Nutrition Update: Anorexia and Cachexia

Kristen Kreamer, AOCNP, APRN-BC, CRNP, MSN
Barbara Rogers, CRNP, AOCN, APN-BC, MN

Fox Chase Cancer Center

National Comprehensive Cancer Network®

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

Nutrition Update: Anorexia and Cachexia

- LEARNING OBJECTIVES:
  - List contributing causes of cancer cachexia
  - Outline the effects of anorexia and cachexia on cancer outcomes
  - Evaluate current and possible future treatment options for patients with cancer cachexia

Cancer Anorexia-Cachexia Syndrome (CACS)

- A complex metabolic syndrome- includes both anorexia and cachexia
- CACS common among patients with cancer
- Many patients with cancer lose desire to eat (anorexia)
- Diagnosis of anorexia is based on reduced appetite, early satiety, taste alterations and nausea
- Anorexia is often associated with reduced food intake
- Cachexia includes physical wasting with loss of skeletal and visceral muscle mass resulting from negative protein and energy balance
- Anorexia contributes to cachexia, but cachexia can occur independently from anorexia.

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

National Comprehensive Cancer Network® (NCCN®) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care, Version 1.2016.

Muliawati et al. (2012). Cancer Anorexia-Cachexia Syndrome. *Acta Medica Indonesiana.* 44:153-162.

Weight Loss

- Involuntary weight loss is very common among patients with cancer
- Weight loss is associated with poor tolerability of cancer treatment, reduced quality of life and survival
- Weight loss and malnutrition are not always synonymous with cachexia
- Often associated with anorexia, inflammatory process, insulin resistance and increased tissue protein turnover rates
- CACS is characterized by loss of lean body mass and fat
  - Cannot be reversed by conventional nutritional support
  - Leads to progressive functional impairment.

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Cachexia

- For cachexia there must be:
  - At least 5% weight loss in 12 months
  - Body mass index of <20 kg/m2
  - Presence of a known chronic disease
  - At least three of the following:
    - Loss of muscle mass
    - Asthenia (lack of energy)
    - Loss of body fat
    - Altered analytical parameters (albumin <3.2 g/dl or increased inflammatory parameters such as interleukin-6 >4.0 pg/ml or C-reactive protein >5.0 mg/l)

- Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Cachexia

- Cachexia also leads to emaciation, impairment of immune system, metabolic dysfunction and autonomic failure
- Cachexia in the patient with cancer can lead to:
  - failure of anti-cancer therapy
  - Increased toxicity from treatment
  - Shorter survival
  - Psychosocial distress

NCCN Guidelines for Palliative Care, Version 1.2016.

Audience Response Question

Are you ready to answer?

National Comprehensive Cancer Network®

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

ARS Question #1

Which of the following cancers has the lowest incidence of weight loss?

1. Pancreatic
2. Colorectal
3. Breast
4. Prostate

Epidemiology of CACS

Tumor Site	Incidence of weight loss
Pancreas	83%
Gastric	83%
Esophagus	79%
Head and neck	72%
Colorectal	55-60%
Lung	50-66%
Prostate	56%
Breast	10-35%
General cancer population	63%

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*
Laviano A, Meguid M, Inui A, et al. Therapy insight: cancer anorexia-cachexia syndrome-when all you can eat is yourself. Nat Clin Pract Oncol. 2005. 2:158-165.

Epidemiology of CACS

- Overall prevalence of CACS:
  - 40% at diagnosis
    - 70-80% in late stages of disease
- Survival of patients with cachexia significantly shorter than those without cachexia – in stomach, pancreatic, prostate, colon and breast cancer
- Risk of CACS higher when treated with radiotherapy and chemotherapy in esophageal, lung and head and neck cancers due to swallowing disorders and mucositis
- CACS can be direct cause of death in more than 20% of patients with cancer

- Muliawati et al. (2012). Cancer Anorexia-Cachexia Syndrome. *Acta Medica Indonesiana.* 44:153-162.

Audience Response Question

Are you ready to answer?

National Comprehensive Cancer Network®

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

ARS Question #2

A body mass index (BMI) less than 25kg/M2 meets the criterion for malnutrition.

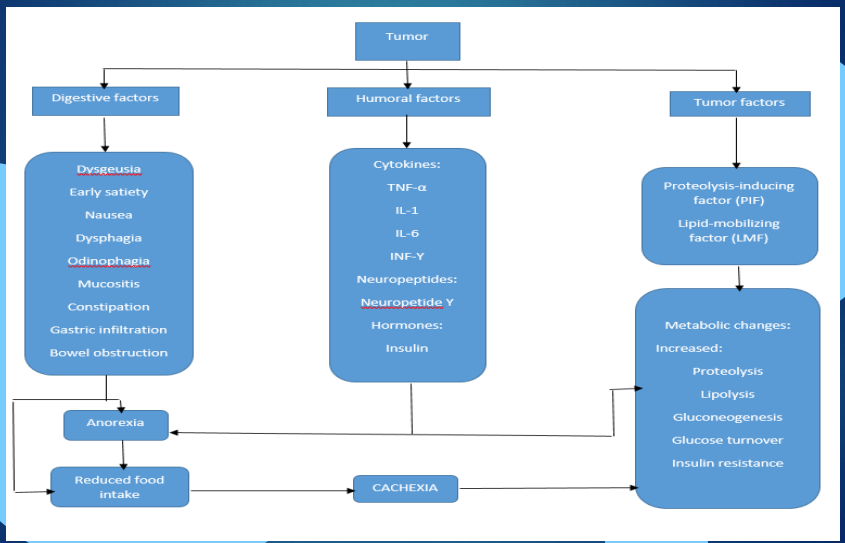
1. True
2. False

Stages of Cancer-Related Cachexia

	Precachexia	Cachexia	Refractory Cachexia	
Normal				Death
	Weight loss ≤5% Anorexia and metabolic change	Weight loss >5% **or** BMI <20 and weight loss >2% **or** sarcopenia and weight loss >2%. Often reduced food intake Systemic inflammation	Cancer both procatabolic and not responsive to anticancer treatment Low performance score <3 months expected survival	

Fearon K, Strasser F, Anker S, et al. (2011). Definition and classification of cancer cachexia: an international consensus. *The Lancet Oncology*, 12: 489-495.

Pathophysiology of Cancer Cachexia



Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology*, 88:625-636.

Pathophysiology of Cancer Cachexia

- Characterized by a persistently increased basal metabolic rate that is not compensated by increasing protein/calorie intake
- Digestive Factors:
  - The digestive factors that can significantly contribute to the onset of CACS include dysgeusia, nausea, dysphagia, odynophagia, mucositis, constipation, malabsorption, and intestinal obstruction.
- Humoral mediators of CACS include cytokines. Different cytokines intervene as humoral mediators of anorexia.
- The best known CACS-mediating tumor factors are proteolysis-inducing factor and lipid mobilization factor.
- Host – Tumor Interaction

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Diagnosis and Assessment of CACS

- The most commonly used anthropometric values are weight loss and body mass index (BMI)
- The amount of weight loss that indicates a risk of CACS is:
  - more than 10% in the last 6 months OR
  - 5% in less than one month
- A BMI of less than 20kg/m2 is a criterion for malnutrition
- Biological values such as albumin, prealbumin, transferrin and C-reactive protein can provide valuable information about nutritional status
  - Albumin-of less than 3.2 g/dl indicates protein depletion and risk of malnutrition
  - Prealbumin-more sensitive than albumin. Prealbumin of <10 mg/dl indicates malnutrition
  - Transferrin-reduced in CACS and a value of <100 mg/dl indicates severe malnutrition
  - C-reactive protein > 5mg/l

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Treatment of CACS

- Treatment of CACS based on 3 factors:
  - Oncologic therapy
  - Nutritional support
  - Pharmacological treatment

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Nutritional Support

- Nutritional support includes:
  - Dietary advice
  - Nutritional supplements
  - Enteral diet
- Helpful recommendations:
  - Fractionated intake (small frequent meals)
  - Food chosen according to the patient's preferences and ability to swallow
  - Avoiding strong smells
  - Carefully presented meals

Nutritional Support

- Eating calorie – rich, high protein supplements has been shown to stabilize weight
- Nutrition interventions may not impact weight gain or energy intake, but can improve quality of life.
- Parenteral nutrition may not be metabolized and can increase the suffering of dying patients

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

NCCN Guidelines for Palliative Care, Version 1.2016.

Treatment of Anorexia and Cachexia

FIX WHAT YOU CAN!

- Reversible causes of anorexia should be addressed (e.g., management of oropharyngeal candidiasis)
- Treatment also includes management of symptoms that interfere with food intake
  - pain
  - constipation
  - nausea/vomiting
  - oral mucositis
  - dyspnea
  - depression

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

NCCN Guidelines for Palliative Care, Version 1.2016.

Pharmacological Treatment of CACS

- Ideal drug in managing CACS should:
  - Increase the appetite
  - Promote weight gain
  - Improve quality of life
  - Not interfere with cancer treatment
  - Have an adequate tolerance profile
- Best way to treat CACS is to cure the cancer.
- Pharmacologic approaches for managing CACS:
  - To fight anorexia (stimulate appetite)
  - Alter metabolic disturbances

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Muliawata et al (2012). Cancer Anorexia-Cachexia Syndrome. *Acta Medica Indonesiana*, 44:154-162.

Drugs with Proven and Potential Activity in CACS

(Varies between various authors)

- Include:
  - Drugs with confirmed efficacy :
    - Megestrol acetate (MA)
    - Corticosteroids
  - Likely effective drugs that require confirmation in more controlled clinical trials
    - Cannabinoids (dronabinol)
    - Bortezomib
    - Non-steroidal anti-inflammatory drugs
  - Drugs the efficacy of which has not been confirmed in controlled clinical trials
    - Prokinetic agents
    - Pentoxifylline
    - Cyproheptadine
    - Hydrazine sulfate
- Investigational drugs with good prospects for efficacy to be confirmed
  - Ghrelin
  - Melanocortin antagonists
  - B2 agonists (formoterol)
  - Anti-IL-6 monoclonal antibodies
  - Selective androgen receptor modulators (SARMS)
  - Thalidomide
  - Oxandrolone

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Use of Progestogens in CACS

- Megestrol acetate (MA)
  - A semi-synthetic progesterone derivative
  - Initially used in treatment of disseminated breast and endometrial cancer
  - Some patients treated with MA gained weight and had increased appetite as side effects
  - In 1993, FDA approved MA for CACS and cachexia associated with other chronic conditions (e.g., AIDS, geriatric cachexia).
- MA Safety Profile
  - Generally well-tolerated
  - **Toxicities: Fluid retention and thromboembolic events**
    - Some authors suggest weight gain may be largely due to fluid retention
  - One-in 4 treated with MA will have increase in appetite, 1 in 12 will have increase in weight; however, 1 in 6 will develop thromboembolic event and 1 in 23 will die.

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*
National Comprehensive Cancer Network® (NCCN®) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care, Version 1.2016.

Audience Response Question

Are you ready to answer?

National Comprehensive Cancer Network®

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

ARS Question #3

A 70 year old female is being treated for gastric cancer. She has been losing weight rapidly and her family is concerned and asking about medication to improve her appetite. Which of the comorbidities would cause you to be reluctant to prescribe megestrol acetate for this patient?

1. COPD
2. Congestive heart failure
3. Psoriasis
4. Peripheral neuropathy

Corticosteroids

- Mechanism of action related to inhibition of IL-1, TNF-alpha and leptin and increase in neuropeptide Y levels
- Various literature reviews indicate that glucocorticoids (dexamethasone 3-6 mg/day), prednisone (15 mg/day) methyl prednisolone (12 mg/day) increase appetite and cause weight gain
- Effect short lived (4 weeks)
- Causes more long-term side effects than placebo and MA (insulin resistance, fluid retention, steroidal myopathy, skin fragility, adrenal insufficiency, sleep and cognitive disorders)

Miller et al. (2014). Use of corticosteroids for anorexia in palliative medicine: A systematic review. *Journal of Palliative Medicine*, 17(4). 482-485.
Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Cannabinoids

- Dronabinol studied at doses from 2.5 mg to 20 mg/day
- Reduction of nausea, increased appetite and tendency to weight stabilization
- Main adverse events are:
  - Euphoria
  - Hallucinations
  - Vertigo
  - Psychosis
  - Cardiovascular disorders
- Contraindicated in patients with:
  - Allergy to sesame oil
  - History of substance abuse/misuse
  - Psychiatric disorders

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88*:625-636.

Bortezomib

- An ubiquitin-proteasome system and NF-κB transcription factor inhibitor used in the treatment of multiple myeloma and other hematologic cancers
- Promising initial data
- Clinical trial in CACS in pancreatic cancer showed no significant effect in weight gain
- While potentially active, further studies necessary

Jatoi, et al. (2005). Is Bortezomib , a proteasome inhibitor, effective in treating cancer-associated weight loss? : Preliminary results from the North Central Cancer Treatment Group. *Supportive Care in Cancer*. 13(6), 381-386.

Antiserotonergic Agents

- Cyproheptadine is an antihistamine and antiserotonergic agent
- Efficacy in CACS not confirmed in clinical trials
- Pizotifen is an antiserotonergic drug used in treatment of anorexia from other causes- has not been studied in patients with cancer

Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Cytokine Inhibitors

- Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) inhibit PIF, TNF-α and IL-6.
  - Efficacy in CACS not fully confirmed in controlled clinical trials.
  - Weight gain of >10% was significantly more common in patients treated with MA.
  - Most authors conclude that ω-3 fatty acids could be potentially active in CACS but further research is required.
- NSAIDS- (Cox-2 Inhibitors)
  - Two controlled clinical trials in CACS show they are effective for gaining weight and muscle mass, especially when combined with MA.
- Pentoxifylline- efficacy in CACS not demonstrated

Lai, V. et al. (2008). Results of a pilot study of the effects of celecoxib on cancer cachexia in patients with cancer of the head, neck and gastrointestinal tract. *Head and* Neck. 30(1), 67-74.
McMillan, DC, et al. (1999). Prospective study of megestrol acetate and ibuprofen in gastrointestinal cancer patient s with weight loss. *British Journal of* Cancer. 79(3-4), 495-500.
Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

Cytokine Inhibitors

- Thalidomide
  - Evidence suggests this agent may increase appetite, weight and feeling of wellbeing in CACS
  - Need confirmation with additional trials
- Melatonin
  - An endogenous hormone secreted by pineal gland that is used in sleep disorders
  - Suggested that its effect can be due to cytokine and TNF-α inhibition
  - Recent study comparing melatonin versus placebo in CACS did not find differences between 2 groups

Gordon, J. et al. (2005) Thalidomide in the treatment of cancer cachexia: A randomized placebo controlled trial. Gut. 54(4), 540-545.
Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*
DelFabbro,E. et al. (2013). Effects of melatonin on appetite and other symptoms in patients with advanced cancer and cachexia: A double-blind placebo controlled trial. *Journal of Clinical Oncology*. 31, 1271-1276.

Anabolic Steroids

- Anabolic steroids studied in CACS:
  - Oxymetholone
  - Oxandrolone
  - Nandrolone
  - Fluoxymesterone (high levels of hepatotoxicity)
- Anabolic effect increases muscle mass with no changes in appetite or amount of food intake
- Ghrelin (natural ligand of growth hormone receptor)
  - Two studies have confirmed its efficacy in increasing appetite and weight in CACS patients
  - Two studies of anamorelin, a ghrelin receptor agonist, suggest that this agent may effectively increase body weight and CACS symptoms in patients with lung cancer
  - Requires additional studies
- Rikkunshito - Japanese herbal medicine - in a study by Ohno et al (2011), Rikkunshito appeared to prevent anorexia induced by cisplatin.

Temel et al. (2015) ASCO 2015. J Clin Oncol 33, 2015 (suppl; abstr 9500)
Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*
Neary, NM. (2004). Ghrelin increases energy intake in cancer patient s with impaired appetite: a randomized placebo-controlled trial. *Journal of Clinical Endocrinology and metabolism. 89(6)2832-2836.*
Ohno et al. (2011). Clin Exp Gastroenterol; 4: 291–296.

Anabolic Steroids

- Hydrazine sulfate
  - Has been studied as a treatment for cancer and for cancer-related anorexia and cachexia
  - Theorized that cachexia occurs because the cancer is using too much of the body's sugar. This causes tissue to die and muscle to waste away and the individual loses weight
  - Also cancer cells have high levels of TNF-alpha that can cause loss of appetite, tiredness and breakdown of muscle tissue. Hydrazine can block the TNF-alpha and stop tumor growth and prevent cachexia.
  - Clinical trials have not confirmed its efficacy in CACS
- Beta-2-agonists
  - Have a known capacity to increase muscle mass
  - Currently in preclinical experiments in CACS

Cancer.gov. Hydrazine Sulfate (PDQ). www.cancer.gov/cancertopics/pdq/cam/hydrazine sulfate/patient/page2. Retrieved 8/5/2014.

Prokinetic Agents

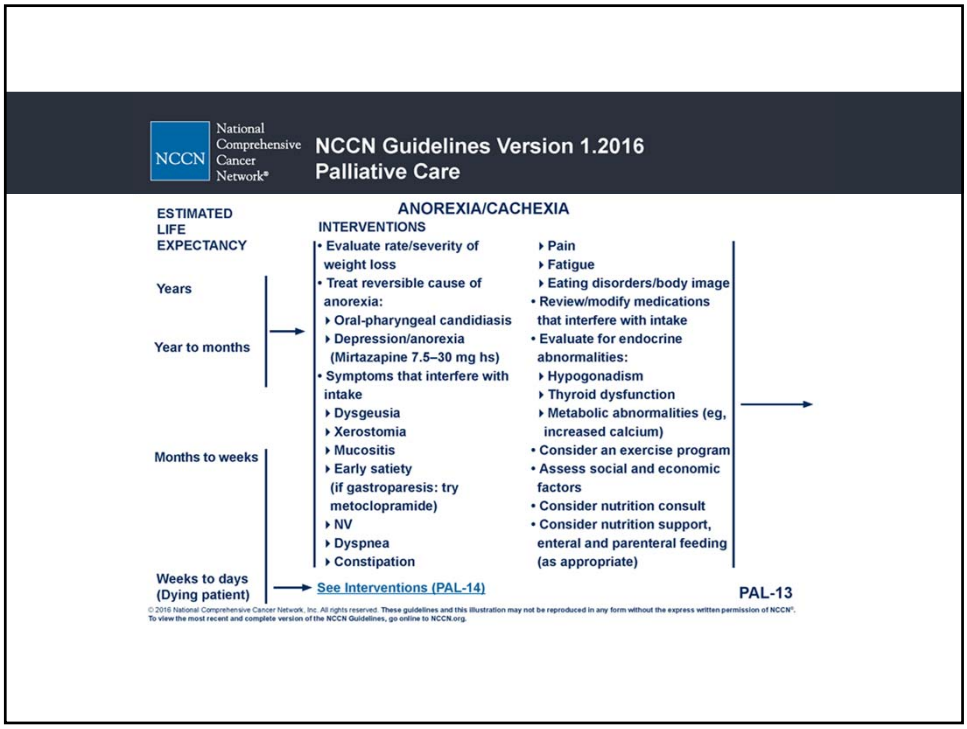
- Metoclopramide or cisapride
  - Are antidopaminergic agents with antiemetic and prokinetic effects
  - May relieve nausea and eating intolerance
  - Controlled trials have shown no efficacy in control of anorexia and weight loss

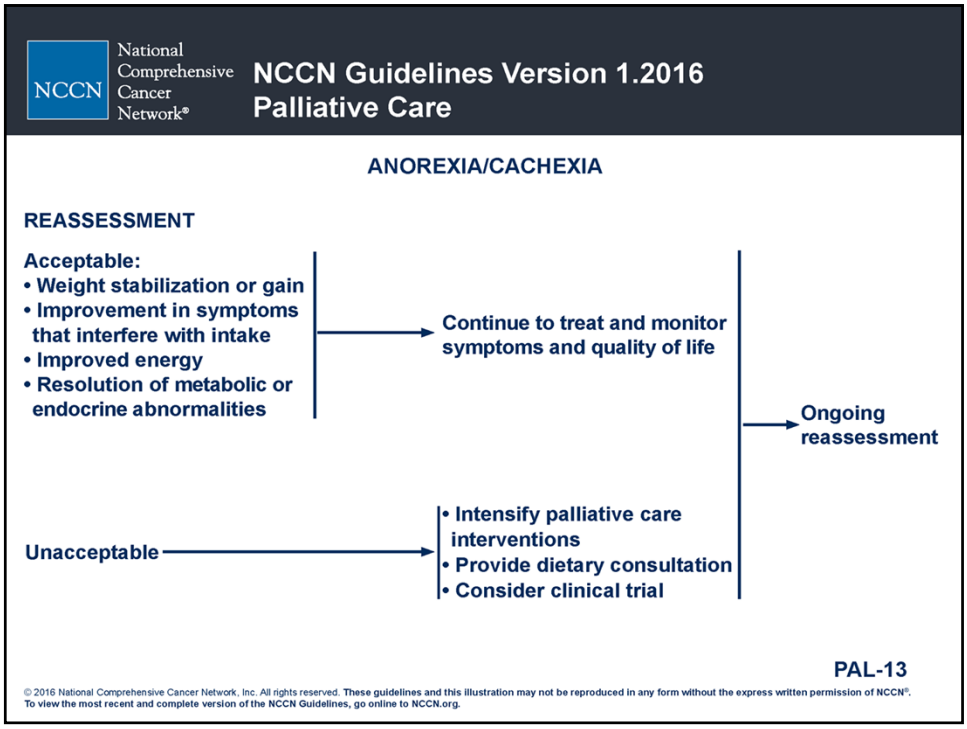
Tuca et al. (2013). Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology, 88:625-636.*

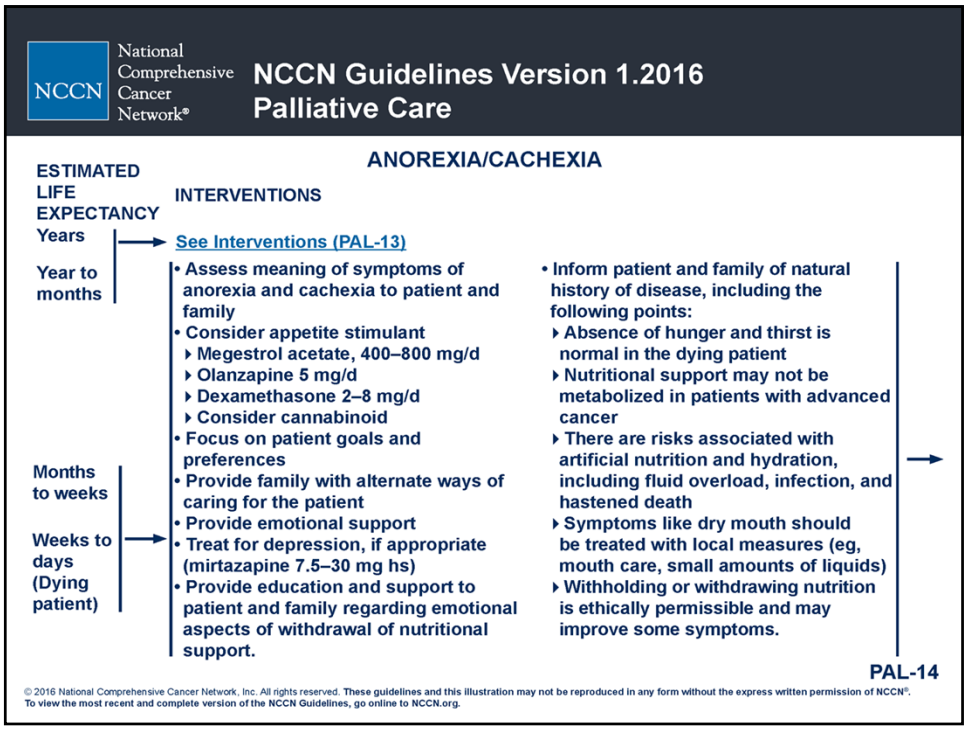
ONS Putting Evidence Into Practice (PEP) Recommendations- Management of Anorexia

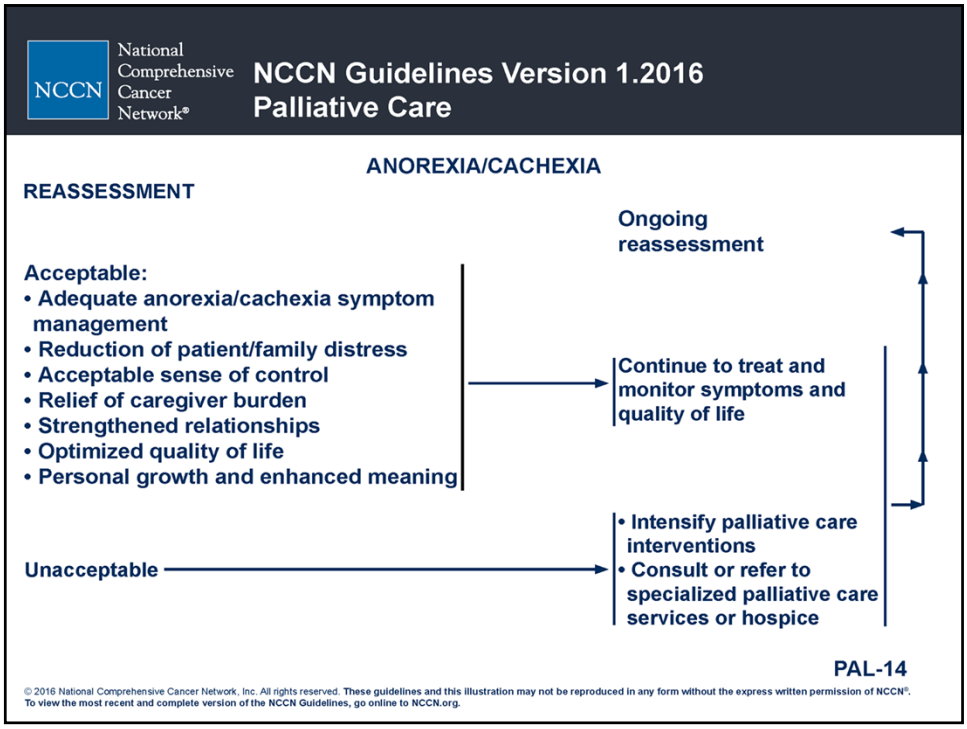
Recommended for Practice	Likely to be Effective	Effectiveness Not Established	Effectiveness Unlikely	Not Recommended for Practice
Corticosteroids, Systemic Progestins	Oral Nutritional Interventions	Astragali Radix Herbal Mix Cyproheptadine Ghrelin Herbal Medicine Melatonin Mirtazapine MS 20 Soybean Extract Multicomponent Rehabilitative Intervention OHR118 Omega 3 (Eicosapentaenoic Acid and others) Oral Branched-Chain Amino Acids Palliative Care Pentoxifylline Rikkunshito Thalidomide Withania Somnifera	Carnitine/L-Carnitine	Cannabis/Cannabinoids

Oncology Nursing Society. (2015). Putting Evidence into Practice. *Anorexia*. www.ons.org. Retrieved 2/24/2016.









Psychosocial Impact of CACS

- Self-image
- Social relationships – What social event doesn't include food?
- Family relationships – tension, frustration, blaming
- Sexuality

Clinical Trials Regarding CACS Listed on clinicaltrials.gov

- Study of the relationship between clinical and para-clinical markers during situations of cachexia and pre-cachexia in patients over 70 years with colorectal surgery
- The safety and efficacy of acupuncture for anorexia in patients with GI Tract and Lung cancers.
- Cannabinoid capsules as treatment to improve cancer related CACS in advanced cancer patients.
- Acupuncture for unintentional weight loss with GI cancer.
- Effect of Sipje-ondaebo-tang for cancer related anorexia in cancer patients.
- QOL after esophagectomy for cancer.
- Efficacy of parenteral nutrition in patients at palliative phase of cancer.
- Pilot study of safety and tolerability of nutrifriend in NSCLS cachexia.

www.clinicaltrials.gov. Retrieved 2/24/2016.

Conclusion

- CACS is a complex metabolic syndrome
- Characterized by weight loss and loss of muscle mass that may include loss of fatty mass
- Associated with anorexia, inflammatory processes, insulin resistance and increase in tissue protein turnover.
- Associated with limited food intake due to tumor growth or the side effects of treatment
- Early diagnosis and a thorough assessment are important in the management of CACS
- Symptomatic treatment of CACS is based on nutritional support and drugs capable of modulating the cascade of metabolic disorders
- The drug most commonly used in CACS is MA.
- Future strategies for CACS include further research on drugs that are potentially effective in CACS.

Conclusion

- Nurses need to be aware of other symptoms that can impact the patient's appetite and intake of food.
- Nurses need to be proactive in addressing other symptoms that can impact the patient's intake
- Nurses need to be aware of potential methods to enhance appetite for food.
- Nurses need to help patients and families understand the complexity of this syndrome and that the patient is not "giving up" because she is losing weight