ASPEN Nutritional Guidelines for Adult Head and Neck Cancer: Protocol

Introduction

Head and neck cancer is defined as tumors or cancerous cells arising from the mucosa of oral cavity, lips, larynx, pharynx, cervical esophagus, nose, sinuses, skin and salivary glands.[1, 2] Globally, in 2017 , head and neck cancers represented 5.3% of all diagnosed cancers and accounted for 890,000 new cancer diagnoses and 507,000 deaths.[3, 4] Patients with head and neck cancer present special nutritional challenges and are at higher risk for malnutrition due to difficulties chewing and swallowing, loss of appetite, and other nutrition impact symptoms related to the tumor, the location of the tumor, the host response to the tumor and treatment toxicities due to the location of the tumor and toxicities related to treatment.[5]

Objective: The objective of this guideline will be to provide nutritional guidance for the care of adult patients with head and neck cancers.

Audience: This guideline is intended for dietitians, nurses, pharmacists, physicians, speech language pathologists and any other medical health professional involved in the nutritional care of adult head and neck cancer patients.

The Panel of Experts

The guideline is comprised of two panels of experts, a clinical expert panel and a bias panel. The current clinical panel is comprised of a Nicole Kiss, PhD (Chair, Dietitian), Jacqui Frowen, PhD, SLP (Speech Language Pathologist), Cathy Kubrak, RN, PhD (Nurse), Whitney Lewis, (PharmD), Jeannine Mills MS, RD (Dietitian), Marie Platek, PhD, RD (Dietitian), and Anurag Singh, MD (Radiation Oncologist). This list is an international mix of ASPEN and non-ASPEN members from the United States, Australia, and Canada.

A second panel, the Bias Panel of experts will be formed to perform all bias analyses and provide commentary on the direct relationship between the recommendations made and the available evidence. The Bias Panel will be comprised of doctoral level researchers with a background in nutrition, but whose research does not specifically focus on clinical nutrition. The purpose for this restriction is to prevent bias in the bias panel. The bias panel will be trained and closely overseen by the methodologist and Editor-in-Chief, Liam McKeever, PhD, RDN, who will guide the entire process and coordinate the actions of the clinical panel and the bias panel.

Conflicts of interest are as follow:

Nicole Kiss, Jacqui Frowen, Cathy Kubrak, Whitney Lewis, Mary Platek, Anurag Singh and Liam McKeever have no conflicts of interest to disclose. Jeannine Mills has consulted for Abbott on issues unrelated to the current project.

Panel members will abstain from voting on any recommendations for which they have a conflict of interest. This includes conflicts of interest that become apparent as the guideline is being carried out. The Editor-in-Chief (L.M.) will be responsible for identifying and acting upon all known conflicts of interest.

Request for Commentary

From the time this protocol is published electronically and up to one month following electronic publication, *we welcome and request commentary on any and every aspect of this protocol*. We would like to hear from all key stake holders including but not limited to all levels of dietitian, physician, nurse, speech language pathologist, pharmacist, epidemiologist, methodologist, public health expert, occupational therapist, etc…. We also welcome you show this list of PICOT questions to select patients to provide us with feedback from the patient perspective.

Timely comments from readers of this protocol are welcomed and requested. Any concerns, comments, or additions should be emailed to Liam McKeever, PhD at LiamMcKeever@nutritioncare.org. We will receive comments for one month after the initial electronic posting of this protocol.

PICOT Questions

Table 1 below contains the list of questions this guideline intends to answer. These are termed PICOT questions because they include the intended **P**opulation, **I**ntervention, **C**omparator or **C**ontrol, **O**utcomes, and **T**imeframe. Below each question is a judgement concerning the question's importance. Questions are assessed for urgency. If the PICOT question concerns life and death decisions that need to made regardless of the evidence, the importance is deemed 'critical'. If the questions is not life or death, but of unquestionable importance to decision making, the question is deemed 'important, but not critical'. If the question is of questionable importance, it is deemed 'of limited importance'. These importance levels are then included in the decision-making process for determining the level of study design quality the group is willing to consider.

Table 1 PICOT Questions

Question 1	In adult patients ≥ 16 years with head and neck cancer receiving definitive chemo-radiation or radiation, does earlier enteral nutrition vs later enteral nutrition change progression-free survival, overall survival, nutritional intake, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicities, unplanned hospital admission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	Prophylactic versus reactive tube, gastrostomy versus nasogastric tube, RIG versus PEG
Question 2a	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does nutrition screening vs not screening change progression-free survival, overall survival, nutritional intake, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion treatment interruptions, treatment toxicities, surgical complications, length of stay, unplanned hospital admission or readmission?				

Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 2b	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does intensive nutrition therapy designed to meet current recommendations for protein intake vs standard care change progression-free survival, overall survival, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission? IMPORTANCE: CRITICAL Note: Current recommendations from ESPEN and Australian head and neck guidelines include protein intake ranging from 1.0 – 1.5g/kg/day. This question will consider differences across treatment modalities.				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 3a	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does intensive nutrition therapy designed to meet current recommendations for protein intake vs standard care change progression-free survival, overall survival, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	Potential differences in type of protein administered, type of formula that accompanies the protein, or route of administration, such as enteral vs parenteral.
Question 3b	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does intensive nutrition therapy designed to meet current recommendations for energy intake vs standard care change progression-free survival, overall survival, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	Potential differences in formula composition administered or route of administration, such

					as enteral vs parenteral.
Question 4a	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does estimating protein requirements based on an alternate body weight or composition vs standard care (actual weight) change progression-free survival, overall survival, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 4b	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality does estimating energy requirements based on an alternate body weight or composition vs standard care (actual weight) change progression-free survival, overall survival, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 5a	In adult patients ≥ 16 years with head and neck cancer, does increasing the frequency of dietetic review versus standard care during chemoradiation or radiation and up to 3 months post-treatment change progression-free survival, overall survival, nutritional intake, time to transition to full oral diet, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion, treatment interruptions, treatment toxicities, unplanned hospital admissions?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 5b	In adult patients >16 years with head and neck cancer, does longer post-operative follow up by a dietitian compared to shorter follow up duration change progression-free survival, overall survival, nutritional intake, time to transition to full oral diet nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, length of stay, surgical complications, hospital readmissions?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment	**RCT's Ethical?**	Yes	**Co-Interventions**	None

	Completion/Treatment Interruptions				
Question 6	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does gastrostomy feeding (via PEG or RIG) versus nasogastric tube feeding change progression-free survival, overall survival, nutritional intake, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, dysphagia, incidence of stricture, fistula development, global quality of life, fatigue, return to work, performance status, treatment completion, feeding tube dependence, time of transition to full oral diet, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 7	In adult patients >16 years with head and neck cancer receiving any treatment modality, does more frequent speech pathology intervention compared to standard of care change time to transition to full oral diet, progression-free survival, overall survival, nutritional intake, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, dysphagia, global quality of life, fatigue, return to work, performance status, treatment completion feeding tube dependence, incidence of stricture, fistula development, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 8	In adult patients ≥ 16 years with head and neck cancer undergoing any treatment modality, does a multidisciplinary approach to nutritional management vs standard care progression-free survival, overall survival, nutritional intake, time to transition to full oral diet, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion feeding tube dependence, treatment interruptions, treatment toxicity, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 9	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does a pharmaceutical appetite stimulant compared to no pharmaceutical appetite stimulant change progression-free survival, overall survival, nutritional intake, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status,				

	treatment completion treatment interruptions, treatment toxicities, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None
Question 10	In adult patients ≥ 16 years with head and neck cancer receiving any treatment modality, does anamorelin compared to no anamorelin change progression-free survival, overall survival, nutritional intake, nutritional status, weight, muscle mass, sarcopenia (skeletal muscle mass + strength), myosteatosis, global quality of life, fatigue, return to work, performance status, treatment completion treatment interruptions, treatment toxicities, surgical complications, length of stay, unplanned hospital admission or readmission?				
Critical Outcomes*	Survival/ Progression-Free Survival/Treatment Completion/Treatment Interruptions	**RCT's Ethical?**	Yes	**Co-Interventions**	None

*All non-critical outcomes were deemed important, but not critical.

The Search Strategy

PubMED/MEDLINE, EMBASE, Cochrane Central, and CINAHL Databases will be searched from 2001 to present. Articles prior to 2001 were restricted due to changes in management of blood glucose after 2001. The basic search strategy for PubMED/MEDLINE is given in Figure 1.

<div style="border:1px solid">

Search Strategy

Text-Based Terms

Head and Neck Cancer Text Terms

(("Head" OR "Neck" OR "Upper aerodigestive Tract" OR "UADT" OR "Oropharynx" OR "Oropharyngeal" OR larynx OR laryngeal OR hypopharynx OR hypopharyngeal OR nasopharynx, OR nasopharyngeal OR sinonasal OR paranasal sinuses OR nasal cavity OR salivary glands OR parotid OR submandibular OR "Oral Cavity")) AND (Cancer OR Cancers OR neoplasms OR malignancy OR malignancies OR tumor OR tumour OR carcinoma))

Text Terms to Capture Nutrition and Nutrition Status

("nutrition support" OR "enteral nutrition" OR "tube feed" OR "tube feeding" OR "tube feeds" OR "enteral feeds" OR "enteral feeding" OR "parenteral feeding" OR "nasogastric" OR "PEG" OR "Percutaneous Endoscopic Gastrostomy" OR "RIG" OR "Radiologically Inserted Gastrostomy" OR "parenteral nutrition" OR "IV feed" OR "IV Feeding OR "intravenously fed" OR "protein" OR "protein needs" OR "protein requirements" OR "calories" OR "calorie needs" OR "calorie requirements" OR "caloric needs" OR "caloric requirements" OR "energy requirements" OR "energy needs" OR "kcal" OR "kcal/kg" OR "Oral Feeding" OR "oral nutrition" OR "nutrition therapy" OR "dietary counseling" OR "Reactive feeding" OR "Prophylactic feeding" OR "malnutritrion" OR "nutrition status" OR "nutritional status" OR "nutrition risk" OR "nutritional risk" OR "Nutrition Screening" OR "nutrition assessment" OR "nutritional assessment" OR "nutrition indices" OR "nutritional indices" OR "nutrition index" OR "nutritional index" OR weight OR "weight loss" OR cachexia OR "muscle wasting" OR "Body Composition" OR "lean mass" OR "fat-free mass" OR "myosteatosis" OR "sarcopenia" OR "muscle mass" OR "muscle strength" OR "Body Mass Index" OR "BMI" OR dysphagia OR "nutritional intake" OR "Nutrition Team" OR "dietitian" OR "dietician" OR "nutrition support team" OR "Anamorelin" OR "prokinetics" OR "ghrelin-receptor antagonists" OR "cannabinoids" OR "Appetite Stimulant")

Medline Search with Medical Subject Headings [MeSH]

Head and Neck Cancer component

"Head and Neck Neoplasms"[Mesh]

Nutrition Component

"Nutrition Assessment"[Mesh] OR "Body Composition"[Mesh] OR "Nutrition Therapy"[Mesh] OR "Nutritional

</div>

Figure 1 The Search Strategy

Analogous searched will be performed for the other databases.
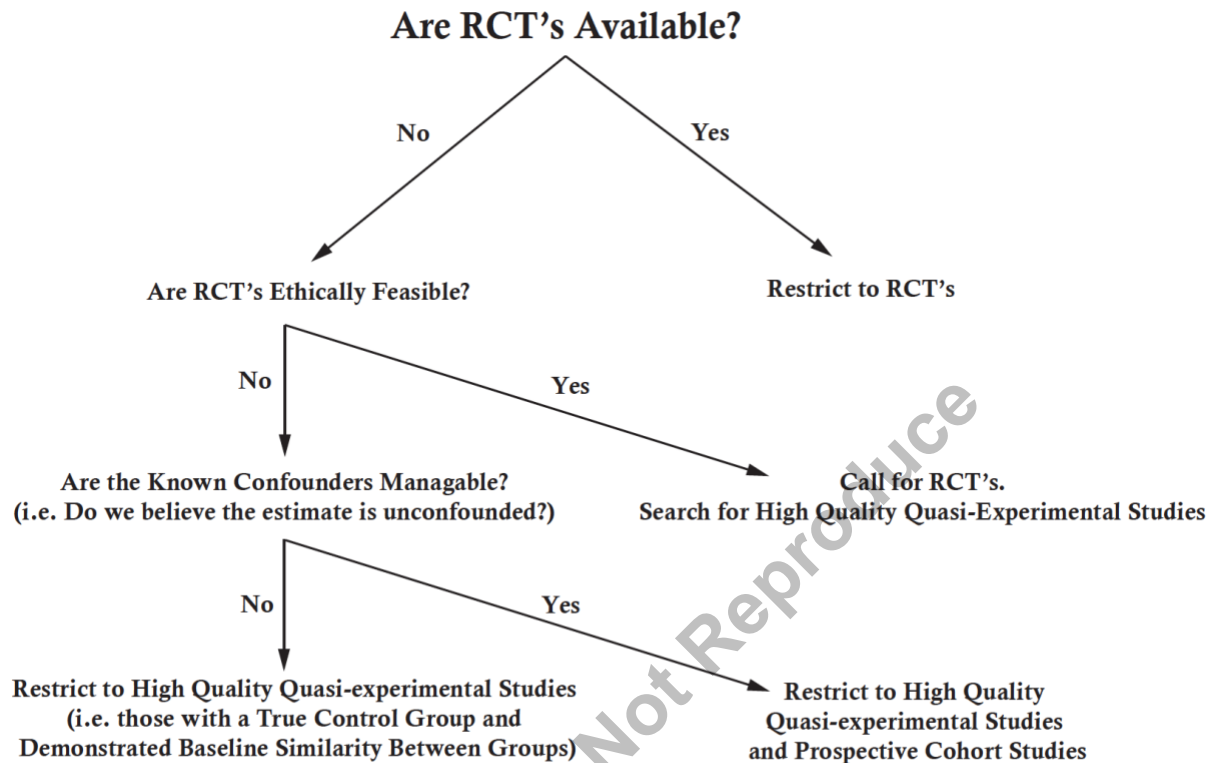
Data Acquisition

Training: Twenty-five citations will be uploaded into Rayyan for the team calibration test. Using their PICOT questions and inclusion criteria, the team will individually screen the 25 studies and determine if they meet inclusion criteria. If the team achieves less than 75% overall percent agreement, the discrepancies will be discussed, 25 new citations will be uploaded, and the group will try again. This will continue until they achieve ≥ 75 overall percent agreement, at which time, they will be permitted to move onto to official citation screening in Covidence.

Screening: All citations will be uploaded into Covidence for screening. For any given article, all steps below will be performed in duplicate (by two reviewers) and discrepancies will be adjudicated by a third reviewer. First, citation titles and abstracts will be screened for relevance to our PICOT questions. Then, a full text review will be performed for any citations that were deemed relevant in the previous phase of review. Articles that meet our inclusion criteria will be moved forward to the final phase of data extraction.

Inclusion/Exclusion Criteria/Study Design Selection

To be included, an article needs to be a study of head and neck cancer patients in patients ≥ 16 years of age, whose primary or secondary objective is directly relevant to at least one of our PICOT questions. The age of 16 rather than 18 was chosen to include European studies which sometimes have younger cutoffs for what they consider 'adults'. For each question, we will restrict the study design most able to answer that specific question. The decision will be made as follows (Figure 2). If randomized control trials (RCT) are available, we will restrict to RCT's. If RCT's are not available, but are ethically feasible, we will call for RCT's and include high quality quasi-experimental designs, defined as those designs that have a true control group and demonstrable baseline similarity between groups. If RCT's are not ethically feasible, we will ask ourselves if there are known confounders in the exposure/outcome relationship that cannot be completely managed through adjustment. If the answer is no, then we will restrict to prospective cohort studies that adjust for the known confounder and high quality quasi-experimental designs. If the answer is yes, we will restrict to only include high quality quasi-experimental designs. To be considered a high-quality quasi-experimental design, the study must have a true control group and demonstrate similarity between the two groups compared. Co-interventions will be permitted only if they can be reasonably assumed to be similar between groups.

For PICOT questions that assess nutrition status as a clinical outcome, studies will need to have assessed malnutrition or sarcopenia using an accepted tool or definition. For malnutrition, these include the Patient-Generated Subjective Global Assessment (PG-SGA), Subjective Global Assessment (SGA), the Global Leadership Initiative on Malnutrition (GLIM) criteria, the European Society for Parenteral and Enteral Nutrition (ESPEN), American Society for Parenteral and Enteral Nutrition (ASPEN), Academy for Nutrition and Dietetics (AND) definitions or ICD-10. For sarcopenia these include computed axial tomography (CT) scan-defined low muscle mass (using sex-specific cutoffs for 'low values')[6, 7] or definitions from the European Working Group on Sarcopenia in Older People (EWGSOP) 1 or 2, the Foundation for the National Institute of Health (FNIH), International Working Group on Sarcopenia (IWGS), Asian Working Group for Sarcopenia (AWGS), Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD), Sarcopenia Definition and Outcomes Consortium (SDOC).

Are RCT's Available?

No / **Yes**

Are RCT's Ethically Feasible? → **Yes** → Call for RCT's. Search for High Quality Quasi-Experimental Studies

Restrict to RCT's

No

Are the Known Confounders Managable?
(i.e. Do we believe the estimate is unconfounded?)

No / **Yes** → Restrict to High Quality Quasi-experimental Studies and Prospective Cohort Studies

Restrict to High Quality Quasi-experimental Studies
(i.e. those with a True Control Group and Demonstrated Baseline Similarity Between Groups)

If No Quality Data Exists, Use Expert Opinion Via Delphi Technique Validated by an External Panel

Figure 2: Algorithm for Determining Study Design Inclusion

Bias Analysis

Study quality will be assessed according to its methodologic vulnerability to bias using different tools for different study types. For RCT's, the Risk of Bias 2 (ROB2)[8] tool will be used. For quasi-experimental studies, the Risk of Bias in Non-randomized Study Interventions (ROBINS-I)[9] tool will be used. For prospective cohort studies, the Newcastle-Ottawa scale[10] will be used. For RCT's the Clinical Panel will create a list of potential co-interventions to consider in the bias assessment. For prospective cohorts, they will determine a list of confounders that require adequate adjustment. These lists will be handed to the Bias Panel who will perform the official bias analysis. All bias analyses will be performed in duplicate. The results of all bias analyses will be published as part of the supplement for this guideline and discussed as strengths and limitations in the body of the guideline.

Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to assess the quality of our evidence in regard to its ability to answer our PICOT questions. This will be used to rate the quality of evidence for each outcome across all studies. The Clinical Panel will then determine which outcomes are most critical and this will be used to inform the overall quality of the evidence for each PICOT question. All data will be tabulated and presented in the supplement as a Summary of Findings Table.

Statistical Analysis

Wherever three or more studies exist with interventions, comparators, outcomes, and populations similar enough to justify conflation, Forest Plots will be created with summary statistics using a random effects model to account for the minor population differences between hospitals. Heterogeneity will be assess using the I^2 statistic. If the I^2 is greater than 0.5, we will perform sub-analyses as an attempt to explain the heterogeneity. Publication bias will be assessed through funnel plots and Egger tests wherever >=10 studies are available for conflation into a forest plot.

Formulation of Recommendations

Recommendations will be formulated using the GRADE Criteria. The GRADE process separates the body of evidence quality rating from the strength of the recommendation permitting a benefits and harms analysis. Evidence quality will be listed underneath each recommendation. Recommendations will be labeled as strong or weak based upon the balance of potential benefit and harm. Where the recommendation is strong, we will use the term "recommend" regarding our guideline recommendation. Where the recommendation strength is weak, we will use the term "suggest".

Wherever possible, these recommendations will be based upon the data analyzed. Where inadequate data is present to guide a recommendation, the clinical panel will formulate a consensus of expert opinions using a modified Delphi technique. Briefly, the clinical panel will meet to discuss the various potential benefits and harms of the intervention in question. Based on this conversation, the chair will formulate recommendations for each PICOT question. This will be sent out to the clinical panel, who will either agree with the wording of the recommendation or return it with comments. These responses will be deidentified and returned to the chair. If each expert opinion recommendation has <70% agreement, the chair will alter the questions to be more agreeable to the panel and send them out again. This process will repeat until ≥70% agreement is achieved. The process will then start over with an external panel of at least 8 outside experts who will receive the current state of the recommendations from the chair and send back de-identified responses. When the external panel has ≥70% agreement on each expert opinion recommendation, the recommendation will be considered finalized. The external panel will have at least 1 patient representative to ensure input from this often-neglected stakeholder.

Review

Upon completion, a draft of the guideline will be sent to both the ASPEN Clinical Practice Committee and the Oncology Section for review. It will also be sent to external reviewers through the Journal of Parenteral and Enteral Nutrition for Review.

Updates

This guideline will be updated every 5 years.

Conclusion

Involvement of all key stakeholders is crucial to the success and generalizability of any guideline. We need your expertise to help make this guideline the best it can be. Please send us your comments and concerns and we will consider them carefully in the next iteration of this protocol.

References

1. Kufe DW, Frei E, Holland JF. *Cancer medicine 7*. 7th ed. Hamilton ; London: Elsevier; 2006.
2. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin.* Mar 2017;67(2):122-137.
3. Auperin A. Epidemiology of head and neck cancers: an update. *Curr Opin Oncol.* May 2020;32(3):178-186.
4. Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* Dec 1 2019;5(12):1749-1768.
5. Pressoir M, Desne S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer.* Mar 16 2010;102(6):966-971.
6. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* Jul 2008;9(7):629-635.
7. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol.* Apr 20 2013;31(12):1539-1547.
8. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* Aug 28 2019;366:l4898.
9. Hinneburg I. ROBINS-1: A tool for asssessing risk of bias in non-randomised studies of interventions. *Med Monatsschr Pharm.* Apr 2017;40(4):175-177.
10. Wells G, Shea, B, O'Connell, D, Peterson, J, Welch, V, Losos,M, Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses:http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.