercise

Study or Subgroup	IMN diet Events	Total	Standard diet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Daly et al	5	41	13	44	3.7%	0.41 [0.16, 1.06]	1992
Wachtler et al	1	20	3	20	0.9%	0.33 [0.04, 2.94]	1995
Schilling et al	3	14	6	14	1.8%	0.50 [0.15, 1.61]	1995
Daly et al	1	30	5	30	1.5%	0.20 [0.02, 1.61]	1995
Gianotti et al	13	87	20	87	5.9%	0.65 [0.35, 1.22]	1997
Senkal et al	12	77	19	77	5.6%	0.63 [0.33, 1.21]	1997
Mc Carter et al	5	13	2	11	0.6%	2.12 [0.51, 8.84]	1998
Braga et al	7	55	10	55	3.0%	0.70 [0.29, 1.71]	1998
Braga et al	14	102	31	104	9.1%	0.46 [0.26, 0.81]	1999
Di Carlo et al	3	33	6	35	1.7%	0.53 [0.14, 1.95]	1999
Senkal et al	9	78	13	76	3.9%	0.67 [0.31, 1.48]	1999
Erdem et al	0	15	1	10	0.5%	0.23 [0.01, 5.12]	2001
Jiang et al	0	60	2	58	0.8%	0.19 [0.01, 3.94]	2001
Braga et al	6	50	16	50	4.7%	0.38 [0.16, 0.88]	2002
Jiang et al	9	60	15	60	4.4%	0.60 [0.28, 1.26]	2004
Farreras et al	2	30	9	30	2.7%	0.22 [0.05, 0.94]	2005
Guoxiang et al	0	20	2	20	0.7%	0.20 [0.01, 3.92]	2005
Satinsky et al	10	21	14	20	4.2%	0.68 [0.40, 1.16]	2005
Lobo et al	24	54	24	54	7.1%	1.00 [0.66, 1.52]	2006
Xu et al	2	30	8	30	2.4%	0.25 [0.06, 1.08]	2006
Klek et al	43	152	60	153	17.7%	0.72 [0.52, 0.99]	2008
Klek et al	21	92	23	91	6.8%	0.90 [0.54, 1.51]	2008
Gunerhan et al	7	13	8	11	2.6%	0.74 [0.40, 1.38]	2009
Okamoto et al	2	30	8	30	2.4%	0.25 [0.06, 1.08]	2009
Klek et al	13	52	15	53	4.4%	0.88 [0.47, 1.67]	2010
Sodergren et al	3	23	3	21	0.9%	0.91 [0.21, 4.04]	2010
Total (95% CI)		**1252**		**1244**	**100.0%**	**0.64 [0.55, 0.74]**	
Total events	215		336				

Heterogeneity: $\chi^2 = 23.13$, $df = 25$ ($P = 0.57$); $I^2 = 0\%$

Test for overall effect: $Z = 6.01$ ($P < 0.00001$)



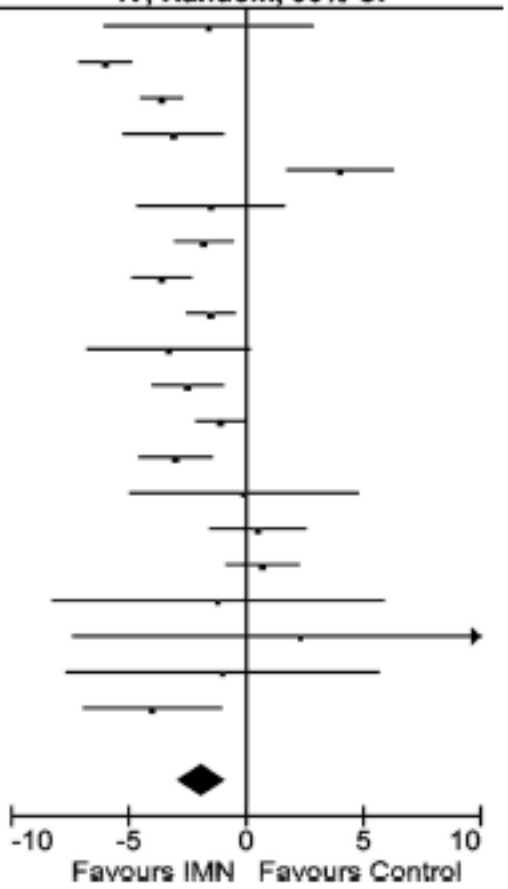
Infectious complications

Marimuthu K, et al, Ann Surg 2012

Study or Subgroup	IMN diet Mean	SD	Total	Standard diet Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Daly et al.	18.8	11.1	41	20.4	9.6	44	3.1%	-1.60 [-6.03, 2.83]	1992
Daly et al	16	0.9	30	22	2.9	30	6.8%	-6.00 [-7.09, -4.91]	1995
Senkal et al.	27	2.3	77	30.6	3.1	77	7.0%	-3.60 [-4.46, -2.74]	1997
Gianotti et al.	16.1	6.2	87	19.2	7.9	87	5.6%	-3.10 [-5.21, -0.99]	1997
Mc Carter et al.	17	3.7	13	13	1.7	11	5.4%	4.00 [1.75, 6.25]	1998
Di Carlo et al.	16.3	6.2	33	17.8	6.9	35	4.4%	-1.50 [-4.61, 1.61]	1999
Braga et al	11.1	4.4	102	12.9	4.6	104	6.6%	-1.80 [-3.03, -0.57]	1999
Senkal et al	22.2	4.1	78	25.8	3.8	76	6.6%	-3.60 [-4.85, -2.35]	1999
Jiang et al.	13	2.5	60	14.5	3	58	6.9%	-1.50 [-2.50, -0.50]	2001
Erdem et al.	15	3	15	18.3	5	10	4.0%	-3.30 [-6.75, 0.15]	2001
Braga et al.	9.5	2.9	50	12	4.5	50	6.4%	-2.50 [-3.98, -1.02]	2002
Guoxiang et al.	10.6	1.2	20	11.7	2	20	6.8%	-1.10 [-2.12, -0.08]	2005
Xu et al.	9	2.2	30	12	3.7	30	6.3%	-3.00 [-4.54, -1.46]	2006
Lobo et al.	20.5	13.1	54	20.6	12.6	54	2.8%	-0.10 [-4.95, 4.75]	2006
Klek et al	12.9	8	92	12.4	5.9	91	5.7%	0.50 [-1.54, 2.54]	2008
Klek et al.	13.1	4.1	52	12.4	3.9	53	6.3%	0.70 [-0.83, 2.23]	2008
Okamoto et al.	23.8	16.6	30	25	10.6	30	1.7%	-1.20 [-8.25, 5.85]	2009
Gunerhan et al.	16.54	14.83	13	14.22	9.12	11	1.0%	2.32 [-7.38, 12.02]	2009
Sodergren et al.	15.5	14.82	23	16.5	6.37	21	1.8%	-1.00 [-7.64, 5.64]	2010
Klek et al.	13.1	13.8	152	17.1	12.2	153	4.6%	-4.00 [-6.92, -1.08]	2010
Total (95% CI)			**1052**			**1045**	**100.0%**	**-1.88 [-2.91, -0.84]**	

Heterogeneity: $Tau^2 = 3.81$; $Chi^2 = 123.03$, df = 19 ($P < 0.00001$); $I^2 = 85\%$

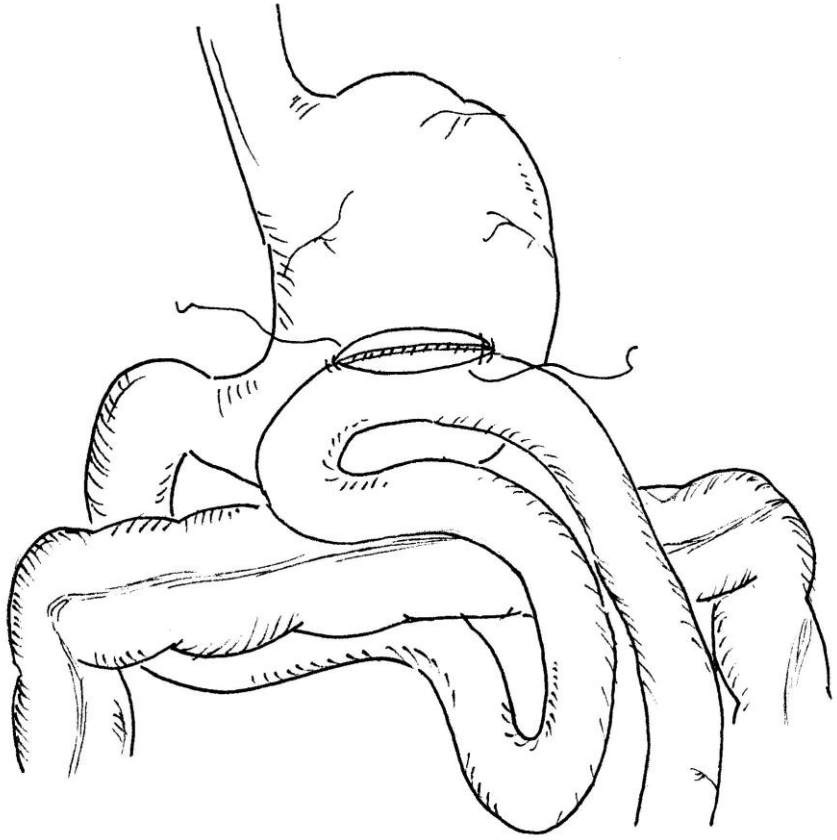
Test for overall effect: $Z = 3.56$ ($P = 0.0004$)

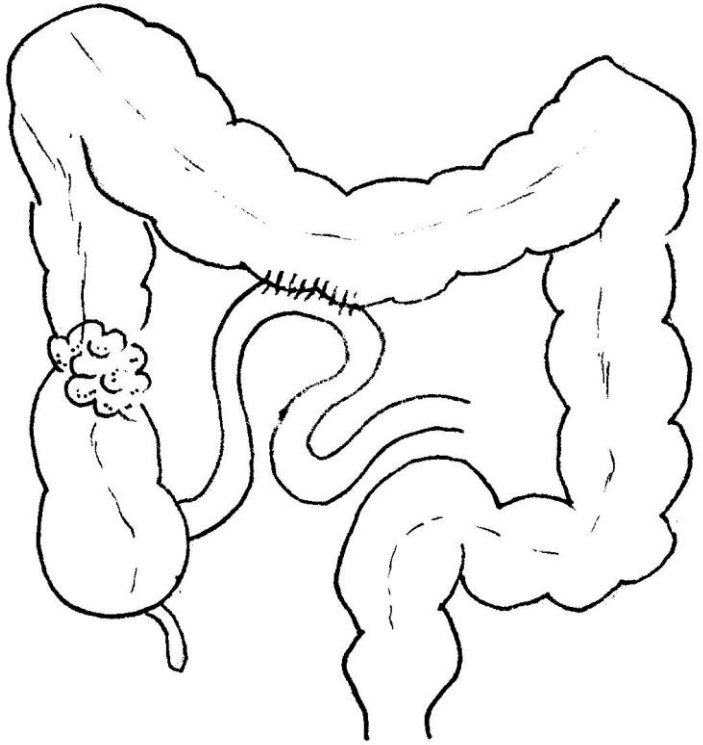


Length of Hospital Stay

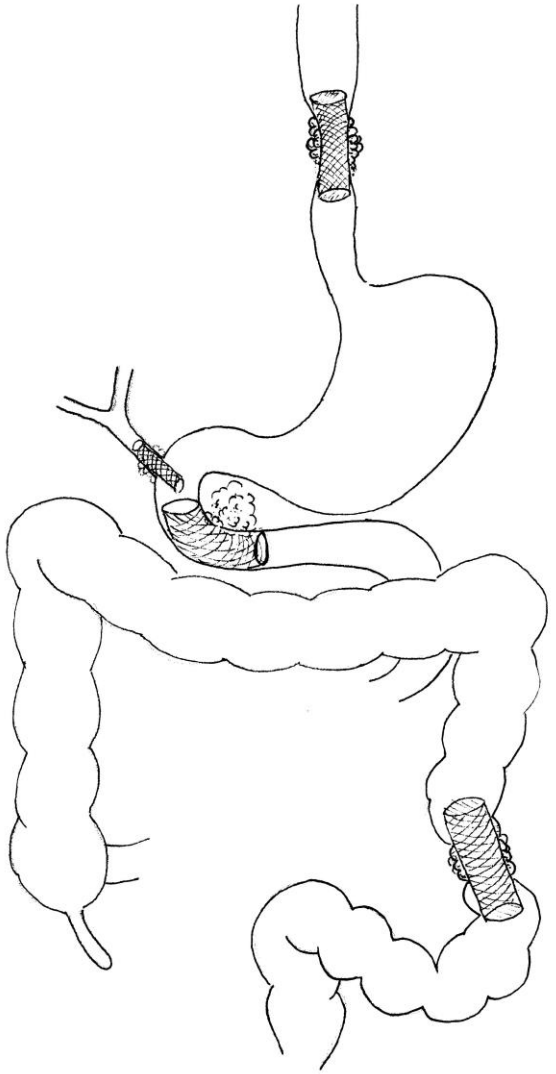
Marimuthu K, et al, Ann Surg 2012

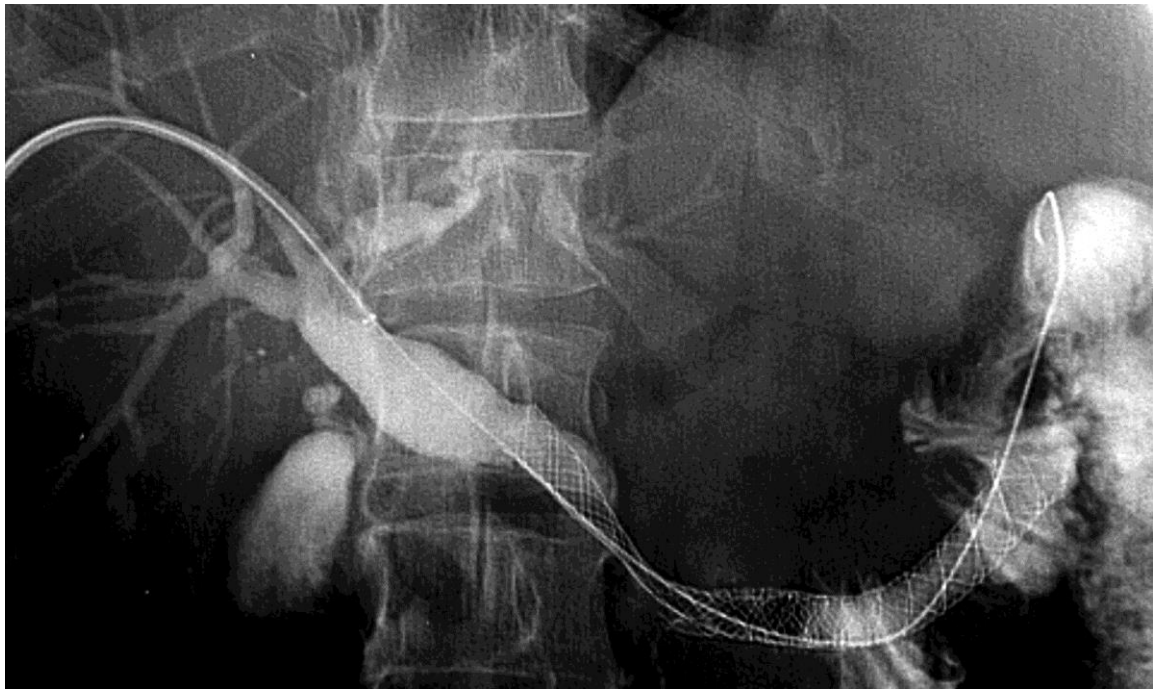
Palliative Measures



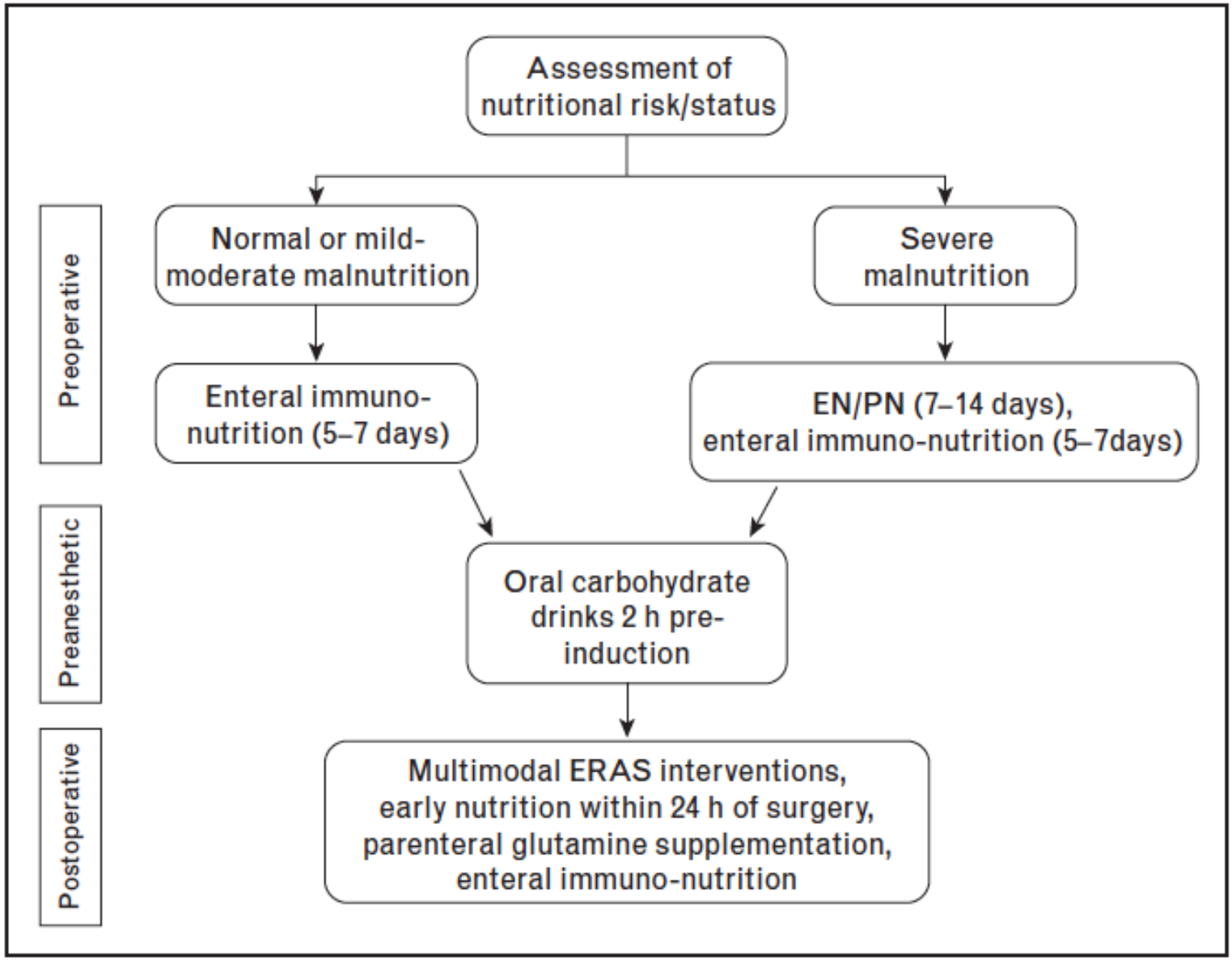


Stents





A Suggested Algorithm



Awad S & Lobo DN, Curr Opin Anesthesiol 2011

Where is the Evidence?

- The quality of evidence is still low and unconvincing
- Many shortcomings in these studies and subsequent meta-analyses
- Systematic review of 15 studies with 3474 patients that there is no evidence to support enteral or parenteral feeding after pancreatoduodenectomy.

Gerritsen et al. Br J Surg 2013

Conclusions

- Nutritional status is a prognostic factor
- Nutritional screening is essential in order to identify patients at risk
- Nutritional support is required if a longer period of inadequate oral intake has to be anticipated
- Multimodal therapy is necessary for cancer cachexia