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

- Poor diet – age, poverty, alcohol, drugs
- Dysphagia
- Obstruction
- Vomiting
- Pancreatic insufficiency
- Malabsorption
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

<table>
<thead>
<tr>
<th>Preop. weight loss</th>
<th>Postop. mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20%</td>
<td>3.5%</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Studley HO, JAMA 1936
Starvation & Weight loss

(After Allison)

Days

% body weight

Decision Box

- Catabolic
- Complete starvation
- Partial starvation
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
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
# Prevalence of Cachexia

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Patients with cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagogastric cancer</td>
<td>85%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>83%</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>61%</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>57%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>56%</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>54%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (unfavourable)</td>
<td>48%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>40%</td>
</tr>
<tr>
<td>Acute non-lymphocytic lymphoma</td>
<td>39%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>36%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (favourable)</td>
<td>31%</td>
</tr>
</tbody>
</table>

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?
• 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

(i) BMI (kg/m²)
   0 = >20.0
   1 = 18.5-20.0
   2 = <18.5

(ii) Weight loss in 3-6 months
   0 = <5%
   1 = 5-10%
   2 = >10%

(iii) Acute disease effect
     Add a score of 2 if there has been or is likely to be no or very little nutritional intake for >5 days

Add scores

OVERALL RISK OF UNDERNUTRITION *

0 1 2 or more
LOW MEDIUM HIGH

Disease Related Malnutrition
Stratton, Green & Elia, 2003
MUST Score and Clinical Outcomes

MUST Score high versus no risk in 100 general surgical patients

- Hospital LOS
- In Hospital Mortality
- Cumulative 6 Month Mortality
- Cumulative 12 Month Mortality

High Risk vs No Risk

Ben-Ishay et al, Gastro Res Prac 2011
How Much is Needed?

- Give $1.0 - 1.3 \times \text{RMR}$
  - 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.
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
Hypokalaemia
Hypomagnesaemia
Hypophosphataemia
Thiamine deficiency
Salt and water retention - oedema

-> Refeeding syndrome

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

↑ Protein and glycogen synthesis

Insulin secretion

Starvation / Malnutrition

Glycogenolysis, gluconeogenesis and protein catabolism

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

Refeeding (switch to anabolism)

Fluid, salt, nutrients (CHO major energy source)

# Interventions for Cachexia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Effect</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Anabolic effects</td>
<td>Total weight gain due to increased fat mass and fluid retention. No increase in lean body mass. Increased sense of well-being</td>
<td>Diabetes, Osteoporosis, Mood swings, Thromboembolism</td>
</tr>
<tr>
<td>Megesterol acetate</td>
<td>Appetite stimulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Inhibits prostaglandin production. Reduces REE and acute phase response</td>
<td>Total weight gain, reduced need for alternative analgesics, improved quality of life. No increase in lean body mass. Prolonged survival in one study</td>
<td>GI upset/haemorrhage</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Appetite stimulant</td>
<td>Ineffective</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (EPA)</td>
<td>Inhibits NFκB</td>
<td>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</td>
<td>Nausea, fishy taste/odour, GI upset</td>
</tr>
<tr>
<td>Fish oils</td>
<td>Inhibits PIF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Inhibits TNFα</td>
<td>Ineffective</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Inhibits TNFα, Effect Th1 to Th2 shift. Inhibit NFκB</td>
<td>Weight stabilization. Attenuated loss of lean body mass. Trend towards prolonged survival</td>
<td>Rash, peripheral neuropathy, daytime somnolence, constipation</td>
</tr>
</tbody>
</table>
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
Infectious complications

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMN diet</th>
<th>Standard diet</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daly et al</td>
<td>5</td>
<td>41</td>
<td>0.41 [0.16, 1.06]</td>
<td>1992</td>
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<tr>
<td>Wachtler et al</td>
<td>1</td>
<td>20</td>
<td>0.33 [0.04, 2.94]</td>
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<tr>
<td>Schilling et al</td>
<td>3</td>
<td>14</td>
<td>0.50 [0.15, 1.61]</td>
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<tr>
<td>Daly et al</td>
<td>1</td>
<td>30</td>
<td>0.20 [0.02, 1.61]</td>
<td>1995</td>
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<tr>
<td>Gianotti et al</td>
<td>13</td>
<td>87</td>
<td>0.65 [0.35, 1.22]</td>
<td>1997</td>
</tr>
<tr>
<td>Senkal et al</td>
<td>12</td>
<td>77</td>
<td>0.63 [0.33, 1.21]</td>
<td>1997</td>
</tr>
<tr>
<td>Mc Carter et al</td>
<td>5</td>
<td>13</td>
<td>2.12 [0.51, 8.84]</td>
<td>1998</td>
</tr>
<tr>
<td>Braga et al</td>
<td>7</td>
<td>55</td>
<td>0.70 [0.29, 1.71]</td>
<td>1998</td>
</tr>
<tr>
<td>Braga et al</td>
<td>14</td>
<td>102</td>
<td>0.46 [0.26, 0.81]</td>
<td>1999</td>
</tr>
<tr>
<td>Di Carlo et al</td>
<td>3</td>
<td>33</td>
<td>0.53 [0.14, 1.95]</td>
<td>1999</td>
</tr>
<tr>
<td>Senkal et al</td>
<td>9</td>
<td>78</td>
<td>0.67 [0.31, 1.48]</td>
<td>1999</td>
</tr>
<tr>
<td>Erdem et al</td>
<td>0</td>
<td>15</td>
<td>0.23 [0.01, 5.12]</td>
<td>2001</td>
</tr>
<tr>
<td>Jiang et al</td>
<td>0</td>
<td>60</td>
<td>0.19 [0.01, 3.94]</td>
<td>2001</td>
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<tr>
<td>Braga et al</td>
<td>6</td>
<td>50</td>
<td>0.38 [0.16, 0.88]</td>
<td>2002</td>
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<tr>
<td>Jiang et al</td>
<td>9</td>
<td>60</td>
<td>0.60 [0.28, 1.26]</td>
<td>2004</td>
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<td>Farreras et al</td>
<td>2</td>
<td>30</td>
<td>0.22 [0.05, 0.94]</td>
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<tr>
<td>Guoxiang et al</td>
<td>0</td>
<td>20</td>
<td>0.20 [0.01, 3.92]</td>
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<tr>
<td>Satinsky et al</td>
<td>10</td>
<td>21</td>
<td>0.68 [0.40, 1.16]</td>
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<td>Lobo et al</td>
<td>24</td>
<td>54</td>
<td>1.00 [0.66, 1.52]</td>
<td>2006</td>
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<tr>
<td>Xu et al</td>
<td>2</td>
<td>30</td>
<td>0.25 [0.06, 1.08]</td>
<td>2006</td>
</tr>
<tr>
<td>Klek et al</td>
<td>43</td>
<td>152</td>
<td>0.72 [0.52, 0.99]</td>
<td>2008</td>
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<tr>
<td>Klek et al</td>
<td>21</td>
<td>92</td>
<td>0.90 [0.54, 1.51]</td>
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<td>Gunerhan et al</td>
<td>7</td>
<td>13</td>
<td>0.74 [0.40, 1.38]</td>
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<tr>
<td>Okamoto et al</td>
<td>2</td>
<td>30</td>
<td>0.25 [0.06, 1.08]</td>
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<td>Klek et al</td>
<td>13</td>
<td>52</td>
<td>0.88 [0.47, 1.67]</td>
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<tr>
<td>Sodergren et al</td>
<td>3</td>
<td>23</td>
<td>0.91 [0.21, 4.04]</td>
<td>2010</td>
</tr>
</tbody>
</table>

Total (95% CI): 1252 events, 1244 events, 100.0% of the total events.

Risk Ratio: 0.64 [0.55, 0.74]

Total events: 215 events, 336 events

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

Test for overall effect: Z = 6.01 (P < 0.00001)
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMN diet Mean</th>
<th>IMN diet SD</th>
<th>IMN diet Total</th>
<th>Standard diet Mean</th>
<th>Standard diet SD</th>
<th>Standard diet Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
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<tbody>
<tr>
<td>Daly et al.</td>
<td>18.8</td>
<td>11.1</td>
<td>41</td>
<td>20.4</td>
<td>9.6</td>
<td>44</td>
<td>3.1%</td>
<td>-1.60</td>
<td>[-6.03, 2.83]</td>
<td>1992</td>
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<tr>
<td>Daly et al</td>
<td>16</td>
<td>0.9</td>
<td>30</td>
<td>22</td>
<td>2.9</td>
<td>30</td>
<td>6.8%</td>
<td>-6.00</td>
<td>[-7.09, -4.91]</td>
<td>1995</td>
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<tr>
<td>Senkal et al.</td>
<td>27</td>
<td>2.3</td>
<td>77</td>
<td>30.6</td>
<td>3.1</td>
<td>77</td>
<td>7.0%</td>
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<td>6.2</td>
<td>87</td>
<td>19.2</td>
<td>7.9</td>
<td>87</td>
<td>5.6%</td>
<td>-3.10</td>
<td>[-5.21, -0.99]</td>
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<td>Mc Carter et al.</td>
<td>17</td>
<td>3.7</td>
<td>13</td>
<td>13</td>
<td>1.7</td>
<td>11</td>
<td>5.4%</td>
<td>4.00</td>
<td>[1.75, 6.25]</td>
<td>1998</td>
</tr>
<tr>
<td>Di Carlo et al.</td>
<td>16.3</td>
<td>6.2</td>
<td>33</td>
<td>17.8</td>
<td>6.9</td>
<td>35</td>
<td>4.4%</td>
<td>-1.50</td>
<td>[-4.61, 1.61]</td>
<td>1999</td>
</tr>
<tr>
<td>Braga et al.</td>
<td>11.1</td>
<td>4.4</td>
<td>102</td>
<td>12.9</td>
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<td>104</td>
<td>6.6%</td>
<td>-1.80</td>
<td>[-3.03, -0.57]</td>
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<tr>
<td>Senkal et al</td>
<td>22.2</td>
<td>4.1</td>
<td>78</td>
<td>25.8</td>
<td>3.8</td>
<td>76</td>
<td>6.6%</td>
<td>-3.60</td>
<td>[-4.85, -2.35]</td>
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<tr>
<td>Jiang et al.</td>
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<td>2.5</td>
<td>60</td>
<td>14.5</td>
<td>3</td>
<td>58</td>
<td>6.9%</td>
<td>-1.50</td>
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<td>50</td>
<td>12</td>
<td>4.5</td>
<td>50</td>
<td>6.4%</td>
<td>-2.50</td>
<td>[-3.98, -1.02]</td>
<td>2002</td>
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<tr>
<td>Guoxiang et al.</td>
<td>10.6</td>
<td>1.2</td>
<td>20</td>
<td>11.7</td>
<td>2</td>
<td>20</td>
<td>6.8%</td>
<td>-1.10</td>
<td>[-2.12, -0.08]</td>
<td>2005</td>
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<tr>
<td>Xu et al.</td>
<td>9</td>
<td>2.2</td>
<td>30</td>
<td>12</td>
<td>3.7</td>
<td>30</td>
<td>6.3%</td>
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<td>[-4.54, -1.46]</td>
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<tr>
<td>Lobo et al.</td>
<td>20.5</td>
<td>13.1</td>
<td>54</td>
<td>20.6</td>
<td>12.6</td>
<td>54</td>
<td>2.8%</td>
<td>-0.10</td>
<td>[-4.95, 4.75]</td>
<td>2006</td>
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<tr>
<td>Klek et al.</td>
<td>12.9</td>
<td>8</td>
<td>92</td>
<td>12.4</td>
<td>5.9</td>
<td>91</td>
<td>5.7%</td>
<td>0.50</td>
<td>[-1.54, 2.54]</td>
<td>2008</td>
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<tr>
<td>Klek et al.</td>
<td>13.1</td>
<td>4.1</td>
<td>52</td>
<td>12.4</td>
<td>3.9</td>
<td>53</td>
<td>6.3%</td>
<td>0.70</td>
<td>[-0.83, 2.23]</td>
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<tr>
<td>Okamoto et al.</td>
<td>23.8</td>
<td>16.6</td>
<td>30</td>
<td>25</td>
<td>10.6</td>
<td>30</td>
<td>1.7%</td>
<td>-1.20</td>
<td>[-8.25, 5.85]</td>
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<tr>
<td>Sodergren et al.</td>
<td>15.5</td>
<td>14.82</td>
<td>23</td>
<td>16.5</td>
<td>6.37</td>
<td>21</td>
<td>1.8%</td>
<td>-1.00</td>
<td>[-7.64, 5.64]</td>
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<td>152</td>
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<td>4.6%</td>
<td>-4.00</td>
<td>[-6.92, -1.08]</td>
<td>2010</td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 1052 / 1045 / 100.00% / -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: $Z = 3.56$ ($P = 0.00004$)
Palliative Measures
A Suggested Algorithm

- Assessment of nutritional risk/status
  - Normal or mild-moderate malnutrition
    - Enteral immunonutrition (5–7 days)
  - Severe malnutrition
    - EN/PN (7–14 days), enteral immunonutrition (5–7 days)

- Preoperative
  - Oral carbohydrate drinks 2 h pre-induction

- Postoperative
  - Multimodal ERAS interventions, early nutrition within 24 h of surgery, parenteral glutamine supplementation, enteral immunonutrition
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.

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