DIET, NUTRITION AND THERAPEUTIC OUTCOMES OF CANCER: A LITERATURE REVIEW

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Roswell Park Cancer Institute
Lecture Outline

• **Background**
  • Nutrition implications of cancer and cancer related treatment

• **Nutritional Interventions in Early Oncology Care**
  • What is the evidence for improving nutritional status
  • What is the evidence for improving treatment complications, disease progression and survival
Population Focus for Lecture

- **Adult oncology outpatients**
  - Receive radiation and/or chemotherapy in outpatient clinics
  - Undergo surgery and are followed up in outpatient clinics
  - Any combination of these (multi-modal therapy)
  - Patients at risk for inadequate nutritional status

- **Early oncology care**
  - Active treatment
  - Recovery from treatment
BACKGROUND
Nutrition Implications of Cancer
Why do Cancer Patients Suffer from Inadequate Nutritional Status?

- Nutrition Imbalances due to
  - Tumor
  - Host response to the tumor
  - Other factors
    - Anxiety
    - Depression
    - Lifestyle factors

Requirements, Digestion, Absorption, Excretion, Intake
Intensity of Consequences Vary

- Stage - Advanced
- Site – GI, Lung, Head and Neck
- Treatment: Multi-Modal
## Treatment Effects

<table>
<thead>
<tr>
<th>Radiation Therapy</th>
<th>Chemotherapy</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>Nausea/Vomiting</td>
<td>Delayed Gastric Emptying</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>Diarrhea</td>
<td>Early Satiety</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Taste Changes and Acquired Food Aversions</td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea/Bloating</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Anorexia</td>
<td>Anorexia</td>
</tr>
</tbody>
</table>

- Nutrition problems **BEFORE** diagnosis may intensify
- Treatment Toxicity is reported more often in patients who are poorly nourished
Implications for Cancer Treatment

- Decreased treatment response
- Increased treatment complications
- Increased treatment toxicity

Alteration of Treatment Schedule
- Treatment interruption
- Dose de-escalation
Total Effect on Clinical Outcomes

- Increased hospital admissions or re-admissions
  - Infections
- Increase length of hospital stay
- Poor quality of life
- Early mortality

**RPCI Head and Neck CCRT Experience:** Each day of delay decreases survival by 5%.

*(Platek *Head and Neck* 2012)*
Is there evidence that nutrition intervention is effective?
RELEVANT ISSUES
Nutrition Evidence
Clinical Setting

- Until recently, no universally agreed upon operational definition for inadequate nutrition states in the setting of cancer
  - Cancer-related malnutrition
  - Cancer Cachexia

- Non-standardized screening, assessment and intervention

- Inadequate availability of nutrition services in the outpatient setting
Availability of Outpatient Nutrition Services

• Telephone Survey of NCI-designated CCCs
  • April-October 2012
  • 32 out of 40 centers surveyed (80%)

• Overall Conclusions
  • Referral or consult-based clinical nutrition service (98%)
    • Not consistently part of multidisciplinary service
      • No assurance that a patient is referred
      • No assurance that a referred patient receives service

Platek et al. JOP 2014
EVIDENCE

Do nutrition interventions impact nutritional outcomes?
2010-2016
<table>
<thead>
<tr>
<th>Literature Search</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Databases:</strong> PubMed and Embase</td>
</tr>
<tr>
<td>Included work from the <strong>Evidence Analysis Library (EAL) Adult Oncology</strong></td>
</tr>
<tr>
<td>• 45 member team, systematic review, practice guidelines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Start: 1980-2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final: 2010-2016</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Article Count</th>
<th>Start: 653</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final: 36 Studies</td>
</tr>
<tr>
<td></td>
<td>2 Systematic Reviews</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Majority of the evidence</th>
<th>Gastrointestinal (GI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head and Neck (HN)</td>
</tr>
</tbody>
</table>
Nutrition Counseling: 2010-2016

- 4 RCTs, 1 Prospective Study
  - Improved weight
  - Improved quality of life
  - Improved nutritional intake
  - Improved nutritional status
  - Decreased toxicity from radiation therapy

- 1 Systematic Review – Head and Neck
  - Improved weight
  - Improved nutritional status
  - Improved global quality of life score
Nutrition Support: 2010-2016

• 11 RCTs, 4 Prospective Studies, 6 Retrospective Reviews
  • **Early** nutrition support improved
    • Nutritional Status
    • GI recovery
    • Immune response
    • Quality of life
  • Decreased
    • Length of hospital stay
    • Surgical complications
    • Readmissions to the hospital
Nutrition Support + Counseling 2010-2016

- 1 RCT, 1 Prospective Study, 2 Retrospective Reviews
  - Improved
    - Weight status
    - Functional walking
    - Recovery from surgery
    - Quality of life
    - Treatment tolerance
  - Decreased
    - Postoperative complications
    - Treatment toxicity to chemoradiation
*Immune Enhancing Nutrition Support 2010-2016

• 4 RCTs, 2 Prospective Studies, 1 Meta-Analysis

• Improved
  • Body weight
  • Lean body mass
  • Performance status

• Decreased
  • Inflammation
  • Length of stay
  • Postoperative complications
  • Infections

*Formulas with 2 of the following: Arginine, Omega-3-fatty acids, Glutamine, Ribonucleic acid
Take Away Message

• It is established that there is a role for
  • *Individualized Dietary Counseling*
  • Nutrition Support
    • Accompanied by education and counseling
    • *Immune enhanced nutrition support in specified surgical patients*
      • Perioperative
Take Away Message

• Intervention is needed especially when treatment is **multimodal**

• Early intervention is best

• Intervention should vary based on the nutritional status of the patient
EVIDENCE

Do nutrition interventions previously identified impact treatment complications, disease progression and survival compared to standard of care?
2010-2016
<table>
<thead>
<tr>
<th>Literature Search</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Databases:</strong> PubMed, Embase, CINAHL, and CENTRAL</td>
</tr>
<tr>
<td><strong>Time Period</strong></td>
</tr>
</tbody>
</table>
| **Focus** | RCT (control=standard care)  
Nutrition-related interventions and therapeutic outcomes (PE/SE)  
- Treatment complications  
- Disease progression  
- Survival |
| **Article Count** | Start: 200 (RCT)  
Final: 16 RCTs |
| **Majority of the evidence** | Gastrointestinal (GI) (n=9)  
Head and Neck (HN) (n=3)  
Lung (L) (n=2)  
Mixed (M) (n=2) |
| **Other** |   |
Overview: Interventions Tested

- Early feeding (n=2)
- Shortened pre-op fast (n=1)
- Biometric nutrition counseling (n=1)
- Nutrition counseling (n=1)
- Nutrition counseling + nutrition support (n=1)
- *Immune nutrition support
  - Enteral (n=5)
  - Oral (n=2)
- Immune nutrition support + nutrition counseling (n=1)
- Synbiotics (n=1)
- Education empowerment (n=1)

*Formulas that include arginine, Omega 3 fatty acids, glutamine, and/or ribonucleic acid
Overview: Outcomes

- **Primary Endpoint or Secondary Endpoint**
  - 69% - Complications (infections, overall morbidity, mortality, chemotherapy tolerance)
  - 38% - Other (length of stay and unplanned readmissions)
  - 19% - Survival (DSS, OS)
  - 19% - Disease Progression
Overview of Studies

- 63% - assessed nutritional status using validated tools and compared status between groups
  - 3 studies only included malnourished
    - 1- cachexia
    - 1-severely malnourished
    - 1-malnourished

- 38% - provided information about statistical power analysis
## Early Feeding Studies (n=2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hur, 2011, Korea GI</td>
<td>n=54</td>
<td>I: Oral diet -3 days</td>
<td>C: Oral diet – 6 days</td>
<td>↓ LOS (p=0.04) ↓ Readmission (p=0.047)</td>
</tr>
<tr>
<td>Barlow, 2011, UK GI</td>
<td>n=121</td>
<td>I: 12 hour post-op</td>
<td>C: 7-10 days post-op</td>
<td>↓ LOS (p=0.02) ↓ Morbidity (p=0.04)</td>
</tr>
</tbody>
</table>
# Shortened Pre-op Fasting (n=1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pexe-Machado, 2013, Brazil GI n=22</td>
<td>SS</td>
<td>*400 ml previous evening + 200 ml 3 hours pre-op</td>
<td>6-8 h pre-op fast</td>
<td>↓ LOS (p=0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*(11% protein, 89% carbohydrate)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Nutrition Counseling (n=1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention(I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravasco, 2012, Portugal</td>
<td>GI</td>
<td>I: 6 weekly counseling + education, regular foods</td>
<td></td>
<td>↑ DSS (p&lt;0.05)</td>
</tr>
<tr>
<td>n=89 (follow-up study)</td>
<td></td>
<td>I2: oral nutritional supplement + regular diet</td>
<td></td>
<td>↑ OS(p&lt;0.01)</td>
</tr>
<tr>
<td>Original Study</td>
<td></td>
<td></td>
<td></td>
<td>↓ Late Radiation Toxicity (p&lt;0.001)</td>
</tr>
<tr>
<td>n=111</td>
<td></td>
<td></td>
<td></td>
<td>Median follow-up=6.5y</td>
</tr>
<tr>
<td>Years: 2000-2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Nutrition Counseling/Support (n=1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention(I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SS</td>
<td>I: Prophylactic NS + NC</td>
<td>C: SOC</td>
<td>Treatment interruption (p=0.08)</td>
</tr>
<tr>
<td>Silander, 2012, Sweden</td>
<td>HN</td>
<td>n=134</td>
<td></td>
<td>No difference in 2 year survival</td>
</tr>
</tbody>
</table>

# Immune Nutrition Support – Enteral (n=3)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felekis, 2010, Greece</td>
<td>SS HN</td>
<td>I: Periop–Impact</td>
<td>C: Periop–SOC</td>
<td>↓ Major complications (p&lt;0.05)</td>
</tr>
<tr>
<td>Sultan, 2012, UK</td>
<td>GI</td>
<td>I: Periop–O-3FA I2: Periop–SOC</td>
<td>C: Postop-SOC</td>
<td>No difference in infections, LOS, morbidity or mortality</td>
</tr>
<tr>
<td>Marano, 2013, Italy</td>
<td>GI</td>
<td>I: Postop-Impact</td>
<td>C: Postop-SOC</td>
<td>↓ Infectious Infections (p=0.04) ↓ LOS (p=0.03)</td>
</tr>
</tbody>
</table>
# Immune Nutrition Support – Oral (n=2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Meij, 2012, Netherlands Lung n=40</td>
<td>I: Prosure (O-3FA) C: SOC</td>
<td>No difference for chemotherapy tolerance or readmissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanchez-Lara, 2014, Mexico Lung n=84</td>
<td>I: Prosure (O-3FA) C: SOC</td>
<td>No difference for OS or PFS HR for PFS=0.53 (p=0.05) Median follow-up=5.8m</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Oral Immune Nutrition Support + Counseling (n=1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabal, 2010, Spain</td>
<td>GI</td>
<td>I: NC + Prosure</td>
<td>C: NC</td>
<td>0% vs. 67% delay due to chemo toxicity</td>
</tr>
<tr>
<td>n=13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Synbiotics (n=1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention(I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sommacul, 2015, Brazil GI</td>
<td>SS</td>
<td>I: Periop synbiotic capsule</td>
<td>C: Periop placebo</td>
<td>↓ Infection (p=0.01)) ↓ Complications (p=0.04) ↓ LOS (p=0.01) ↓ Mortality (p=0.02)</td>
</tr>
</tbody>
</table>
# All Malnourished (n=3)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buijs, 2010, Netherlands</td>
<td>HN</td>
<td>Severely Malnourished</td>
<td>Periop Arg formula</td>
<td>↑ OS (p=0.02) ↑ DSS (p=0.02) ↑ PFS(p=0.03)</td>
</tr>
<tr>
<td></td>
<td>n=32</td>
<td></td>
<td>Periop Std formula</td>
<td></td>
</tr>
<tr>
<td>Klek, 2011, Poland</td>
<td>GI</td>
<td>All Malnourished</td>
<td>Immune formula</td>
<td>↓ Complications (p=0.04) ↓ LOS (p=0.01) ↓ Mortality (p=0.02) ↓ Morbidity (p=0.02)</td>
</tr>
<tr>
<td></td>
<td>n=305</td>
<td></td>
<td>Standard formula</td>
<td></td>
</tr>
<tr>
<td>DeWaele, 2015, Belgium</td>
<td>Mixed</td>
<td>Cachectic</td>
<td>NC based on indirect calorimetry and physical activity measure; ONS/EN or PN</td>
<td>↓ Progression ↑ 2 year OS (p&lt;0.01) ↓ Readmission (p=0.01)</td>
</tr>
<tr>
<td></td>
<td>n=20</td>
<td></td>
<td>Standard NC</td>
<td></td>
</tr>
</tbody>
</table>
## Education Empowerment (n=1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Intervention (I)</th>
<th>Control (C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt, 2015, Germany</td>
<td>Mixed</td>
<td>I: Informational booklet designed by medical professionals</td>
<td>C: Standard Information</td>
<td>No difference in LOS or post-op complications</td>
</tr>
<tr>
<td></td>
<td>n=652</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary for the Current Decade

• Early and validated nutrition screening/assessment and intervention
• Repetitive and intensive individualized nutrition counseling with nutrition support
• Malnourished surgical patient
  • Perioperative nutrition support
  • In very specific cases, evidence is emerging to support consideration of immune enhanced formulas (arginine with O-3FA)
General Limitations of Nutrition Research

• Observational studies
  • Lack of a true comparison group
  • Inconsistent measurement of nutritional status

• Poorly measured outcomes
  • Inconsistent use of standardized measurement tools

• Vague description of intervention

• Trials - not powered for primary objective
Moving Forward
NEW DEFINITIONS AND DIAGNOSTIC CRITERIA

Cancer-related Malnutrition
Cancer-related Cachexia
Cancer-Related Malnutrition

- Etiology Based Approach
  - Inflammatory Response

- New nomenclature
  - Starvation-related malnutrition
    - Chronic starvation without inflammation
  - Chronic disease-related malnutrition
    - Chronic inflammation of mild-moderate degree
      - Example – Cancer
  - Acute disease or injury-related malnutrition
    - Inflammation is acute and of severe degree

White et al
JPEN, 2012
Diagnostic Criteria

• Energy Intake
• Weight loss
• Changes in
  • body fat
  • muscle mass
  • fluid accumulation
  • grip strength
Cancer Cachexia

Multifactorial syndrome
- Ongoing loss of skeletal muscle mass (with or without loss of fat)
  - Negative protein and energy balance
  - Driven by decreased food intake and abnormal metabolism (Fearon et al. Lancet Oncol 2011)

- 50-80% of cancer patients
- Leads to death in 20% of cancer patients

Cancer Cachexia Continuum

- **Precachexia**: Weight loss ≤5%
  - Anorexia and metabolic change

- **Cachexia**: Weight loss >5% or
  - BMI <20 and weight loss >2%
  - Sarcopenia and weight loss >2%
  - Often reduced food intake/systemic inflammation

- **Refractory cachexia**: Variable degree of cachexia
  - Cancer disease both pro-catabolic and not responsive to anticancer treatment
  - Low performance score
  - <3 months expected survival

Death
Validated Measurements

- NRS-2002
- SF PG-SGA
- PG-SGA
- EORTC QLQ
Future Direction

• Robust study designs
  • Attention to nutritional status of patients in the trial
  • Powered to examine primary objectives of complications, disease progression and survival
    • Multi-institutional prospective cohort

• Testing of precise, individualized nutrition therapy WITH exercise therapy combinations for patients undergoing treatment in the outpatient setting
## Unintentional Weight Loss: Clinical Definitions

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Significant Loss</th>
<th>Severe Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Days</td>
<td>1-2%</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>30 Days</td>
<td>5%</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>90 Days</td>
<td>7.5%</td>
<td>&gt;7.5%</td>
</tr>
<tr>
<td>180 Days (6 months)</td>
<td>10%</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>
Three Clinically Relevant Stages

• **Stage 1: Precachexia**
  - Weight loss ≤ 5%
  
  • Early clinical and metabolic signs
    - Anorexia
    - Impaired glucose tolerance
    - Often occur before substantial involuntary weight loss

• Risk of progression varies depending on
  - Cancer type and stage
  - Systemic inflammation
  - Low food intake
  - Lack of response to anticancer therapy

Fearn *Lancet Oncol* 2011
Three Clinically Relevant Stages

• **Stage 3: Refractory Cachexia**
  - Active catabolism
    - Management of weight loss is no longer possible
  - Characterized by
    - Low performance status
    - Life expectancy less than 3 months
Severity of Cachexia

• Classification of severity
  • Rate of ongoing weight loss
  • Degree of depletion of energy stores
  • Degree of depletion of body protein mass

• A loss of 5 kg/m² for BMI of 20 vs. 35 shows more severe complications

• At BMI of 30 risk increases if weight loss is associated with loss of LBM
Cachexia

Anorexia

Food Intake
Intestinal Absorption
Gastric Emptying
Dysphagia
Hypogeusia
Hyposmia

Metabolic Disturbances

Energy Expenditure
Inflammation
Glucose Intolerance
Fat Mobilization
Protein Breakdown

Bodyweight

Lean Body Mass

Physical Performance

QOL

Fat Mass

Survival
Weakness of Previous Cachexia Related Trials –

- Included patients in terminal stage alongside earlier stage

- Allowed for varied degree of weight loss
  - Patients grouped together with extremely wide ranges of weight loss

- Used life expectancy of > 6 months/unreliable
  - Substantial proportion of patients died within just a few weeks of randomization

- Most trials investigated single agents in unselected patients presenting with weight loss of any etiology
LITERATURE REVIEW: NUTRITION OUTCOMES

2010-2016
Nutrition Counseling: 2010-2016

• 4 RCTs, 1 Prospective Study
  • Improved weight
  • Improved quality of life
  • Improved nutritional intake
  • Improved nutritional status
  • Decreased toxicity from radiation therapy
Nutrition Counseling: Systematic Review

• Head and Neck Cancer (up to January 2012)
  • 10 RCTs identified
  • 4 out of the 10 examined effects of
    • Individualized nutrition counseling vs. no counseling vs. nutritional advice by a nurse
      • Nutritional Status
      • Quality of life

Langius et al. Clinical Nutrition 2013
Nutrition Counseling: Systematic Review

• **Head and Neck Cancer (up to January 2012)**
  - Superior results with counseling group
    - 4/4 positive effects on nutritional status for those who received counseling only
      - 3/4 ↓ weight loss
      - 3/4 ↓ malnutrition
    - 2/4 assessed quality of life
      - ↓ decline in global score with counseling

Langius et al. Clinical Nutrition 2013
Nutrition Support: 2010-2016

- 11 RCTs, 4 Prospective Studies, 6 Retrospective Reviews
  - **Early** nutrition support improved
    - Nutritional Status
    - GI recovery
    - Immune response
    - Quality of life
  - Decreased
    - Length of hospital stay
    - Surgical complications
    - Readmissions to the hospital
Nutrition Support + Counseling 2010-2016

- 1 RCT, 1 Prospective Study, 2 Retrospective Reviews
  - Improved
    - Weight status
    - Functional walking
    - Recovery from surgery
    - Quality of life
    - Treatment tolerance
  - Decreased
    - Postoperative complications
    - Treatment toxicity to chemoradiation
Nutrition Support using Immune Enhancing Nutrition (IEN)

- Formulas with at least 2 of the following:
  - Arginine
  - Omega-3-fatty acids
  - Glutamine
  - Ribonucleic acid
Meta–Analysis IEN (until 2014)

- Evaluated effects of different IEN support regimes for patients who underwent surgery for resectable GI malignancy
  - 27 RCTs
  - IEN support vs. standard nutrition support
  - IEN support preoperative vs. postoperative vs. perioperative
- Outcomes
  - Infectious complications
  - Non-infectious complications
  - Length of postoperative hospitalization

Song et al Medicine 2015
IEN Meta-Analysis Results

- **Infectious Complications**
  - Preoperative IEN vs. Standard
    - RR=0.58 (0.43-0.78)
  - Postoperative IEN vs. Standard
    - RR=0.63 (0.52-0.76)
  - Perioperative IEN vs. Standard
    - RR=0.46 (0.34-0.62)

- **Other**
  - Perioperative IEN ↓incidence of noninfectious complications (RR=0.65, 0.44-0.95)
  - Postoperative and perioperative ↓LOS

Song et al Medicine 2015
<table>
<thead>
<tr>
<th>Author/Year/Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Site/Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Werf 2015/ Netherlands</td>
<td>RCT n=110</td>
<td>GI (L)C</td>
<td>INC RD</td>
<td>Dietary Intake • Exercise</td>
<td>Results pending Prevention of LBM (NCT01998152)</td>
</tr>
<tr>
<td>Poulsen 2011/ Denmark</td>
<td>RCT n=61</td>
<td>GI (U/L) GYN CRT</td>
<td>INC</td>
<td>I hour/week • If accepted EPA (2.2g) supplement</td>
<td>↑ weight maintenance • ↑ calorie and protein intake</td>
</tr>
<tr>
<td>Ravasco 2012/ Portugal</td>
<td>RCT n=111</td>
<td>GI (L)R</td>
<td>INC + education Supplements+diet</td>
<td>Regular diet</td>
<td>Early INC • ↓R toxicity • ↑ diet/nutrition status • ↑ QOL</td>
</tr>
</tbody>
</table>
# Nutritional Counseling

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>SD SS</th>
<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capozzi</td>
<td>2016</td>
<td>Canada</td>
<td>RCT</td>
<td>HN</td>
<td>Optimal Timing</td>
<td>↑ Adherence after R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=60</td>
<td>During R CRT</td>
<td>• Lifestyle</td>
<td>Moderate ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After R CRT</td>
<td>• Resistance Training</td>
<td>• Fitness, QOL, Nutritional Status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 12 week</td>
<td></td>
</tr>
<tr>
<td>van den Berg</td>
<td>2010</td>
<td>Netherlands</td>
<td>P O</td>
<td>HN</td>
<td>INC</td>
<td>Early/RD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=38</td>
<td>R</td>
<td>• Early</td>
<td>• ↓ Weight Loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRT S R</td>
<td>• RD</td>
<td>• ↓ Malnutrition</td>
</tr>
</tbody>
</table>
## Nutritional Support

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
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<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding</td>
<td>2015</td>
<td>China</td>
<td>RCT</td>
<td>GI (U)</td>
<td>One week Preoperative EN</td>
<td>↑ PA and IgG levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=106</td>
<td>S</td>
<td></td>
<td>↓ IL-6 levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Potential immune and inflammation benefit</td>
</tr>
<tr>
<td>Li</td>
<td>2015</td>
<td>China</td>
<td>RCT</td>
<td>GI (U)</td>
<td>Early EN or PN</td>
<td>Early EN accelerates GI recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=68</td>
<td>S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Nutritional Support

<table>
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<tr>
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<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Huang         | 2015 | China     | RCT   | GI      | EN + PN                       | EN+PN superior  
• ↓ Postop complications  
• ↑ immunity  
• ↓ LOS             |
|               | n=105| (60-85 yo)| S     | EN      | PN                            |                                                             |
|               | CRT  |           |       | EN      | + PN                          |                                                             |
| Cong          | 2015 | China     | RCT   | GI (U)  | Nutrition Support Team (NST) vs. Radiotherapists | NST superior  
• ↑ Nutritional status  
• ↓ Complications  
• ↓ LOS |
|               | n=50 | GIT       | CRT   | EN      | + PN                          |                                                             |
|               | CRT  |           |       | EN      | + PN                          |                                                             |
# Nutritional Support

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<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Rajabi       | 2015 | Iran    | RCT n=40 | GI (U) S | EN PN         | EN superior  
• ↓ Inflammation  
• ↑ Immune response  
• ↑ Return to GI function  
• ↓ Cost |
| Li           | 2015 | China   | RCT n=300 | GI S    | Early Postop EN | • ↑ Nutritional status  
• ↑ Immune response  
• ↑ Return to GI function |
## Nutritional Support

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Wang        | 2015 | China   | RCT   | GI      | Preop EN               | • ↑ Nutritional status  
• ↑ Immune response  
• ↑ Return to GI function |
|             |      |         | n=200 | S       |                        |                                                 |
| Li          | 2015 | China   | RCT   | GI      | Early EN Postop        | • ↑ Nutritional status  
• ↑ Immune response |
|             |      |         | n=400 | S       |                        |                                                 |
# Nutritional Support

<table>
<thead>
<tr>
<th>Author</th>
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<th>Country</th>
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<th>Site</th>
<th>Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barlow</td>
<td>2011</td>
<td>United Kingdom</td>
<td>RCT n=128</td>
<td></td>
<td>GI (U)</td>
<td>S</td>
<td>Early EN</td>
<td>↓ LOS ↑ Clinical Outcomes</td>
</tr>
<tr>
<td>Bowrey</td>
<td>2015</td>
<td>United Kingdom</td>
<td>RCT n=54</td>
<td></td>
<td>GI (U)</td>
<td>S</td>
<td>6 weeks home JT feedings Vs. usual</td>
<td>Feasible, safe, acceptable</td>
</tr>
</tbody>
</table>
## Nutritional Support

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<tr>
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<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senesse</td>
<td>2015</td>
<td>France</td>
<td>P O</td>
<td>GI</td>
<td></td>
<td>HPN for malnourished</td>
<td>↑ QOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=370</td>
<td></td>
<td></td>
<td></td>
<td>↑ weight status</td>
</tr>
<tr>
<td>Vyawahare</td>
<td>2013</td>
<td>India</td>
<td>P O</td>
<td>HN</td>
<td></td>
<td>Early vs. Delayed Feeding following PEG</td>
<td>Early Feeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=110</td>
<td></td>
<td></td>
<td></td>
<td>• Well tolerate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ↓ LOS</td>
</tr>
</tbody>
</table>
# Nutritional Support

<table>
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<tr>
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<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang</td>
<td>2015</td>
<td>China</td>
<td>PO</td>
<td>GI (U)</td>
<td>S</td>
<td>EN</td>
<td>Safe within 48 h of surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=208</td>
<td></td>
<td></td>
<td>• 48 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 48 h–72 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• &gt; 72 h</td>
<td></td>
</tr>
<tr>
<td>Burney</td>
<td>2015</td>
<td>United States</td>
<td>RO</td>
<td>HN</td>
<td>S + CRT</td>
<td>PEG Feeding</td>
<td>Safe and efficacious</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=565</td>
<td></td>
<td></td>
<td></td>
<td>• ↓ weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Stable nutritional status</td>
</tr>
</tbody>
</table>
## Nutritional Support

<table>
<thead>
<tr>
<th>Author Year Country</th>
<th>SD SS</th>
<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takesue 2015 Japan</td>
<td>RCT n=47</td>
<td>GI (U) S</td>
<td>Postop EN vs. TPN EN</td>
<td>EN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ↓ Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ↓ Pneumonia</td>
</tr>
<tr>
<td>Liu 2015 Taiwan</td>
<td>CS n=121</td>
<td>GI (L)</td>
<td>Preop TPN +vitamins/trace elements</td>
<td>Preop TPN only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ↓ Inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ↑ Prognosis</td>
</tr>
</tbody>
</table>
**Nutritional Support**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>SD</th>
<th>Site</th>
<th>Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw</td>
<td>2015</td>
<td>Canada</td>
<td>Systematic</td>
<td>HN</td>
<td>PEG</td>
<td>Prophylactic</td>
<td>Unclear impact on swallowing Need RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Review</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 Observation Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qiu</td>
<td>2015</td>
<td>China</td>
<td>P O n=830 C</td>
<td>GI (U)</td>
<td>NS</td>
<td>Stage IV NRS ≥3</td>
<td>NRS ≥3 independent prognostic factor NS might improve survival</td>
</tr>
</tbody>
</table>
## Nutritional Support

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>Site</th>
<th>Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda</td>
<td>2015</td>
<td>Japan</td>
<td>R</td>
<td>O</td>
<td>GI</td>
<td>(U)</td>
<td>S</td>
<td>↓ SSI in malnourished with well-managed NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Nutritional Support and Counseling

<table>
<thead>
<tr>
<th>Author Year Country</th>
<th>SD SS</th>
<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligthart-Melis 2013</td>
<td>R O n=65</td>
<td>GI (U) S</td>
<td>RD INC/NS</td>
<td>↓ Weight</td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td></td>
<td>↓ Postop complications</td>
</tr>
<tr>
<td>Paccagnella 2010</td>
<td>R O n=72</td>
<td>HN CRT</td>
<td>INC/NS before, during and after CRT</td>
<td>↑ Treatment tolerance</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td>↓ Hospital readmissions</td>
</tr>
</tbody>
</table>
## Nutritional Support and Counseling

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillis 2015</td>
<td></td>
<td>Canada</td>
<td>RCT n=48</td>
<td>GI (L) S</td>
<td>INC + Whey INC</td>
<td>INC + Whey • ↑ Functional walking and recovery</td>
</tr>
<tr>
<td>Valentini 2012</td>
<td></td>
<td>Italy</td>
<td>P O n=21</td>
<td>Head and Neck</td>
<td>INC during CRT + ONS</td>
<td>↓ CRT related toxicity</td>
</tr>
</tbody>
</table>
# Nutritional Support and Counseling Systematic Review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>SD SS</th>
<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Languis</td>
<td>2013</td>
<td>Netherlands</td>
<td>12 Study Reports</td>
<td>Head and Neck</td>
<td>INC vs. none or SCO Nutrition Support</td>
<td>INC superior • ↑QOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 10 Different studies</td>
<td></td>
<td>• ONS vs. Tube Feeding</td>
<td>NS findings inconsistent</td>
</tr>
</tbody>
</table>
## Immune Enhancing Nutrition

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Study Design, N</th>
<th>Cancer Site</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Luis 2015 Spain</td>
<td>RCT n=84</td>
<td>HN</td>
<td>EN</td>
<td>High dose</td>
</tr>
</tbody>
</table>
|                       |                | S           | • Low dose arginine  
|                       |                |             | • Medium dose arginine  
|                       |                |             | • High dose arginine  |
|                       |                |             |             | ↓ LOS      |
|                       |                |             |             | ↓ Complications |
| Mocellin 2013 Brazil  | RCT n=11       | GI (L)      | Supplementation of 2 g/day of fish oil for 9 weeks | ↓ C-reactive protein  
|                       |                | C           |             | Change in plasma fatty acid  
|                       |                |             |             | Potential to promote optimal CRP/Alb ratio, ↓ inflammation and weight loss |
## Immune Enhancing Nutrition

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>Site Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma 2015</td>
<td>Taiwan</td>
<td>RCT</td>
<td>n=99</td>
<td>GI</td>
<td>TPN + IE TPN + Standard</td>
<td>Addition of IE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=195</td>
<td>S</td>
<td></td>
<td></td>
<td>↑ Fat metabolism ↓ Inflammation</td>
</tr>
<tr>
<td>Rowan 2016</td>
<td>United States</td>
<td>P O</td>
<td>n=195</td>
<td>HN</td>
<td>Pre/Post OP IE NS</td>
<td>↓ Postop complications ↓ LOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=195</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Nutritional Counseling and Immune Enhancing Nutrition

<table>
<thead>
<tr>
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<th>Year</th>
<th>Country</th>
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<th>Site</th>
<th>Tx</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faber</td>
<td>2015</td>
<td>Netherlands</td>
<td>RCT</td>
<td>GI</td>
<td>(U)</td>
<td>INC IEN Food Pre-treatment</td>
<td>↑ body weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=47</td>
<td>NR</td>
<td></td>
<td></td>
<td>↑ Performance status</td>
</tr>
</tbody>
</table>
## Immune Enhancing Nutrition

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<th>Site</th>
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<th>Conclusion</th>
</tr>
</thead>
</table>
| de Luis         | 2013   | Spain     | P  | O n=33 | HN   | S + R | Postop 12 weeks IE formula          | ↑ seric protein  
                              |                                                 | ↑ weight, LBM, Fat % in those without R          |
| Song            | 2015   | Multiple  | 27 RCTs | Meta-Analysis | GI   | S   | Immuno-enhanced NS vs. standard NS | Immuno-enhanced  
                              |                                                 | ↓ Infections  
                              |                                                 | ↓ Other complications  
                              |                                                 | ↓ LOS |

'SD' stands for Study Design, 'SS' for Study Setting, 'Site' for Site of the Study, 'Tx' for Treatment.
Traditional pair-wise meta-analysis on postoperative infectious complications: (A) preoperative EIN versus SEN
Traditional pair-wise meta-analysis on postoperative infectious complications:

(B) post- operative EIN versus SEN
Traditional pair-wise meta-analysis on postoperative infectious complications: (C) perioperative EIN versus SEN
Traditional pair-wise meta-analysis on postoperative infectious complications: (D) preoperative EIN versus perioperative EIN
Traditional pair-wise meta-analysis on postoperative infectious complications: (E) perioperative EIN versus postoperative EIN