Assessment of malnutrition in patients with head and neck cancer: a multidimensional approach

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Assessment of Malnutrition in Patients with Head and Neck Cancer: a Multidimensional Approach

Martine Sealy

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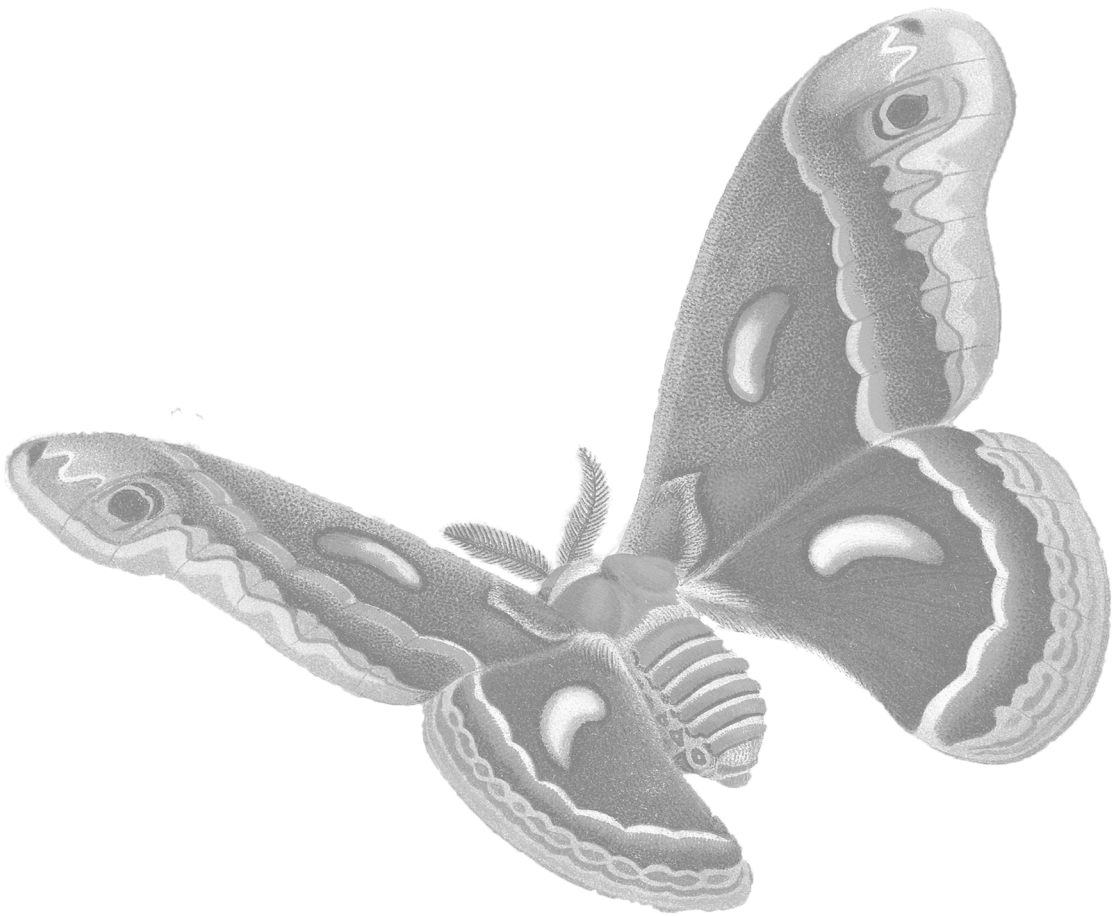
Chapter 1. Introduction



Malnutrition

The first broadly accepted definition of malnutrition was published in 2006 by the European Society of Clinical Nutrition and Metabolism (ESPEN).[1,2] In this definition, malnutrition was described as follows: "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 form (body shape, size and composition) and function, and clinical outcome".[1,2] Another influential organization, the American Society of Parenteral and Enteral Nutrition (ASPEN), proposed the following definition of disease-related malnutrition in 2012: “An acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity has led to a change in body composition and diminished function”.[3,4] From these definitions we can derive that malnutrition is a multidimensional construct. In this construct, four domains can be distinguished: 1. Nutrient balance (nutritional intake vs. nutritional requirements/expenditure); 2. Body shape, body size and body composition; 3. Body function; and in some instances 4. Inflammatory factors.[5] Malnutrition has been widely confirmed as an important factor in adverse clinical outcomes in patients with cancer.[6,7] However, it is unclear to what extent methods used for assessment of malnutrition in patients with cancer include assessment of these domains.

Head and neck cancer and malnutrition

Head and neck cancer includes cancer of the oral cavity, nasal cavity, paranasal sinuses, oropharynx, hypopharynx, and larynx (Figure 1). In 2017, a number of 3081 new patients with head and neck cancer were diagnosed in the Netherlands. As a result, head and neck cancer is currently the seventh most common malignancy in men and the ninth most common malignancy in women in the Netherlands.[8] Although the majority of patients with head and neck cancer present with locally advanced disease, these patients are generally treated with curative intent. The treatment approach is aggressive and consists of primary surgery or radiotherapy. Surgical resection of high stage tumors is followed by radiotherapy. Primary radiotherapy and postoperative radiotherapy can be combined with concomitant systemic therapy, like chemotherapy or biologicals. In patients not eligible for surgery due to irresectable tumors, combined concomitant chemo-radiotherapy is preferred.[9-11]

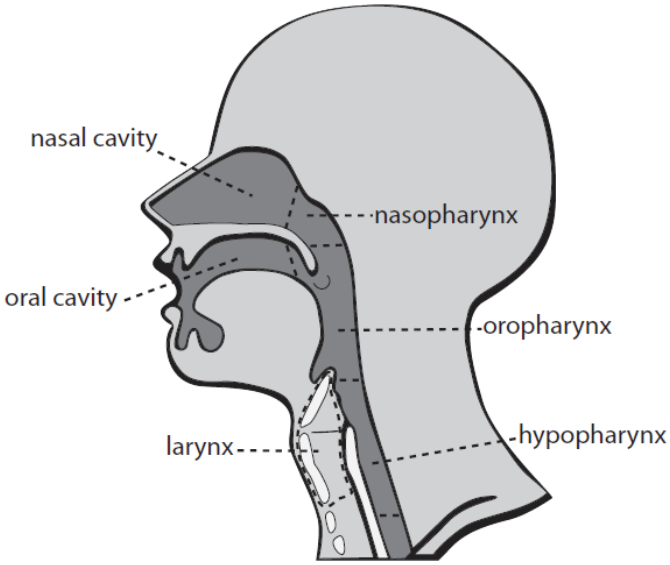


Figure 1. Head and neck anatomy. Printed with permission.[12]

In patients with head and neck cancer, the localization of the tumor in the upper aero-digestive tract combined with the aggressive treatment often lead to development of risk factors for malnutrition, such as chewing disabilities, swallowing problems, anorexia, and sore mouth.[13,14] Due to these risk factors, patients with head and neck cancer often have problems with food intake that can result in a disturbed nutritional balance.[15] Prior to treatment, 19% to 31% of patients with head and neck cancer already show critical weight loss, and are at risk of malnutrition.[13,16] During the cancer treatment, the risk of developing disease-related malnutrition increases, as a result of treatment-induced nutrition impact symptoms that further disturb nutrient balance.[15] In addition, the disease and treatment can stimulate protein breakdown by inflammatory activity, which may induce inflammatory activity.[3] During treatment for head and neck cancer, patients often loose muscle mass and strength.[15,17] Even patients with an energy and protein intake that is considered sufficient lose lean body mass while undergoing head and neck cancer treatment.[18-20] This indicates increased protein breakdown is present in patients with head and neck cancer, which, in part, may be related to inflammatory activity during treatment and recovery.[21] Inflammatory activity prior to treatment may reflect presence of cachexia, which is also reported in head and neck cancer patients.[22] Cachexia has been defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[23] Cachexia has been described as a subtype of disease-related malnutrition with inflammation.[24] Finally, apart from disease-related malnutrition, psychological factors such as depression and socio-economic factors may further contribute to decline of the nutritional status in patients with head and neck cancer. In head and neck cancer survivors, nutrition impact symptoms, psychological factors and socio-economic

factors may continue to cause or maintain malnutrition.[25] In conclusion, patients with head and neck cancer have an increased risk of malnutrition before, during and after treatment.[26] The relation between head and neck cancer (treatment) and different etiology-based types of malnutrition is presented in Figure 2.[24] The figure shows that malnutrition induces changes in body composition such as loss of muscle mass, and patients may show decline of physical, immunological, and cognitive function.[1,3] These processes can negatively influence outcomes of head and neck cancer, especially in older and frail patients.[27,28] Studies in patients with head and neck cancer show that malnourished patients have a higher risk of treatment interruptions due to toxicity, infections, longer hospital stay, lower quality of life, and lower survival.[13,29-31] A multi-dimensional approach towards malnutrition assessment that includes indicators that identify problems with nutrient balance, body composition, body function, and inflammatory factors, may facilitate development of a treatment approach that is aligned with the etiology of malnutrition and that is tailored to the needs of patients with head and neck cancer. Although it is established that malnutrition is an important problem, it is still not clear which nutritional assessment methods are most appropriate to measure malnutrition in patients with head and neck cancer.

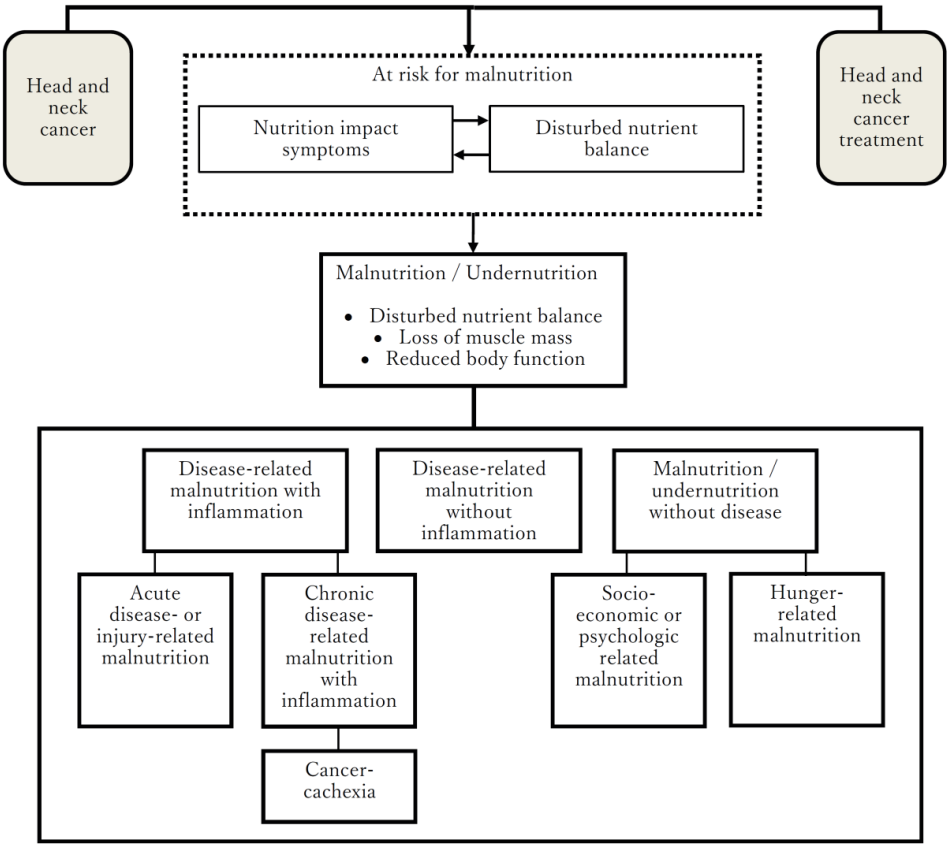


Figure 2. Relation between head and neck cancer (treatment) and different types of malnutrition. Adapted from Cederholm et al., 2016

Nutritional assessment

Malnutrition, if not properly and early treated, may slow down recovery, may induce clinical complications, and in some cases may involve cachexia. Timely detection of malnutrition and its risk factors (e.g., nutrition impact symptoms) is needed to enable early treatment, or even prevention of malnutrition. Therefore, assessment of nutritional status, to diagnose malnutrition, is considered an important step in the nutrition care process in cancer patients.[6] A broad variety of methods are used to operationalize nutritional status in patients with cancer.[32] In general, three types of methods can be distinguished. First, assessment questionnaires are available that provide a nuanced overview of indicators of malnutrition and consist of a variety of items that typically assess different aspects of malnutrition. Additionally, these questionnaires often also assess presence of nutrition impact symptoms. Information regarding nutrition impact symptoms may assist in tailoring nutritional interventions to the specific needs of the patient. Since these methods aim for accurate assessment of nutritional status and nutrition impact symptoms, both sensitivity and specificity of the instrument need to be high. Examples are the Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), and the Patient-Generated Subjective Global Assessment (PG-SGA).[33-35] Second, malnutrition screening tools are available. These short questionnaires generally consist of three to six items that are selected with the aim to provide a quick scan of malnutrition and/or to detect patients that are at risk of developing malnutrition. Sensitivity of these tools should be high, in order not to miss patients with malnutrition(risk). Examples of screening tools are: the Malnutrition Universal Screening Tool (MUST), Nutritional Risk Index (NRI), Nutritional Risk Screening 2002 (NRS 2002) and PG-SGA Short Form.[36-38] Finally, single measurements are available that focus on a single aspect of nutritional status. These measurements focus

on a specific indicator of nutritional status. If these indicators are robustly associated with malnutrition-related health outcomes, they can serve as indicators of problems in one domain of the nutritional status.[39-41] Examples of these indicators are: weight loss, body mass index (BMI), and various types of body composition analysis.

PG-SGA

The Scored Patient-Generated Subjective Global assessment (PG-SGA; copyright FD Ottery, 1996, 2001, 2005, 2006) is a questionnaire with a versatile character. It can be used to screen and/or assess nutritional status and risk factors, as an interventional triage for malnutrition, and as a monitor for interventional success in treatment of malnutrition. Additionally, the PG-SGA is unique in that it was designed to be partially completed by the patient and partially by the clinician, thus combining information from both the patients' and professionals' perspective.[42] The PG-SGA was first validated in the oncology setting and has since been utilized as a reference method to evaluate nutritional status in patients with cancer.[43-47] As a result, the PG-SGA could provide additional value to the instruments that are currently available in The Netherlands, such as the Malnutrition Universal Screening Tool (MUST) and the Short Nutritional Assessment Questionnaire (SNAQ).[36,48] However, the PG-SGA was originally developed in English, and an official Dutch translation has not been available. To enable use of the PG-SGA in the Dutch setting, a high quality version of the original English PG-SGA was needed. However, straight forward translation of the PG-SGA may alter its purpose and meaning, as a result of differences between the source culture and the target culture.[49,50] If instead a cultural adaptation process for the target culture is employed, several levels of equivalence can be

safeguarded.[49,51] Therefore, a systematical translation and cultural adaptation of the original English PG-SGA is needed for the Dutch setting.

Body composition analysis

Altered body composition, i.e. low muscle mass, is an indicator of deteriorated nutritional status.[52] Patients with head and neck cancer are at risk of muscle mass and strength before, during and after head and neck cancer treatment.[15,17] Loss of muscle mass in patients with head and neck cancer is problematic, because low muscle mass is firmly associated with lower survival and higher local-regional cancer recurrence after treatment.[53] Currently, a wide range of methods to assess (aspects of) body composition is available, for instance: anthropometric measurements, such as skin fold thickness measurements; and body volume or density measurements, such as underwater weighing, bioelectrical impedance analysis (BIA); and imaging techniques, such as dual energy x-ray absorptiometry (DEXA) analysis, magnetic resonance imaging (MRI), and computed tomography (CT) analysis.[54] For these methods to be useful in routine patient care, the clinical implications of the body composition analysis for the patient need to be clear. Methods for body composition analysis vary in complexity of performing the measurement, complexity of analyzing the measurement results, reliability of the results, financial costs, and the amount of radiation exposure.[52] CT can be used to analyze the body composition on tissue level and is considered a gold standard for assessing lean body mass, or more specific muscle mass.[55] Although CT imaging is an expensive procedure and a considerate amount of radiation is involved, it is still feasible to use CT analysis of body composition in many cancer patients, since diagnostic CT images are often already available and these images can be used for body composition analysis.[56] Transverse CT images at the level of the third lumbar

vertebrae (L3) provide an accurate estimate of total lean body mass and are associated with increased risk of mortality in cancer patients.[41] Currently, the relation between muscle mass and chemotherapy treatment tolerance is being studied in cancer patients.[57,58] Even though patients with head and neck cancer often lose muscle mass, the relation between low L3 muscle mass and early termination of chemotherapy is still unclear in these patients.

Nutritional status and physical activity

In addition to loss of muscle mass, loss of muscle function has been considered a characteristic of malnutrition.[1,5] Prevention of loss of muscle mass and function is important to maintain nutritional status and physical fitness.[59,60] Recent findings suggest that maintaining physical activity may prevent loss of muscle mass and function during and after completion of head and neck cancer treatment.[61-63] Lifestyle interventions that include not only dietary treatment, but also therapy to increase physical activity may provide an important means to improve nutritional status in patients with head and neck cancer.[62,64] However, although little is known about the average pre-diagnosis level of physical activity in patients with head and neck cancer, lifestyle behavior is often suboptimal.[65] Also, head and neck cancer treatment may result in long-term barriers for physical activity, such as dry mouth or throat, difficulty swallowing, and pain.[66] As a result, attaining and maintaining an adequate level of physical activity after treatment may pose a challenge for patients recovering from head and neck cancer.[67] Although some studies have explored PA intention of patients with HNC,[66,68] little is known about actual PA behavior of these patients. To be able to positively influence physical activity behavior, we need to gain knowledge on both perceived and actual physical activity behavior of head and neck cancer patients. In

addition, we need better insight into the psychological mechanisms that influence physical activity in patients with head and neck cancer.

Aim of the thesis

The general aim of this thesis has a threefold character. Firstly the aim was to describe the diagnostic value of malnutrition assessment methods, including body composition assessment with CT analysis. Secondly, the aim was to adapt the PG-SGA for Dutch practice. Finally, the aim was to explore psychological mechanisms that may influence physical activity behavior in patients with head and neck cancer.

Therefore, the objectives of this thesis were:

To provide an overview of malnutrition assessment methods used in adult cancer patients in the recent literature, and to determine their content validity based on consensus-based definitions of malnutrition (Chapter 2).

To translate and culturally adapt the original English PG-SGA for the Dutch setting, including exploration of content validity as perceived by healthcare professionals, and exploration of comprehensibility and difficulty as perceived by patients and healthcare professionals (Chapter 3).

To evaluate change of perceived comprehensibility and difficulty in the use of the PG-SGA in dietitians after a training (Chapter 4).

To study the association between low pre-treatment muscle area measured with CT-analysis and toxicity-related early termination of chemotherapy treatment in patients with head and neck cancer (Chapter 5).

To describe views on physical activity and reports of physical activity of head and neck cancer survivors and compare these views with objectively measured physical activity (Chapter 6).

References

1. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: An evidence-based approach to treatment. Cabi; 2003.

2. Lochs H, Allison SP, Meier R, et al. Introductory to the ESPEN guidelines on enteral nutrition: Terminology, definitions and general topics. Clin Nutr. 2006;25(2):180-186.

3. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren,M.A., et al. A rational approach to nutritional assessment. Clin Nutr. 2008;27(5):706-716.

4. Teitelbaum D, Guenter P, Howell WH, Kochevar ME, Roth J, Seidner DL. Definition of terms, style, and conventions used in A.S.P.E.N. guidelines and standards. Nutr Clin Pract. 2005;20(2):281-285.

5. Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: A proposal for etiology-based diagnosis in the clinical practice setting from the international consensus guideline committee. JPEN J Parenter Enteral Nutr. 2010;34(2):156-159.

6. Santarpia L, Contaldo F, Pasanisi F. Nutritional screening and early treatment of malnutrition in cancer patients. Journal of cachexia, sarcopenia and muscle. 2011;2(1):27-35.

7. Laviano A, Renvyle T, Yang Z. From laboratory to bedside: New strategies in the treatment of malnutrition in cancer patients. Nutrition. 1996;12(2):112-122.

8. Nederlandse kankerregistratie (NKR), IKNL. Nederlandse kankerregistratie Web site. www.cijfersoverkanker.nl. Updated 2018. Accessed 11/11, 2018.

9. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945-1952.

10. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843-850.

11. Licitra L, Felip E, ESMO Guidelines Working Group. Squamous cell carcinoma of the head and neck: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20 Suppl 4:121-122.

12. Jager-Wittenaar H. Pre-and post-treatment malnutrition in head and neck cancer patients. University Library Groningen][Host]; 2010.

13. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer--prevalence and risk factors at diagnosis: An explorative study. Support Care Cancer. 2007;15(9):1045-1050.

14. Kubrak C, Olson K, Jha N, et al. Nutrition impact symptoms: Key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. Head Neck. 2010;32(3):290-300.

15. Jager-Wittenaar H, Dijkstra PU, Vissink A, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. Head Neck. 2011;33(6):863-870.

16. Pressoir M, Desne S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in french comprehensive cancer centres. Br J Cancer. 2010;102(6):966-971.

17. Nishikawa D, Hanai N, Suzuki H, Koide Y, Beppu S, Hasegawa Y. The impact of skeletal muscle depletion on head and neck squamous cell carcinoma. ORL J Otorhinolaryngol Relat Spec. 2018;80(1):1-9.

18. Sauerwein H, van Schijndel RS. Perspective: How to evaluate studies on peri-operative nutrition?: Considerations about the definition of optimal nutrition for patients and its key role in the comparison of the results of studies on nutritional intervention. Clinical Nutrition. 2007;26(1):154-158.

19. Arends J, Bodoky G, Bozzetti F, et al. ESPEN guidelines on enteral nutrition: Non-surgical oncology. Clinical nutrition. 2006;25(2):245-259.

20. Jager-Wittenaar H, Dijkstra PU, Vissink A, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. Head Neck. 2011;33(6):863-870.

21. Guadagni M, Biolo G. Effects of inflammation and/or inactivity on the need for dietary protein. Current Opinion in Clinical Nutrition & Metabolic Care. 2009;12(6):617-622.

22. Jager-Wittenaar H, Dijkstra PU, Dijkstra G, et al. High prevalence of cachexia in newly diagnosed head and neck cancer patients: An exploratory study. Nutrition. 2017;35(22 Pt 1):114-118.

23. Evans WJ, Morley JE, Argilés J, et al. Cachexia: A new definition. Clinical nutrition. 2008;27(6):793-799.

24. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49-64.

25. Hammerlid E, Taft C. Health-related quality of life in long-term head and neck cancer survivors: A comparison with general population norms. Br J Cancer. 2001;84(2):149.

26. Gorenc M, Kozjek NR, Strojan P. Malnutrition and cachexia in patients with head and neck cancer treated with (chemo)radiotherapy. Rep Pract Oncol Radiother. 2015;20(4):249-258.

27. Adams P, Ghanem T, Stachler R, Hall F, Velanovich V, Rubinfeld I. Frailty as a predictor of morbidity and mortality in inpatient head and neck surgery. JAMA Otolaryngology–Head & Neck Surgery. 2013;139(8):783-789.

28. Linn BS, Robinson DS, Klimas NG. Effects of age and nutritional status on surgical outcomes in head and neck cancer. Ann Surg. 1988;207(3):267-273.

29. Capuano G, Gentile PC, Bianciardi F, Tosti M, Palladino A, Di Palma M. Prevalence and influence of malnutrition on quality of life and performance status in patients with locally advanced head and neck cancer before treatment. Support Care Cancer. 2010;18(4):433-437.

30. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-99.

31. Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: A systematic review. J Cancer Surviv. 2018.

32. van Bokhorst-de van der Schueren,M.A., Guaitoli PR, Jansma EP, de Vet HC. Nutrition screening tools: Does one size fit all? A systematic review of screening tools for the hospital setting. Clin Nutr. 2014;33(1):39-58.

33. Vellas B, Guigoz Y, Garry PJ, et al. The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition. 1999;15(2):116-122.

34. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.

35. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.

36. Weekes CE, Elia M, Emery PW. The development, validation and reliability of a nutrition screening tool based on the recommendations of the british association for parenteral and enteral nutrition (BAPEN). Clin Nutr. 2004;23(5):1104-1112.

37. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991;325(8):525-532.

38. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): A new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-336.

39. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-99.

40. Toledo DO, Carvalho AM, Oliveira AMRR, et al. The use of computed tomography images as a prognostic marker in critically ill cancer patients. Clin Nutr ESPEN. 2018;25:114-120.

41. 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. 2013;31(12):1539-1547.

42. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: Role of the patient-generated subjective global assessment. Curr Opin Clin Nutr Metab Care. 2017;20(5):322-329.

43. Ottery FD. Patient-generated subjective global assessment. In: McCallum PA, Elliot L, Molseed LL, Grant B, eds. The clinical guide to oncology nutrition. Chicago, Il: The American Dietetic Association; 2006:44-53.

44. Boleo-Tome C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the malnutrition universal screening tool (MUST) in cancer. Br J Nutr. 2012;108(2):343-348.

45. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: The role of disease and diet. Clin Oncol. 2003;15(8):443-450.

46. Read JA, Crockett N, Volker DH, et al. Nutritional assessment in cancer: Comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). Nutr Cancer. 2005;53(1):51-56.

47. Abbott J, Teleni L, McKavanagh D, Watson J, McCarthy AL, Isenring E. Patient-generated subjective global assessment short form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients. Support Care Cancer. 2016.

48. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren,M.A. Development and validation of a hospital screening tool for malnutrition: The short nutritional assessment questionnaire (SNAQ). Clin Nutr. 2005;24(1):75-82.

49. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-3191.

50. Sartorius N, Kuyken W. Translation of health status instruments. In: Orley J, Kuyken W, eds. Quality of life assessment: International perspectives. Berlin Heidelberg: Springer Verlag; 1994:3-18.

51. Acquadro C, Conway K, Hareendran A, Aaronson N, European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. Value Health. 2008;11(3):509-521.

52. Prado CM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. JPEN J Parenter Enteral Nutr. 2014;38(8):940-953.

53. Grossberg AJ, Chamchod S, Fuller CD, et al. Association of body composition with survival and locoregional control of radiotherapy-treated head and neck squamous cell carcinoma. JAMA Oncol. 2016;2(6):782-789.

54. Siervo M, Jebb SA. Body composition assessment: Theory into practice: Introduction of multicompartment models. IEEE Engineering in Medicine and Biology Magazine. 2010;29(1):48-59.

55. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85(1):115-122.

56. Prado CM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. J Parenter Enteral Nutr. 2014;38(8):940-953.

57. Prado CM, Maia YL, Ormsbee M, Sawyer MB, Baracos VE. Assessment of nutritional status in cancer--the relationship between body composition and pharmacokinetics. Anticancer Agents Med Chem. 2013;13(8):1197-1203.

58. Sjoblom B, Gronberg BH, Benth JS, et al. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. Lung Cancer. 2015;90(1):85-91.

59. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low - dose induction chemotherapy. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2007;29(10):893-900.

60. Langius JA, Zandbergen MC, Eerenstein SE, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo) radiotherapy: A systematic review. Clinical nutrition. 2013;32(5):671-678.

61. Lonbro S, Dalgas U, Primdahl H, et al. Progressive resistance training rebuilds lean body mass in head and neck cancer patients after radiotherapy--results from the randomized DAHANCA 25B trial. Radiother Oncol. 2013;108(2):314-319.

62. Zhao SG, Alexander NB, Djuric Z, et al. Maintaining physical activity during head and neck cancer treatment: Results of a pilot controlled trial. Head Neck. 2016;38 Suppl 1:E1086-96.

63. Sandmael JA, Bye A, Solheim TS, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: A pilot randomized trial. Cancer. 2017;123(22):4440-4448.

64. Buffart LM, Kalter J, Sweegers MG, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev. 2017;52:91-104.

65. Duffy SA, Ronis DL, McLean S, et al. Pretreatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. J Clin Oncol. 2009;27(12):1969-1975.

66. Rogers LQ, Courneya KS, Robbins KT, et al. Physical activity correlates and barriers in head and neck cancer patients. Support Care Cancer. 2008;16(1):19-27.

67. Sandmael JA, Bye A, Solheim TS, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: A pilot randomized trial. Cancer. 2017;123(22):4440-4448.

68. Buffart LM, de Bree R, Altena M, et al. Demographic, clinical, lifestyle-related, and social-cognitive correlates of physical activity in head and neck cancer survivors. Support Care Cancer. 2017.

Chapter 2. Limited content validity across methods of malnutrition assessment in patients with cancer: a systematic review

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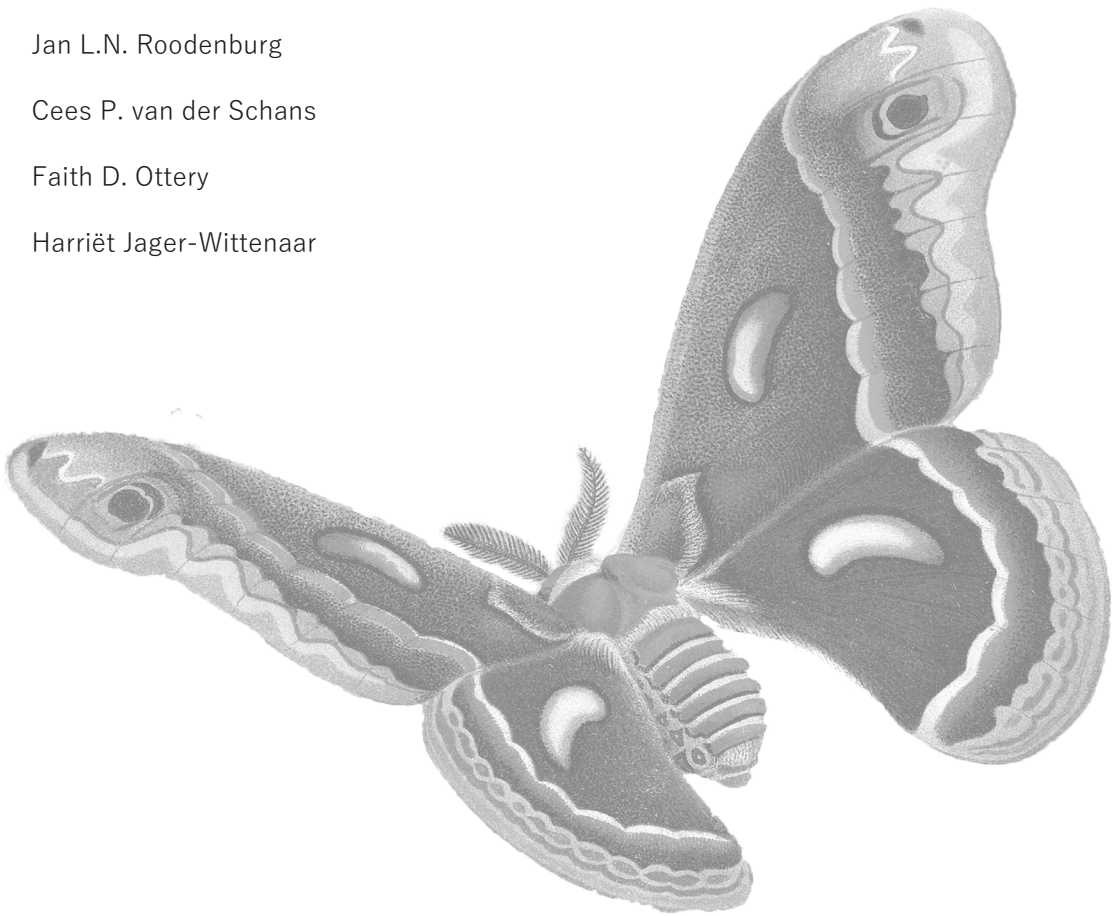

Abstract

Objective: To identify malnutrition assessment methods in cancer patients and assess their content validity based on internationally accepted definitions for malnutrition.

Study design: Systematic review of studies in cancer patients that operationalized malnutrition as a variable, published since 1998. Eleven key concepts, within the three domains reflected by the malnutrition definitions acknowledged by European Society for Clinical Nutrition and Metabolism and the American Society for Parenteral and Enteral Nutrition: A: Nutrient balance; B: Changes in body shape, body area and body composition; and C: Function, were used to classify content validity of methods to assess malnutrition. Content validity indices ($M\text{-}CVI_{A\text{-}C}$) were calculated per assessment method. Acceptable content validity was defined as $M\text{-}CVI_{A\text{-}C} \geq 0.80$.

Results: Thirty-seven assessment methods were identified in the 160 included articles. Mini Nutritional Assessment (MNA; $M\text{-}CVI_{A\text{-}C}=0.72$), Scored Patient-Generated Subjective Global Assessment (PG-SGA; $M\text{-}CVI_{A\text{-}C}=0.61$) and Subjective Global Assessment (SGA; $M\text{-}CVI_{A\text{-}C}=0.53$) scored highest $M\text{-}CVI_{A\text{-}C}$.

Conclusion: A large number of malnutrition assessment methods is used in cancer research. Content validity of these methods varies widely. None of these assessment methods has acceptable content validity, when compared against a construct based on ESPEN and ASPEN definitions of malnutrition.

Introduction

Early recognition and adequate diagnosis of malnutrition is considered an important element in the nutrition care process of cancer patients. Malnutrition in cancer patients is associated with poorer quality of life, poorer clinical outcome and decreased survival.[1-4] Malnutrition can occur in all phases of cancer, from diagnosis to palliative care or survivorship, due to symptoms caused by both illness and treatment.[1,5]

To adequately diagnose malnutrition, the construct of malnutrition needs to be clearly defined. Although a conceptual definition of malnutrition has been discussed for several decades,[6] the first consensus-based definition of malnutrition was published no earlier than 2006. The European Society for Clinical Nutrition and Metabolism (ESPEN) used the following definition for malnutrition in their Guidelines on Enteral Nutrition: "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 form (body shape, size and composition) and function, and clinical outcome".[7,8] We will further refer to this definition as “the ESPEN definition of malnutrition”. Another influential organization, the American Society for Parenteral and Enteral Nutrition (ASPEN), proposed the following definition of disease-related malnutrition in 2012: “An acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity has led to a change in body composition and diminished function”.[9] We will further refer to this definition as “the ASPEN definition of malnutrition”. Although important steps have been taken towards describing diagnostic criteria for malnutrition,[10-12] international consensus on the operationalization, i.e. a strict process of defining abstract concepts into measurable factors,[13] of ESPEN and ASPEN definitions for malnutrition assessment has not been reached.[14]

Because a gold standard for the operationalization of malnutrition is currently lacking, it is difficult to establish diagnostic performance of assessment methods. However, because malnutrition is a problem that impacts several domains, assessment should include nutritional (im)balance, as well as the effects on body composition and function.[7,15] Adequate operationalization of malnutrition assessment may improve the accuracy of malnutrition diagnosis in research and in clinical practice. Content validity has been described as "the degree to which a sample of items, taken together, constitute an adequate operational definition of a construct".[16] Several instruments and methods are available to diagnose malnutrition, many of which are used in patients with cancer, but the extent to which these methods adequately cover all dimensions of malnutrition as defined by the ESPEN and ASPEN definitions has not been systematically reviewed. With this systematic review, we aim to provide an overview of the methods used for assessing malnutrition in adult cancer patients in the recent literature, and to determine their content validity based on the consensus-based definitions of malnutrition.

Materials and methods

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used in this systematic review of methods to the best possible extent (Online Supplement I).[17]

Search strategy and criteria

From May 4 2013 until July 29 2013, CINAHL, EMBASE, PUBMED, and Cochrane CENTRAL were searched for studies and study protocols of trials in the English, Dutch or German language. A sensitive and broad search strategy was developed, which was tailored

to each database. Details on the search strategy can be found in the Online supplement II. For feasibility reasons we restricted the time frame of publications, starting in January 1998 and ending in June 2013, providing a 15-year time frame to include studies.

Since we focused on assessment methods employed, rather than on the outcome of the studies, we considered randomized controlled trials as well as observational studies and quasi-experimental studies for inclusion. Both the ESPEN and the ASPEN definition suggest that malnutrition can indicate undernutrition as well as overnutrition.[7,9] In this systematic review we focus on undernutrition as subtype of malnutrition. All studies that specifically operationalized malnutrition, undernutrition, protein-energy malnutrition or protein-calorie malnutrition either as a co-variable or an outcome variable were considered eligible. All types of assessment methods, e.g. clinical observations, anthropometric measurements, functional tests, biochemical tests or questionnaires were included. Instruments originally developed as screening tools were included if they were put to use in a study to assess malnutrition. Studies had to be performed in adult patients (aged 18 years and older) who were diagnosed with any type of cancer, regardless of disease stage, phase and type of treatment, tumor site or tumor type.

Case studies, qualitative research and conference abstracts were excluded, as were studies that assessed malnutrition only with the purpose to include or exclude participants from the study, since the description of malnutrition assessment in such publications is usually limited which could preclude adequate judgment of content validity. Reviews were excluded because they do not concern original research. Studies assessing overnutrition or depletion of single micronutrients were excluded. Furthermore, studies that employed methods with the specific aim to assess risk of malnutrition or risk of undernutrition were excluded, because such methods have different requirements than methods used to assess

manifest malnutrition. If a study employed methods to assess risk of malnutrition in addition to methods that assess malnutrition, only the methods relating to malnutrition assessment were included.

In patients with cancer, cachexia can be the underlying mechanism causing malnutrition. Cancer cachexia can be described as a metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[18] Whereas imbalance of nutrients is the main cause of malnutrition, underlying disease and the related changes in metabolism and inflammatory activity are the main causes of cachexia.[18,19] Since the construct of malnutrition served as the reference standard for content validity of methods, studies with a primary focus on cachexia instead of malnutrition were excluded. Studies that assessed malnutrition in populations including both cancer patients and non-cancer patients were excluded only if the focus was not on cancer patients.

Study selection and data collection

After removal of duplicates, a first selection based on title was made by one author. For the remaining records, all abstracts were screened by two authors independently for judging eligibility. The final selection based on full text articles was also performed by two authors independently. Any disagreements on inclusion or exclusion of studies after judging eligibility based on full text articles were resolved by consulting a third author, who independently decided. In cases where multiple articles represented a single study, the article that described the largest number of methods for assessing malnutrition used and provided the most detailed information on the methods was selected for inclusion. Data on methods used to assess malnutrition from included studies were extracted by two authors

independently. Any disagreement on data properties that could not be resolved by consensus was resolved by consulting a third author who independently decided. A standardized data collection file was used to manage the data. Besides the description of methods used to assess malnutrition, the following study characteristics were collected from each study: citation of article, study design, country, and number, age, sex and type of cancer of included patients. For this systematic review we aimed to provide an overview of methods that are used to assess malnutrition in cancer patients and summarize the characteristics of these methods in terms of content validity. As the current systematic review was on content validity and not on outcomes, a risk of bias assessment was not applicable.

Operationalization of the construct

As a first step of our approach to judge the content validity of the methods used for assessment of malnutrition (undernutrition), each method was viewed as a sample of one or more items that together operationalize the construct of malnutrition as viewed by expert panels. To test the adequacy of an operationalization, the items of an assessment method were assigned to domains and key concepts derived from the consensus based ESPEN and ASPEN definitions for malnutrition. The three common domains in these definitions are A: nutrient balance; B: body shape, body size and body composition; and C: function,[7] which we used in our primary analysis. The ASPEN definition includes a fourth domain (D): inflammatory factors.[11,12] We performed sensitivity analyses to assess how strongly our conclusions would be affected by including this fourth domain.

TABLE 1. Key concepts of malnutrition per domain

Domain	Key concept
A. Assessment of nutrient balance	1. Deficiency or imbalance of overall nutrient intake when compared to the past *(PI)*
	2. Deficiency or imbalance of overall nutrient intake *(OI)*
	3. Deficiency or imbalance of energy *(EN)*
	4. Deficiency or imbalance of protein *(PR)*
B. Assessment of body weight, body area and body composition	5. Adverse change in tissue/body shape and body size when compared to past *(WC)*
	6. Adverse effects on tissue/body shape and body size *(WS)*
	7. Subjective assessment of adverse effects on body composition *(SC)*
	8. Objective assessment of adverse effects on body composition *(OC)*

Domain	Key concept
C. Assessment of muscle, immune and cognitive function	1. Adverse effects on muscle function and physical activity *(MP)*
	2. Adverse effects on immune function *(IF)*
	3. Adverse effects on cognitive function *(CF)*
D. Measurement of inflammatory factors	4. Adverse effects assessed by inflammatory biomarkers *(IB)*
	5. Adverse effects assessed by other markers of inflammatory status *(IO)*

Description
Assessment of nutritional intake in the past, changes in nutritional intake in the last month(s)
Assessment of current or expected nutritional intake
Assessment of nutritional balance. Energy intake and losses. For instance intake assessment focused on energy, and losses such as vomiting, nutritional malabsorption or diarrhea (inflammatory factors are scored separately in domain D)
Assessment of nutritional balance focused on protein intake and depletion
Assessment of changes in body weight by measurement or inquiry
Comparisons to ideal body weight, assessment of body weight or body surface area through body mass index (BMI), or assessment of body circumferences (upper arm circumference)
Observation of visible musculature, visible fat depositories, visible disturbances of fluid balance (ascites, edema, skin tension).
Assessment based on measurements of muscle mass, fat mass and body water (e.g. anthropometric measurements, bioelectrical impedance analysis, DXA scan)
Description
Assessment of muscle function by tests of strength or assessment of physical activity or physical function. For instance by means of handgrip strength test or questionnaires
Assessment of immune function, e.g. by means of biochemical markers of immune function
Assessment of cognitive function, e.g. by means of questionnaires, cognitive tests etc.
Assessment of biochemical key concepts of inflammation
Assessment of changes in body temperature, inquiry on medication that is prescribed to suppress inflammation, etc.

To categorize all assessment methods within the domains, key concepts were identified to characterize different aspects of the construct of malnutrition. These key concepts fit within the aim of this study and are based directly on both definitions and publications by ESPEN and/or ASPEN on defining malnutrition.[7,10-12] For domain A (nutrient balance) the key concepts were: deficiency or imbalance of overall nutrition, deficiency or imbalance of energy and deficiency or imbalance of protein. For domain B (body shape, size and composition) the concepts were: adverse effects on tissue/body shape and body size, and adverse effects on body composition. For domain C (function) the key concepts were: adverse effects on muscle function and physical activity, adverse effects on immune function, and adverse effects on cognitive function. For the additional domain D (inflammatory activity), adverse effects of inflammatory activity was used. Additionally, we identified a general key concept: acute, subacute or chronic state of undernutrition which refers to the speed of development of malnutrition. This was incorporated in the model by adding adverse changes in overall intake when compared to the past in domain A and adverse change in tissue/body shape and body size when compared to past to domain B.

Key concepts were divided when they might reflect different aspects of biological function. Objective markers (measurements) and subjective markers (clinical observations) for body composition could reflect different aspects of altered body composition, therefore two separate key concepts were constructed for 'adverse effects on body composition' in domain B. As biochemical markers and observations of inflammatory status could reflect different aspects of inflammatory activity, two separate key concepts were also constructed for 'adverse effects of inflammatory activity' in domain D. Thus, eleven key concepts were constructed within domain A, B and C. In addition, we formulated two key concepts within domain D. All key concepts of malnutrition per domain are shown in Table 1.

Data analysis

Characteristics of each method used to assess malnutrition were recorded and the number of studies in which each method was used was counted. To our knowledge, no pre-existing instrument for quantitative analysis was available for a systematic review of content validity of methods. In original articles a widely used approach to quantifying content validity is the calculation of a content validity index (CVI).[16,20,21] In this approach a sample of experts rates each item of a scale or instrument to be relevant or not for the construct to be measured. From these ratings an item content validity index (I-CVI) is calculated. The I-CVIs are averaged for the instrument into a weighted summary score, the scale content validity index (S-CVI). The higher the S-CVI, the more consensus on the nature of the construct can be assumed.[21] In this systematic review, an adequate level of consensus was warranted by relying on two definitions that were based on broad expert consensus. We focused on assessing to what extent this multidimensional consensus construct was adequately reflected in methods that operationalize it. Therefore, the CVI-approach was adapted for this study as follows: every assessment method was compared to the fixed set of key concepts within the domains as described above (Table 1). Presence of a key concept in the method was scored as '1' (present) or '0' (not present). All items that could be graded as present for an indicator had equal weight. Subsequently domain content validity index (D-CVI), instead of I-CVI, was calculated per domain, by dividing the number of key concepts within the domain considered present by the total number of key concepts within the domain. For instance, if in a method two out of four key concepts are present in domain B, the D-CVI for domain B ($D\text{-}CVI_B$) would be 2/4=0.50. All key concepts within a domain carry equal weight within the D-CVI equation. A weighted summary score resembling S-

CVI and representing the content validity index of the method (M-CVI) was obtained by calculating the average of the D-CVI scores. For instance: if an assessment method scores the following D-CVI for domain A-C: $D\text{-}CVI_A$ 0.17, $D\text{-}CVI_B$ 0.50 and $D\text{-}CVI_C$ 0.00, then $M\text{-}CVI_{A\text{-}C}$ for this method would be (0.17+0.50+0.00)/3=0.22. For S-CVI, a cut off value of ≥ 0.80 has been reported as acceptable.[21,22] This threshold for acceptable content coverage of 0.80 is based on the assumption that the minimum coverage of I-CVI, the score we adapted to D-CVI, should be around 0.79 in order to safeguard good coverage of items or domains.[21] In our study, we also considered an M-CVI value ≥0.80 acceptable.

Although M-CVI score ranges from 0 to 1, it can be considered a nominal key concept score transformed to a weighted average score. For this reason, median CVI scores were reported and non-parametric statistical methods were applied. Kendall's tau-b test was used to explore if there is a trend towards improved scores for $M\text{-}CVI_{A\text{-}C}$ per year from 1998 until 2013.

Sensitivity analysis

The M-CVI calculated from the composite range of key concepts could be sensitive to alternative choices in arrangement of key concepts. Also, applying unweighted average instead of weighted average could influence outcome. Therefore, for all methods robustness of $M\text{-}CVI_{A\text{-}C}$ was tested and alternative scores were calculated in three ways. The first alternative scenario included adding measurement of inflammatory factors (domain D) to the primary scenario. Similar to the primary scenario, method-items were scored either 'present' or 'not present' for each key concept and scores were weighted per domain. Summarized content validity scores for the four domains ($M\text{-}CVI_{A\text{-}D}$) were calculated for each assessment method. Because the number of key concepts per domain can influence

outcome, a second sensitivity analysis was performed by combining key concepts that could be interpreted as overlapping. Therefore, in this analysis the key concept 'deficiency or imbalance of overall nutrition' was combined with 'deficiency or imbalance of energy intake', and 'subjective assessment of adverse effects on body composition' was combined with 'objective assessment of adverse effects on body composition'. In this way, an alternative set of nine key concepts within domain A-C was constructed with three key concepts in each domain. Again method-items were scored either 'present' or 'not present' for each key concept and scores were weighted per domain. The weighted summary score calculated per method for these nine key concepts is referred to as M-CVI$_{9A\text{-}C}$. In the third sensitivity analysis, each of the eleven key concepts was given equal importance. We calculated an unweighted average score for the key concepts from domain A to C (Ave$_{A\text{-}C}$) by dividing the amount of key concepts covered per method in domain A-C, by the total of 11 key concepts. The correlation between the M-CVI$_{A\text{-}C}$ and the three alternative scores was calculated using Spearman's rho.

Results

The search process resulted in 4421 articles after removal of duplicates. After screening by title and abstract, 504 full text articles were assessed for eligibility. Initial agreement between selecting authors was 93.1%. Consensus resulted in final inclusion of 160 studies. A list of all included references including years of publication and methods can be found in Online supplement III. A flow diagram, describing the selection process in detail, is presented in Figure 1. Characteristics of included studies and methods are summarized in Table 2. Because some studies used multiple methods for assessing malnutrition, an

operationalization of malnutrition was reported 209 times, using a total of 37 different methods. A concise description of all methods is provided in Online supplement IV.

Figure 2 shows coverage of domains and frequency of use per method. Only five out of 37 assessment methods (14%) were represented by items in the three domains A, B and C: Malnutrition Screening Tool for Cancer patients (MSTC),[23] Mini Nutritional Assessment (MNA),[24] Nutritional Screening Questionnaire (NSQ),[25] Patient-Generated Subjective Global Assessment (PG-SGA),[26] and Subjective Global Assessment (SGA).[27] Four methods addressed all four domains A-D: MNA, NSQ, PG-SGA and SGA. Of all methods, 15 (41%) were classified in one domain only. Twelve methods (32%) contained one or more items belonging to domain A, 26 methods (70%) had items belonging to domain B, thirteen methods (35%) included domain C, and 23 methods (62%) included domain D. 'Change in body weight and surface' was the key concept most frequently present, in 20 (54%) of the methods. The key concept 'cognitive function' was represented once (3%) in MNA.

The methods, the number of method-items per domain and the M-CVI$_{A\text{-}C}$ scores are presented in Table 3[23-53] and distribution of method-items across key concepts and domains is presented in Online supplement V. The median total of present key concepts per method was 2 out of 13 (Interquartile Range [IQR]: 1-4). Median M-CVI$_{A\text{-}C}$ of 37 methods was 0.17 (IQR: 0.08-0.25). Unidimensional methods that address only one domain of the construct of malnutrition produced a median M-CVI$_{A\text{-}C}$ score of 0.08 (IQR: 0.00-0.11). Methods that addressed domains A-C produced a median M-CVI$_{A\text{-}C}$ score of 0.53 (IQR: 0.40-0.67). All individual methods scored M-CVI$_{A\text{-}C}$ <0.80. Of all methods, MNA scored lowest M-CVIA-C score (0.00). Kendall's tau-b test did not reveal a trend towards a significant change in scores for M-CVIA-C.over the years (τ -b=–0.02, p=0.65).highest (M-CVI$_{A\text{-}C}$=0.72), PG-SGA scored second highest (M-CVI$_{A\text{-}C}$=0.61) and SGA scored third

highest (M-CVI$_{A\text{-}C}$ =0.53). Albumin, Albumin/Prealbumin ratio,[28] Prealbumin[31] and Prognostic Inflammatory and Nutritional Index (PINI)[30] scored the

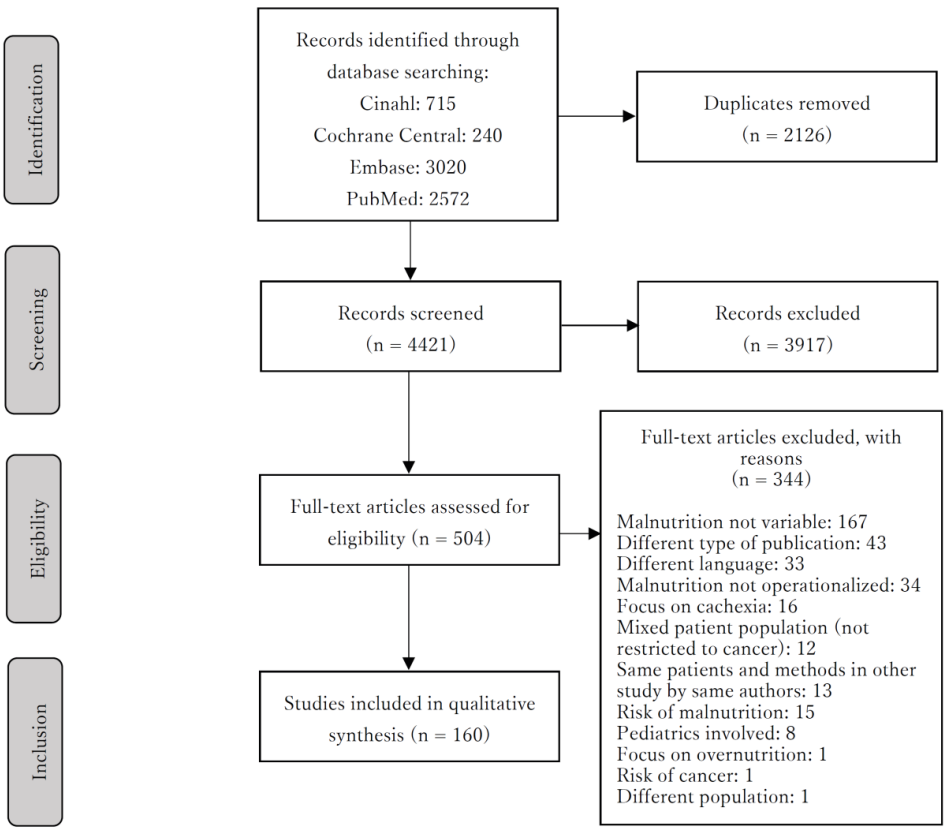

FIGURE 1. Flow diagram of the selection process of studies describing malnutrition assessment

TABLE 2. Characteristics of studies

Characteristics of selected studies		**N (%)**
Studies	*Total* (Patients: N=32.862)	*160 (100)*
Study design	Prospective observational	60 (37.5)
	Cross-sectional	53 (33.1)
	Retrospective observational	28 (17.5)
	Randomized controlled trial	12 (7.4)
	Case control	7 (4.4)
Tumor localization/study	One tumor localization	85 (53.1)
	Head and neck	27 (16.9)
	Colorectum	20 (12.5)
	Lung	11 (6.9)
	Stomach	9 (5.8)
	Esophagus	7 (4.3)
	Pancreas	4 (2.5)
	Other (N=6)*	7 (4.3)
	Multiple localizations	72 (45.0)
	Unclear	3 (1.9)
Methods (n = 37) operationalizing malnutrition/study	1 method used	127 (79.4)
	2 methods used	25 (15.6)
	3 methods used	4 (2.5)
	4-6 methods used	4 (2.5)
Country of origin (n = 32)	Australia	24 (15.0)
	France	21 (13.1)
	The Netherlands	13 (8.1)
	United States of America	10 (6.3)
	China	9 (5.6)
	Italy	7 (4.4)
	Spain	7 (4.4)
	Sweden	7 (4.4)
	Japan	6 (3.8)
	Portugal	6 (3.8)
	Brazil	6 (3.8)
	South Korea	5 (3.1)
	Taiwan	5 (3.1)
	Other (N=19)**	34 (31.0)

* breast, hematopoietic and lymphoid tissues, liver, ovary, prostate, thorax

** Austria, Belgium, Canada, Czech Republic, Croatia, Denmark, Germany, Greece, India, Iran, Ireland, Lithuania, Mexico, Norway, Poland, Singapore, Swiss, Turkey, United Kingdom

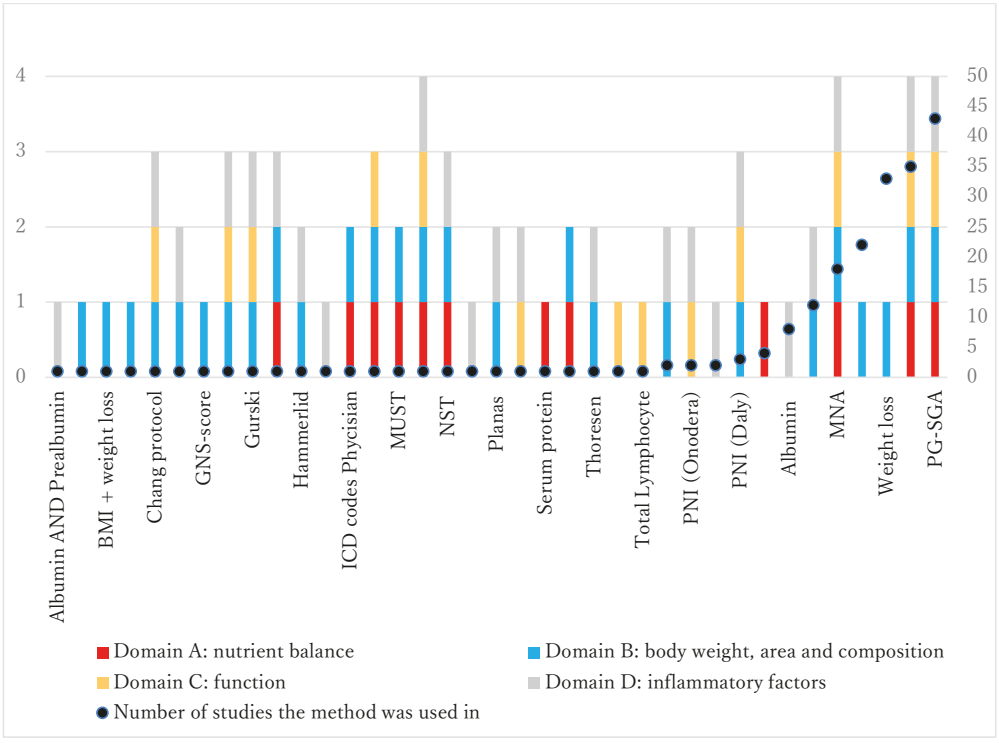

FIGURE 2. Frequency of use and coverage of domains per method

TABLE 3. Distribution of method-items per domain

	Domain A*	Domain B¥	Domain C¥	Domain D§	Domain A-C	Domain A-D	
Method	key concepts: N=4‖	key concepts : N=4‖	key concepts: N=3‖	key concepts : N=2‖	Total key concepts: N=11‖	Total key concepts: N=13‖	M-CVI$_{A-C}$¶
Albumin	0	0	0	1	0	1	0.00
Albumin and Prealbumin[28]	0	0	0	1	0	1	0.00
Hemoglobin[29]	0	0	0	1	0	1	0.00
Prognostic Inflammatory and Nutritional Index (PINI)[30]	0	0	0	1	0	1	0.00
Prealbumin[31]	0	0	0	1	0	1	0.00
Creatine Hight Index (CHI)[32]	1	0	0	0	1	1	0.08
Bio-impedance measurement[33]	0	1	0	0	1	1	0.08
Body mass index (BMI)	0	1	0	0	1	1	0.08
BMI loss[34]	0	1	0	0	1	1	0.08
Dietitian judgement[35]	0	1	0	1	1	2	0.08
Nutritional Risk Index (NRI)[36]	0	1	0	1	1	2	0.08
Serum protein[37]	1	0	0	0	1	1	0.08
Weight loss	0	1	0	0	1	1	0.08
Prognostic Nutritional Index (PNI, Onodera)[38]	0	0	1	1	1	2	0.11
Selzer Index[39]	0	0	1	1	1	2	0.11
Total Leucocyte count[29]	0	0	1	0	1	1	0.11
Total Lymphocyte count[37]	0	0	1	0	1	1	0.11
Short Nutritional Assessment Questionnaire (SNAQ)[40]	1	1	0	0	2	2	0.17
BMI + weight loss[41]	0	2	0	0	2	2	0.17
GNS-score[42]	0	2	0	0	2	2	0.17
HAS guidelines[43]	0	2	0	1	2	3	0.17
Gogos[44]	0	1	1	1	2	3	0.19

* Domain A= nutrient balance; ¥ Domain B = body weight, body area and body composition; ¥ Domain C = function; § Domain D = inflammatory factors; ‖ (N) = number of key concepts per domain; ¶ M-CVIA-C = Method Content Validity Index for domain A-C.

Key concepts are perceived either present or not present for CVI calculation. Example calculation M-CVIA-C for "weight loss": ((Domain A: no key concepts = D-CVIA=0) + (Domain B: 1 key concept present out of four = D-CVIB=0.25) + (Domain C: no key concepts = D-CVIc=0))/3=0.08

TABLE 3. continued

Method	Domain A* key concepts : N=4‖	Domain B¥ key concepts : N=4‖	Domain C¥ key concepts : N=3‖	Domain D§ key concepts : N=2‖	Domain A-C Total key concepts: N=11‖	Domain A-D Total key concepts: N=13‖	M-CVI$_{A-C}$¶
Prognostic Nutrititional Index (PNI, Buzby)[45]	0	1	1	1	2	3	0.19
Hammerlid[46]	0	3	0	1	3	4	0.25
ICD codes Physician[35]	1	2	0	0	3	3	0.25
Malnutrition Universal Screening Tool (MUST)[47]	1	2	0	0	3	3	0.25
Nottingham Screening Tool (NST)[48]	1	2	0	1	3	4	0.25
Planas[49]	0	3	0	1	3	4	0.25
Thoresen[50]	0	3	0	1	3	4	0.25
Chang protocol[51]	0	2	1	1	3	4	0.28
Hackl scoring system[52]	2	2	0	1	4	5	0.33
Gurski[53]	0	3	1	1	4	5	0.36
Malnutritition Screening Tool for Cancer patients (MSTC)[23]	1	2	1	0	4	4	0.36
Nutritional Screening Questionnaire (NSQ)[25]	2	2	1	2	5	7	0.44
Subjective Global Assessment (SGA)[26]	2	3	1	1	6	7	0.53
Patient-Generated Subjective Global Assessment (PG-SGA)[27]	3	3	1	1	7	8	0.61
Mini Nutritional Assessment (MNA)[24]	4	2	2	1	8	9	0.72

* Domain A= nutrient balance; ¥ Domain B = body weight, body area and body composition; ¥ Domain C = function; § Domain D = inflammatory factors; ‖ (N) = number of key concepts per domain; ¶ M-CVIA-C = Method Content Validity Index for domain A-C.

Key concepts are perceived either present or not present for CVI calculation. Example calculation M-CVIA-C for "weight loss": ((Domain A: no key concepts = D-CVIA=0) + (Domain B: 1 key concept present out of four = D-CVIB=0.25) + (Domain C: no key concepts = D-CVIc=0))/3=0.08

Sensitivity analysis

The three alternative calculations for the 37 methods yielded a median M-CVI$_{A-D}$ of 0.19 (IQR: 0.06-0.31; min-max: 0.06-0.67), median Ave$_{A-C}$ of 0.18 (IQR: 0.09-0.27; min-max: 0.00-0.73), and median M-$_{CVI9A-C}$ of 0.22 (IQR: 0.11-0.33;min-max: 0.00-0.78) respectively. The primary outcome M-CVI$_{A-C}$ strongly and significantly correlated to each of the alternative indices: M-CVI$_{A-D}$ ($r=0.83$, $p<0.001$), Ave$_{A-C}$ ($r=0.99$, $p<0.01$) and M-CVI$_{9A-C}$ ($r=0.98$, $p<0.001$). The primary outcome M-CVI$_{A-C}$ produced slightly lower scores than M-CVI$_{9A-C.}$ The ranking of the methods by content validity index score was the same for scenarios Ave$_{A-C}$ and M-CVI$_{9A-C}$ when compared to the primary scenario M-CVI$_{A-C}$. In the alternative scenario M-CVI$_{A-D}$, the seven methods that scored above the 75th percentile also scored above the 75th percentile in the primary scenario M-CVI$_{A-C}$. Malnutrition assessment methods with items solely scoring in domain D scored a M-CVI$_{A-D}$ of 0.13, whereas these methods scored a M-CVI$_{A-C}$ of 0.00.

Discussion

The results of this systematic review of studies document that a collection of 37 methods have been used to assess malnutrition in cancer patients between January 1998 and June 2013. Our study also shows that content validity of methods used to assess malnutrition in adult patients with cancer varies widely, as M-CVI$_{A-C}$ scores ranged from 0.00 to 0.72. All methods used for malnutrition assessment have a content validity score below the commonly used threshold of acceptability (0.80), when compared to a set of key concepts within domains derived from the ESPEN and ASPEN definitions for malnutrition. Additionally, we did not find an improvement

in scores for M-CVI$_{A-C}$ over the years. Thus, malnutrition assessment in studies in cancer patients is currently not in accordance with the construct of malnutrition reflecting two consensus based definitions of malnutrition. While the majority of methods included domain B (body weight, area and composition), approximately a third of assessment methods covered one or more key concepts of domain A (nutrient balance), and domain C (function). This underrepresentation of domain A and C largely explains low median M-CVI$_{A-C}$ scores.

Of the methods identified, the top three M-CVI$_{A-C}$ scores in all scenarios consisted of MNA, PG-SGA and SGA. MNA distinguishes itself from all other methods by containing items that address protein intake. MNA is also the only instrument that addresses more than one key concept concerning function: 'muscle function' and 'cognitive function'. Although the MNA has been used in both the general[54-57] and elderly[58-72] population with cancer, it should be noted that the MNA is an instrument specifically designed and validated for assessing malnutrition in the elderly. This is reflected by its items on for example dementia, independent living and a higher cut-off for Body Mass Index.[24]

Obviously, when compared to multidimensional methods, unidimensional methods cover the construct of malnutrition less accurately, which is reflected by lower CVI scores. With no gold standard available for malnutrition assessment in patients with cancer,[14] we hypothesize that methods with higher content validity may positively impact accuracy of malnutrition diagnosis. This is supported by a study in which a unidimensional instrument including BMI and weight loss was used, low sensitivity (59%) and moderate specificity (75%) were found when compared to the multidimensional instrument SGA as a reference.[74] Two studies in patients with cancer that compared multidimensional methods PG-SGA to SGA as a reference and one

study that compared MNA to PG-SGA as a reference, demonstrated strong agreement between the methods for classifying patients as malnourished, and sensitivity ranging from 0.97 to 0.98.[55,74,75] Compared to SGA as a reference, PG-SGA has also demonstrated good specificity: 0.82 and 0.86.[74,75] However in the cancer population MNA lacked specificity when compared to PG-SGA as a reference: 0.54.[55] This latter finding may be explained, in part, by the tailoring of the MNA to an elderly population, whereas the study concerned a mixed adult population.

A number of methods used in the included articles to assess malnutrition, for instance Nutritional Risk Index (NRI) and Malnutrition Universal Screening Tool (MUST), were developed for screening purposes rather than diagnosis or comprehensive assessment of malnutrition.[7,36,47] Although these methods were assigned low content validity scores for assessment of malnutrition in our review, this does not disqualify these instruments as clinically useful tools for early detection of risk of malnutrition.

Strengths and limitations

Previous systematic reviews on malnutrition focused on patients with head and neck cancer and hospital patients[76,77] and based their methods on a definition of cancer cachexia[76] or focused on malnutrition screening tools.[77] While research on criterion validity has the advantage of being able to use measures such as sensitivity and specificity, research on criterion validity also requires a gold standard in order to provide accurate outcome.[78] In this systematic review we did not choose this strategy because a 'gold' standard for malnutrition assessment is currently not available.[14] Instead, a novel and pragmatic approach to assess content validity

was used in which two internationally agreed upon definitions, developed by expert panels, served as a reference to identify domains and key concepts. We chose to assign equal weight to all key concepts within the separate domains, since there is no broad agreement on hierarchy within key concepts. Content validity assessment shows some natural limitations due to the nominal level on which it operates by grading method-items present or not present, regardless of individual item qualities. However, this approach did enable us to explore agreement between 37 assessment methods and the construct of malnutrition and express our observations in a quantitative manner.

Method-items covering individual key concepts may be influenced by cancer-specific disease factors and cancer treatment modalities.[12] While some method-items may be more reliable indicators of malnutrition in certain groups of cancer patients, there is variability within the population and their treatments. To our knowledge, there is no broad agreement on which method-items are most appropriate to use in the general population of patients with cancer. The approach of malnutrition as a multidimensional framework of key concepts may reduce noise caused by factors of disease or treatment, because a disease factor that affects one key concept, may not affect other key concepts.

While composing the set of key concepts, we occasionally came across ambiguities that were solved to the best possible extent by consensus between authors. One could argue that M-CVI$_{A\text{-}C}$ scores of the methods might have been influenced by the authors' choices when constructing the set of key concepts. However, the sensitivity analysis showed that median scores were similar in all scenarios and correlation was significant and strong, method ranking was stable and only influenced when items from domain D were included in the scenario. The

results were robust, especially for the highest scoring methods. The more conservative estimates produced by the M-CVI$_{A\text{-}C}$ scenario when compared to the M-CVI$_{9A\text{-}C}$ scenario can be explained by the fact that this nine indicator model is less sensitive by nature than the primary scenario with eleven key concepts.

Although our framework of key concepts could also apply to malnutrition in the sense of overnutrition, malnutrition assessment methods that are used in patients with cancer tend to focus on signs of undernutrition and are often not designed to detect and assess signs of overnutrition. Hence, we chose to limit to studies that portrayed malnutrition in the sense of undernutrition.

Implications and applications for research and practice

The findings of this study suggest that the overall level of content validity of malnutrition assessment methods could be improved. These findings are of importance for research and practice since accuracy of malnutrition assessment may be affected by the variance in level of content validity. Further research is urgently needed on sensitivity, specificity and interactions of method-items that are used to assess malnutrition in cancer patients. With this information, the current set of key concepts that covers the theoretical construct of malnutrition, could evolve to a set of method-items that accurately identifies malnutrition in patients with cancer. Such a set could also guide interventions that effectively impact nutritional status of patients. Safeguarding adequate coverage of the construct of malnutrition by the method(s) chosen might be a sensible strategy to improve accuracy of malnutrition assessment and, consequently,

efficacy of interventions to treat malnutrition. In the absence of a single comprehensive method, combining currently well accepted methods that score higher on content validity, and that are tested for their predictive value for clinical outcome in cancer patients, such as PG-SGA or SGA[52,79,80] with additional key concepts could provide a sensible strategy. For instance, combining items of the PG-SGA with the MNA items on protein intake and cognitive function would result in an adequate M-CVI score of 0.81. However, in clinical practice, it may not always be feasible to apply items from more than one method to assess malnutrition. In such instances we suggest to use methods that include items addressing at least the domains A, B and C of the malnutrition definition.

Implementation of malnutrition assessment methods with higher content validity could be perceived as more complex by clinicians. Providing additional training may be helpful to improve perceived difficulty and comprehensibility. We will report on the influence of training on difficulty and comprehensibility as perceived by clinicians seperately in the future. The potentially positive influence of training or practice in use of multidimensional assessement methods is supported by a study on interrater reliability (IRR) of the SGA. More experienced dietitians (>5 years after graduation) showed an IRR of 89-100% when compared to a well trained and experienced dietitian (>20 years after graduation), whereas less trained and experienced dietitians (1-2 years after graduation) showed an IRR of 56-100%.[81]

We found that a unidimensional approach was applied in 15 (41%) of all methods. In 40 (25%) of all included studies a single unidimensional method was used to assess malnutrition. This unidimensional approach in malnutrition assessment may lead to an over- or underestimation of malnutrition prevalence in cancer patients. Therefore, we would advise against the use of a

single unidimensional method to assess malnutrition in cancer patients. Alternatively, we suggest that unidimensional methods are used to operationalize the measures they actually reflect. For example, loss of body weight operationalized as ‘weight loss’ is preferred instead of loss of body weight operationalized as ‘malnutrition'.

Conclusion

A large number of methods are used to assess malnutrition in cancer research. Content validity of these methods was variable and below acceptable levels when compared with a construct based on ESPEN and ASPEN definitions. MNA, PG-SGA and SGA best covered the breadth of the definitions and were classified with the highest content validity.

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References

1. Dewys WD, Begg C, Lavin PT,et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med.* 1980;69(4):491-7.
2. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. *Nutr J. 2012*;24:11-27.
3. Pressoir M, Desne S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Brit J Cancer*. 2010;102(6):966-971.
4. Tian J, Chen ZC, Hang LF. Effects of nutritional and psychological status in gastrointestinal cancer patients on tolerance of treatment. *World J Gastroentero*. 2007;13(30):4136-4140.
5. Tu MY, Chien TW, Lin HP, Liu MY. Effects of an intervention on nutrition consultation for cancer patients. *Eur J Cancer Care*. 2013;22(3):370-6. doi: 10.1111/ecc.12040.
6. Roubenoff R, Heymsfield SB, Kehayias JJ, Cannon JG, Rosenberg IH. Standardization of nomenclature of body composition in weight loss. *Am J Clin Nutr*. 1997;66(1):192-6.
7. Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider S, et al. Introductory to the ESPEN Guidelines on Enteral Nutrition: Terminology, definitions and general topics. *Clin Nutr.* 2006;25(2):180-6.
8. Stratton, R.J., Green, C.J., Elia, M. Disease-related malnutrition: an evidence based approach to treatment. in: R.J. Stratton, C.J. Green, M. Elia (Eds.) *Prevalence of disease-related malnutrition*. CABI Publishing, Wallingford, UK; 2003:3.
9. American Society for Parental and Enteral Nutrition (A.S.P.E.N.) Definition of Terms, Style, and Conventions Used in A.S.P.E.N. Board of Directors-Approved Documents. 2012

10. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren MA, Schols JM, Halfens RJ, Meijers JM, van Gemert WG. A rational approach to nutritional assessment. *Clin Nutr*. 2008;27(5):706-16. doi: 10.1016/j.clnu.2008.07.009.

11. Jensen GL, Mirtallo J, Compher C, et al. International Consensus Guideline Committee. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN-Parenter Enter.* 2010;34(2):156-9. doi: 10.1177/0148607110361910.

12. White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN-Parenter Enter.* 2012;36(3):275-83. doi: 10.1177/0148607112440285.

13. Mueller, Charles W. "Conceptualization, Operationalization, and Measurement." In *The SAGE Encyclopedia of Social Science Research Methods*, edited by Michael S. Lewis-Beck, Alan Bryman and Tim Futing Liao, 162-66. Thousand Oaks, CA: Sage Publications, Inc., 2004.

14. Meijers JM, van Bokhorst-de van der Schueren van MA, Schols JM et al. Defining malnutrition: mission or mission impossible. *Nutrition* 2010;26:432-440.

15. Soeters PB, Schols AM. Advances in understanding and assessing malnutrition. *Curr Opin Clin Nutr*.2009;12(5):487–494.

16. Polit DF, Beck CT. The content validity index: are you sure you know what's being reported? Critique and recommendations. *Res Nurs Health*. 2006; 29(5): 489-497.

17. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(6): e1000097. doi:10.1371/journal.pmed1000097

18. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr.* 2008;27(6):793-9. doi: 10.1016/j.clnu.2008.06.013.

19. Muscaritoli, M., Anker SD, Argilés J, et al. "Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG)"cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics"." *Clin Nutr.* 29.2 (2010): 154-159.

20. Tilden VP, Nelson CA, May BA. Use of qualitative methods to enhance content validity. *Nurs Res.* 1990; 39(3): 172-175.

21. Polit DF, Beck CT, Owen SV. Is the CVI an acceptable indicator of content validity? Appraisal and recommendations. *Res Nurs Health.* 2007; 30(4): 459-467.

22. Davis, L. L. (1992). Instrument review: Getting the most from a panel of experts. *Appl Nurs Res*, 1992;5(4), 194-197.

23. Kim JY, Wie GA, Cho YA, et al. Development and validation of a nutrition screening tool for hospitalized cancer patients. *Clin Nutr.* 2011;30(6):724-729.

24. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The mini nutritional assessment as part of the geriatric evaluation. *Nutr Rev.* 1996;54(1 Pt 2):S59-65.

25. Juretic A, Vegar V, Predrijevac D, et al. Nutritional screening of patients undergoing surgery or oncological treatment in four croatian hospitals. *Croat Med J.* 2004;45(2):181-187.

26. Ottery FD. Patient-Generated Subjective Global Assessment. In: McCallum, PA: *Nutrition screening and assessment in oncology*. The Clinical Guide to Oncology Nutrition, 2nd. ed., Elliot L, Molseed LL, McCallum PD, Grant B, (eds.). The American Dietetic Association: Chicago 2006, pp. 44– 53.

27. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN-Parenter Enter.* 1987;11(1):8-13.

28. Bagan P, Berna P, De Dominicis F, et al. Nutritional status and postoperative outcome after pneumonectomy for lung cancer. *Ann Thorac Surg.* 2013;95(2):392-396.

29. Friedlander AH, Tajima T, Kawakami KT, Wang MB, Tomlinson J. The relationship between measures of nutritional status and masticatory function in untreated patients with head and neck cancer. *J Oral Maxil Surg*. 2008;66(1):85-92.

30. Ingenbleek Y, Carpentier YA. A prognostic inflammatory and nutritional index scoring critically ill patients. *Int J Vitam Nutr Res*. 1985;55(1):91-101.

31. Antoun S, Rey A, Beal J, et al. Nutritional risk factors in planned oncologic surgery: What clinical and biological parameters should be routinely used? *World J Surg*. 2009;33(8):1633-1640.

32. Bistrian BR, Blackburn GL, Sherman M, Scrimshaw NS. Therapeutic index of nutritional depletion in hospitalized patients. *Surg Gynecol Obstet*. 1975;141(4):512-516.

33. Buntzel J, Krauss T, Buntzel H, et al. Nutritional status and prognosis of head and neck cancer disease. *Trace Elem Electroly*. 2012;29(2):132-136.

34. Martin L, Jia C, Rouvelas I, Lagergren P. Risk factors for malnutrition after oesophageal and cardia cancer surgery. *Brit J Surg*. 2008;95(11):1362-1368.

35. Platek M, E, Popp J, V, Possinger C, S, Denysschen C, A., Horvath P, Brown J, K. Comparison of the prevalence of malnutrition diagnosis in head and neck, gastrointestinal, and lung cancer patients by 3 classification methods. *Cancer Nurs*. 2011;34(5):410-416.

36. Buzby GP, Williford WO, Peterson OL, et al.: A randomized clinical trial of total parenteral nutrition in malnourished surgical patients: the rationale and impact of previous clinical trials and pilot study on protocol design. *Am J Clin Nutr*. 1988, 47:357-365.

37. Budrewicz-Czapska K, Szelachowski P, Strutynska-Karpinska M, Nienartowicz M, Pelczar P. Assessment of nutritional status in patients with esophageal and esophago-gastric cancer. *Adv Clin Exp Med*. 2011;20(2):199-203.

38. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi*. 1984;85(9):1001-1005.

39. Seltzer MH, Bastidas JA, Cooper DM, Engler P, Slocum B, Fletcher HS. Instant nutritional assessment. *J Parenter Enteral Nutr*. 1979;3(3):157-9.

40. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren,M.A. Development and validation of a hospital screening tool for malnutrition: The short nutritional assessment questionnaire (SNAQ). *Clin Nutr*. 2005;24(1):75-82.

41. Percival C, Hussain A, Zadora-Chrzastowska S, White G, Maddocks M, Wilcock A. Providing nutritional support to patients with thoracic cancer: Findings of a dedicated rehabilitation service. *Respir Med*. 2013;107(5):753-761.

42. Brookes GB. Nutritional status-a prognostic indicator in head and neck cancer. *Otolaryng Head Neck*. 1985-2;93(1):69-74.

43. Haute Autorite de Sante: Nutritional support strategy for protein-energy malnutrition in the elderly, 2007. Accessed at http://www.has.sante.fr/portail/upload/docs/application/pdf/malnutrition elderly guidelines.pdf

44. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: A randomized control trial. *Cancer*. 1998;82(2):395-402.

45. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. 1980;139(1):160-167.

46. Hammerlid E, Wirblad B, Sandin C, et al. Malnutrition and food intake in relation to quality of life in head and neck cancer patients. *Head Neck*. 1998;20(6):540-548.

47. Weekes CE, Elia M, Emery PW. The development, validation and reliability of a nutrition screening tool based on the recommendations of the British association for parenteral and enteral nutrition (BAPEN). *Clin Nutr*. 2004;23(5):1104-1112.

48. Dintinjana RD, Guina T, Krznaric Z, Radic M, Dintinjana M. Effects of nutritional support in patients with colorectal cancer during chemotherapy. *Collegium Antropol*. 2008;32(3):737-740.

49. Planas M, Penalva A, Burgos R, et al. Guidelines for colorectal cancer: Effects on nutritional intervention. *Clin Nutr*. 2007;26(6):691-697.

50. Thoresen L, Fjeldstad I, Krogstad K, Kaasa S, Falkmer UG. Nutritional status of patients with advanced cancer: The value of using the subjective global assessment of nutritional status as a screening tool. *Palliative Med*. 2002;16(1):33-42.

51. Chang RW. Nutritional assessment using a microcomputer. 1. programme design. *Clin Nutr*. 1984;3(2):67-73.

52. Hackl JM. Parenteral and enteral feeding. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 1998;33(11):731-752.

53. Gurski RR, Schirmer CC, Rosa AR, Brentano L. Nutritional assessment in patients with squamous cell carcinoma of the esophagus. *Hepato-gastroenterol*. 2003;50(54):1943-1947.

54. Hsu W, Tsai A, C., Chan S, Wang P, Chung N. Mini-nutritional assessment predicts functional status and quality of life of patients with hepatocellular carcinoma in Taiwan. *Nutr Cancer*. 2012;64(4):543-549.

55. Read JA, Crockett N, Volker DH, et al. Nutritional assessment in cancer: Comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). *Nutr Cancer*. 2005;53(1):51-56.

56. Slaviero KA, Read JA, Clarke SJ, Rivory LP. Baseline nutritional assessment in advanced cancer patients receiving palliative chemotherapy. *Nutr Cancer*. 2003;46(2):148-157.

57. Vanis N, Mehmedovic A, Mesihovic R. Use of nutritional status screening tests in evaluation of malnutrition of oncological patients. *Libri Oncol*. 2010;38(1-3):9-15.

58. Aaldriks AA, Giltay EJ, le Cessie S, et al. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy. *Breast*. 2013;22(5):753-60

59. Aaldriks AA, Maartense E, le Cessie S, et al. Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Crit Rev Oncol Hemat*. 2011;79(2):205-212.

60. Aaldriks AA, van der Geest LG, Giltay EJ, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol*. 2013;4(3):218-26.

61. Caillet P, Canoui-Poitrine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. *J Clin Oncol*. 2011;29(27):3636-3642.

62. Chaibi P, Magne N, Breton S, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. *Crit Rev Oncol Hemat*. 2011;79(3):302-307.

63. Kim YJ, Kim JH, Park MS, et al. Comprehensive geriatric assessment in Korean elderly cancer patients receiving chemotherapy. *J Cancer Res Clin*. 2011;137(5):839-847.

64. Luce S, De Breucker S, Van Gossum A, et al. How to identify older patients with cancer who should benefit from comprehensive geriatric assessment? *J Geriatr Oncol*. 2012;3(4):351-358.

65. Massa E, Madeddu C, Lusso MR, Gramignano G, Mantovani G. Evaluation of the effectiveness of treatment with erythropoietin on anemia, cognitive functioning and functions studied by comprehensive geriatric assessment in elderly cancer patients with anemia related to cancer chemotherapy. *Crit Rev Oncol Hemat*. 2006;57(2):175-182.

66. Paillaud E, Liuu E, Laurent M, et al. Geriatric syndromes increased the nutritional risk in elderly cancer patients independently from tumoursite and metastatic status. the ELCAPA-05 cohort study. *Clin Nutr*. 2014 33(2)330-5 Epub 2013.

67. Shin D-, Lee J-, Kim YJ, et al. Toxicities and functional consequences of systemic chemotherapy in elderly Korean patients with cancer: A prospective cohort study using comprehensive geriatric assessment. *J Geriatr Oncol*. 2012;3(4):359-367.

68. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol*. 2012;30(15):1829-1834.

69. Terret C, Albrand G, Droz JP. Geriatric assessment in elderly patients with prostate cancer. *Clin Prostate Cancer*. 2004;2(4):236-240.

70. Toliusiene J, Lesauskaite V. The nutritional status of older men with advanced prostate cancer and factors affecting it. *Support Care Cancer*. 2004;12(10):716-719.

71. Zhang L, Su Y, Wang C, et al. Assessing the nutritional status of elderly Chinese lung cancer patients using the Mini-Nutritional Assessment (MNA®) tool. *Clin Interv Aging*. 2013;8:287-291.

72. Zhang L, Wang C, Sha SY, et al. Mini-nutrition assessment, malnutrition, and postoperative complications in elderly Chinese patients with lung cancer. *J BUON*. 2012;17(2):323-326.

73. Bauer J, Capra S. Comparison of a malnutrition screening tool with subjective global assessment in hospitalised patients with cancer--sensitivity and specificity. *Asia Pac J Clin Nutr*. 2003;12(3):257-260.

74. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr*. 2002;56(8):779-785.

75. Gabrielson D, K., Scaffidi D, Leung E, et al. Use of an abridged scored Patient-Generated Subjective Global Assessment (abPG-SGA) as a nutritional screening tool for cancer patients in an outpatient setting. *Nutr Cancer*. 2013;65(2):234-239.

76. Dechaphunkul T, Martin L, Alberda C, Olson K, Baracos V, Gramlich L. Malnutrition assessment in patients with cancers of the head and neck: a call to action and consensus. *Crit Rev Oncol Hemat*. 2013;88(2):459-76.

77. Van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting. *Clin Nutr.* 2014;33(1):39-58. Epub 2013

78. Streiner, David L., Geoffrey R. Norman, and John Cairney. *Health measurement scales: a practical guide to their development and use*. Ch. 10 Validity. Oxford university press, 2008.

79. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: A prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck*. 2005;27(8):659-668.

80. Isenring E, Bauer J, Capra S. The scored Patient-generated Subjective Global Assessment (PGSGA) and its association with quality of life in ambulatory patients receiving radiotherapy. *Eur J Clin Nutr*. 2003; 57(2): 305-309.

81. Steenson J, Vivianti A, Isenring E (2013) New clinicians require ongoing training to ensure high inter-rater reliability of the Subjective Global Assessment. *Nutrition*. 2013; 29(1):361-2. doi: 10.1016/j.nut.2012.03.005.30.

Chapter 3. Translation and cultural adaptation of the scored Patient-Generated Subjective Global Assessment (PG-SGA): an interdisciplinary nutritional instrument appropriate for Dutch cancer patients

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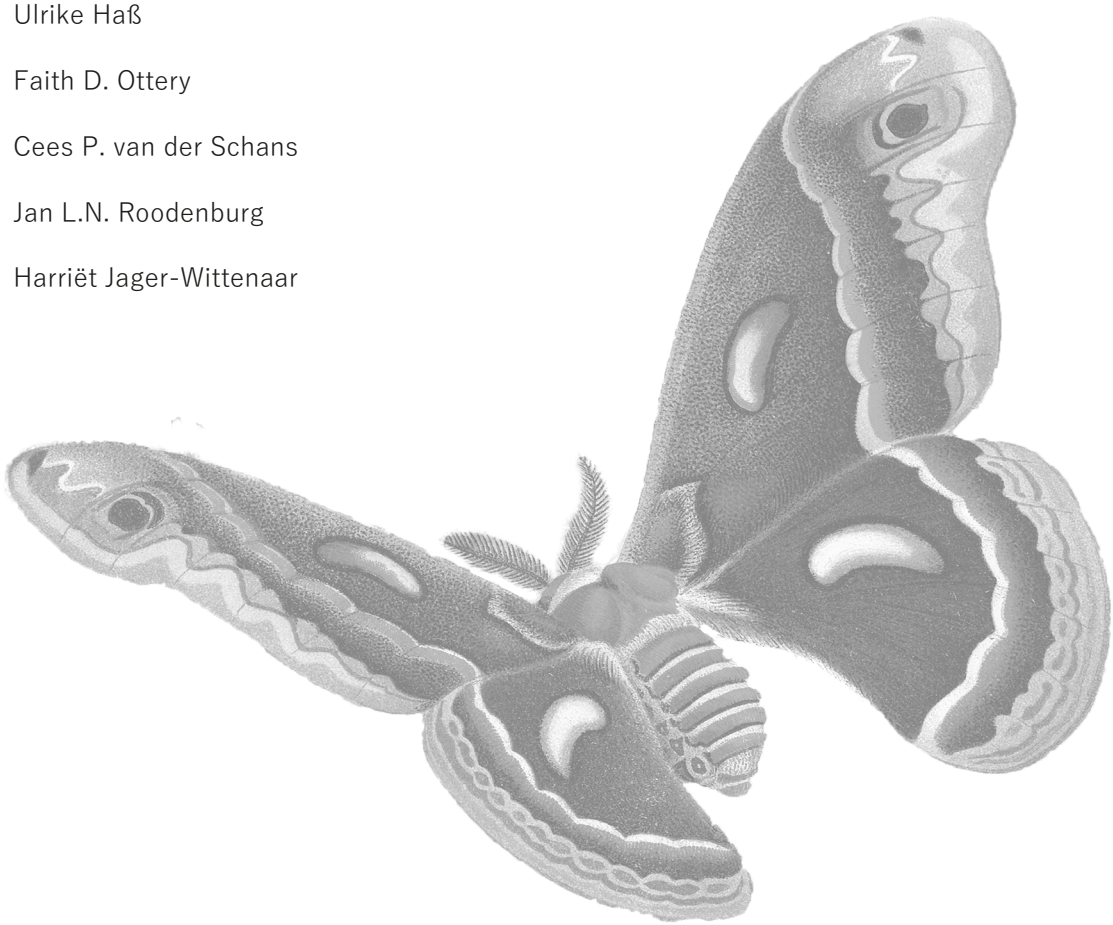

Abstract

Background: The Scored Patient-Generated Subjective Global Assessment (PG-SGA) is an instrument that enables interdisciplinary assessment of malnutrition and its risk factors, which is not available in Dutch.

Objective: Translation and cultural adaption of the original English PG-SGA to the Dutch setting.

Methods: The Scored PG-SGA was translated and culturally adapted, following ISPOR principles. Perceived content validity, comprehensibility and difficulty were explored among a multidisciplinary sample of healthcare professionals and their cancer patients. Content validity, comprehensibility and difficulty were operationalized by calculating item and scale indices. On scale level, indices of 0.80-0.90 were considered acceptable and indices of ≥0.90 were considered excellent.

Results: Consensus was reached on 91 and 8 differences in the forward and back translations respectively. Scale Content Validity Index was 0.89. Scale Comprehensibility Index (S-CI) and Scale Difficulty Index (S-DI) of the patient-generated component of the PG-SGA were 0.99 and 0.96, respectively. S-CI and S-DI of the professional component were 0.81 and 0.55, respectively.

Conclusions: Translation and cultural adaptation of the PG-SGA according to ISPOR principles resulted in a Dutch version that maintained purpose, meaning and format and has acceptable content validity. Now a Dutch version of the PG-SGA is available that is considered comprehensible and easy by patients, and comprehensible and relevant by professionals.

However, the professional component was considered difficult by the PG-SGA naive healthcare professionals, which indicates a need for training of professionals.
Implications for Practice: A similar systematic approach for future translations of the PG-SGA is recommended, to safeguard cultural equivalence.

Introduction

Malnutrition has been defined as "An acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition and inflammatory activity has led to a change in body composition and diminished function".[1] Patients with cancer who develop malnutrition during the course of their illness are at risk for treatment complications, more frequent and longer hospital stays, reduced quality of life and higher mortality.[2-5] Patients with cancer often have symptoms that may negatively impact nutritional intake, such as loss of appetite, nausea, and fatigue, due to the disease itself or due to treatments such as surgery, chemotherapy and radiotherapy.[6,7] For this reason, patients with cancer are particulary at risk for developing malnutrition. Prevalence of malnutrition in cancer patients is estimated to range from 30 to 60%.[4,8,9] However, these estimations depend on the malnutrition criteria used and on the cancer type and timing of the assessment.[6,10] When there is no effective assessment of malnutrition and its underlying risk factors,[11] malnutrition often goes unrecognized by medical and nursing staff, hindering effective treatment to improve nutritional status.[12,13] To enable more proactive rather than reactive nutritional care for patients with cancer, interdisciplinary collaboration of healthcare professionals that are involved in the nutrition care process, such as nurses, dietitians and physicians, is needed.[14] Hence, a validated

instrument that assesses malnutrition and its underlying risk factors, and that facilitates interdisciplinary care, is required to enable routine provision of appropriate nutritional care for cancer patients.[15]

Scored Patient-Generated Subjective Global Assessment

The Scored Patient-Generated Subjective Global assessment (PG-SGA; Copyright FD Ottery, 1996, 2001, 2005, 2006) is a tool that is recognized widely in the nutritional field and exhibits a unique set of properties: 1) the PG-SGA is reportedly a simple instrument to use[16] and can be used as a nutritional screen and assessment;[17,18] 2) the PG-SGA addresses the full breath of the construct of malnutrition as defined, containing items concerning nutrient balance; body shape, size and composition; function; and inflammatory activity;[1,19] 3) the PG-SGA helps identifying problems that may disguise malnutrition such as imbalance in fluid status;[16] 4) the PG-SGA includes both patient- and professional-reported items, thus providing accumulated insight from both perspectives in the nutritional status of the patient; 5) the PG-SGA identifies specific nutritional impediments allowing personalized medical and nutritional interventions;[20] and 6) the PG-SGA facilitates interdisciplinary planning of the global patient care process by triaging for interventions by nurse, dietitian and/or physician.[14,15] The PG-SGA was first validated in the oncology setting.[18,21-23] It has subsequently been validated in other settings, such as the nephrology and geriatric setting.[24,25] In addition, the PG-SGA has been utilized as a reference method to evaluate nutritional status in patients with cancer. [26-28] The totality of publications worldwide, well over 100 articles as referenced in PubMed with the search term 'PG-SGA', reflects the extensive clinical and research interest in this instrument.[29]

The PG-SGA was developed as a modification of the Subjective Global Assessment tool.[30] The scored version of the PG-SGA consists of two components. First, the patient-generated component was designed to be completed by the patient. For clarity, the items in this component were delineated as four Boxes.[21] Box 1 addresses weight history and addresses intermediate (1 month), chronic (6 months), and acute (2 weeks) weight change. Box 2 addresses food intake, including changes in type, amount and consistency of nutrient intake. Box 3 addresses symptoms and other impediments that may negatively influence food intake. Examples of nutrition impact symptoms can include no appetite, nausea, constipation, and problems with swallowing. Box 4 includes activity and function based on the Eastern Cooperative Oncology Group (ECOG) performance status, converted to layman's language.[31] These four Boxes were designed to reflect approximately 80-90% of the scorefor any given patient, and are officially known as the PG-SGA Short Form (PG-SGA SF), at times referred to in the literature as the abridged PG-SGA.[23] The PG-SGA SF has been validated as an independent screening tool for malnutrition and its risk factors.[17,32]

Second, the items in the professional component were developed as Worksheets to provide self-contained training and raise awareness of contributors to malnutrition that in clinical practice may easily be overlooked, such as metabolic stress, e.g. fever and corticosteroids.[21] The professional component includes five Worksheets and is completed by the healthcare professional; this may include the dietitian, nurse, physician, physiotherapist or others involved in the clinical care of the patient. Worksheet 1 includes instructions on how to score the percentage weight loss relevant to Box 1. Worksheet 2 addresses multiple conditions that may increase nutritional risk or requirements. Additionally, age >65 years was included as a factor

related to risk for malnutrition. Worksheet 3 addresses metabolic stress, based on fever (degree and duration), and use of corticosteroids. Worksheet 4 addresses the scoring of muscle status (i.e., deficit/loss of muscle mass and/or muscle tone), fat stores, and fluid status (specifically fluid excess), based on the nutrition focused physical examination. Worksheet 5 categorizes the overall global assessment of the patient, utilizing the findings of the patient-generated component (Boxes 1-4) and the physical exam (Worksheet 4). Categories include Stage A = Well nourished; Stage B = Moderately malnourished or suspected malnutrition; or Stage C = Severely malnourished.[21]

In contrast to the categorical assessment, the PG-SGA numerical score allows triage for interdisciplinary interventions as well as a means to monitor outcomes of these interventions. The additive score is used to guide interdisciplinary interventions including patient and carer education, symptom management including pharmacologic intervention, and nutritional intervention (food, nutritional supplements, enteral, or parenteral nutrition).

Triage recommendations based on PG-SGA point score are as follows:

0-1 No intervention required at this time. Re-assessment on routine and regular basis during treatment.

2-3 Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.

4-8 Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).

≥ 9 Indicates a critical need for improved symptom management and/or nutrient intervention options.[22]

Rationale for translation and cultural adaptation

Given the ability to identify both malnutrition and its underlying risk factors, as well as providing nutritional triage recommendations that may facilitate tailored interdisciplinary care, in the Netherlands the PG-SGA could provide a valuable addition to the instruments that are currently available, such as Malnutrition Universal Screening Tool (MUST)[33] and Short Nutritional Assessment Questionnaire (SNAQ)[34]. However, the PG-SGA was originally developed in English, and until now an official Dutch translation was not available. To enable use of the PG-SGA in other lingual and cultural settings than the original one, high quality versions of the original English PG-SGA in other languages are needed. However, straight forward translation of the PG-SGA may alter its purpose and meaning, since differences exist between languages, and additionally differences may exist between the corresponding cultures. Cultures comprise ideas, customs and social behavior of a group of people and include their concepts of health and illness and levels of literacy.[35] Differences between the source culture and the target culture may influence the cultural equivalence of an instrument.[36-38] However, if instead a cultural adaptation process for the target culture is employed, several levels of equivalence can be safeguarded.[35,36] Conceptual equivalence refers to the level to which the concept that is measured by the instrument exists, is relevant, and is accepted in both the source culture and the target culture.[39] The degree to which the instrument has an appropriate sample of items for the concept being measured has been defined as content validity.[40] Semantic equivalence is obtained when the meaning of the instrument is maintained in both the target and source language. This implies the items should be perceived equally comprehensible and difficult in the target and the original culture.[35,39] Comprehensibility, i.e.

clarity or understandability, is related to the clarity of the wording used in the instrument. Difficulty is related to the level of knowledge or skills of the person completing the instrument. Additionally, operational equivalence is obtained when the level to which the mode of administration, the format of the instrument, the reading level and the item format are appropriate for the target culture. In this study, we aimed to systematically translate and culturally adapt the original English PG-SGA for the Dutch setting, while safeguarding conceptual, semantic and operational equivalence and including exploration of content validity as perceived by healthcare professionals, and of comprehensibility and difficulty as perceived by patients and healthcare professionals.

Methods

Authorization

We received authorization from the key developer and copyright holder of the PG-SGA to translate the original English PG-SGA into Dutch (reference 9601.2016). All documentations pertaining to the translation, including item history, cognitive debriefing, and decisions made, were made available to the key developer of the PG-SGA. All the translation steps and the final Dutch version of the PG-SGA have been approved by the key developer of the PG-SGA. The Medical Ethics Committee of the University Medical Center Groningen ruled that no permission was needed to perform the study (reference M13.137580), because the study was not under regulation of the Medical Research Involving Human Subjects Act.

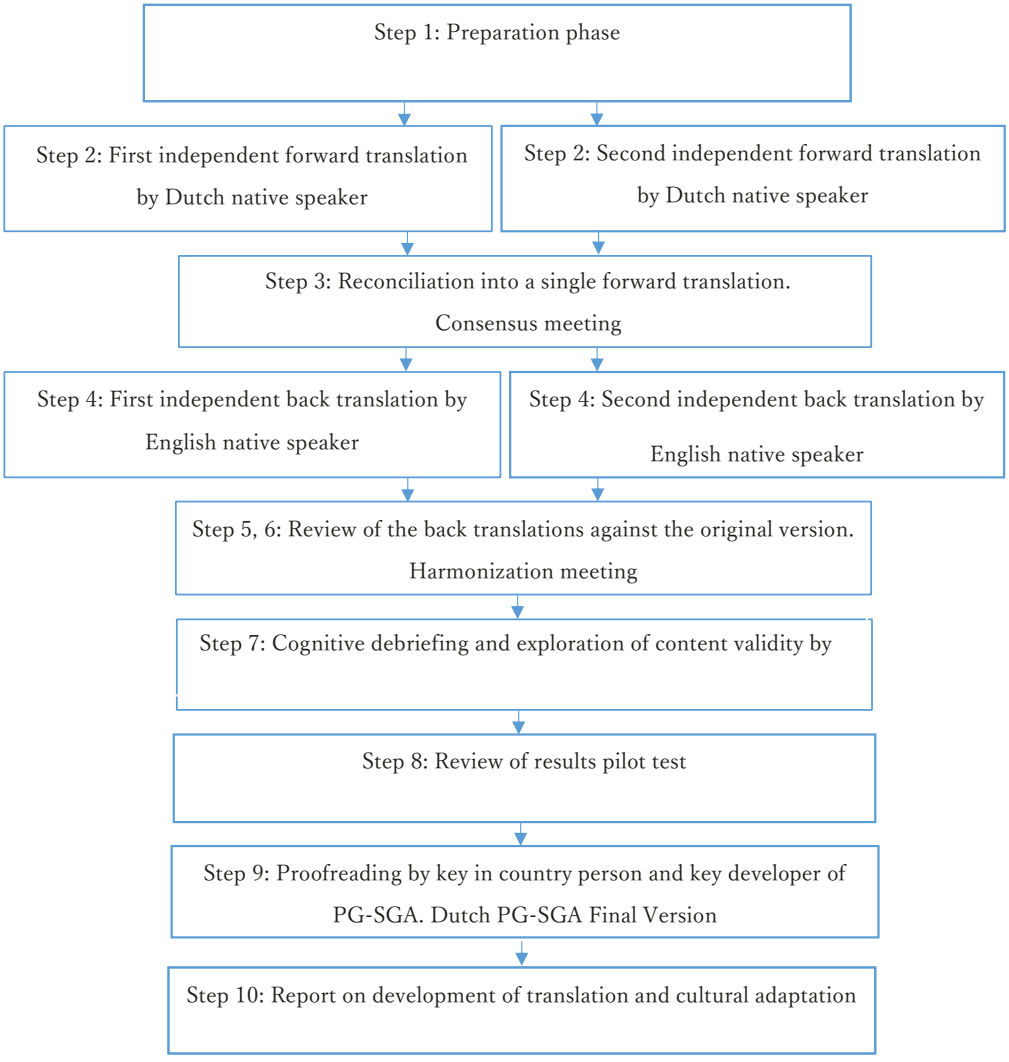

Figure 1. Flowchart of development Dutch PG-SGA ISPOR Principles of Good Practice for the Translation and Cultural Adaption Process for PRO Measures

Procedures

Between February 2013 and August 2014, the Dutch version of the PG-SGA was developed according to the ten steps of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) *Principles of Good Practice for the Translation and Cultural Adaptation Process for PRO Measures* (further referred to as ISPOR principles)[41] (Figure 1). Conceptual, semantic, and operational equivalence were addressed and tested by following the first nine steps of the ISPOR guideline, to validate the translation and adaptation process.

Step 1 Preparation Phase. During the preparation phase, the project coordinator initiated first contact with the key developer of the original version of the PG-SGA and with professional translators for the forward and back translations.

Step 2 Forward translation. The initiator of the project, further referred to as the 'key country person', provided the first forward translation of a large print version of the PG-SGA (©FD Ottery, 2005), using a landscape orientation. She is a native Dutch speaker with sufficient knowledge of the English language, an experienced dietitian in the cancer setting, and an expert on the subject of nutritional assessment. Additionally, a professional and native Dutch speaking translator with no special knowledge of patients with cancer or nutritional assessment was instructed to conceptually translate the same version of the English PG-SGA and independently provided a second forward translation.

Step 3 Reconciliation. The project coordinator, the key country person, and the corresponding author in the role of independent translator discussed conceptual and semantic differences between the two independent forward translations into Dutch that were the result of Step 2. Both forward translations were compared to the original English version and discussed, until

consensus was reached on all nuances. This step resulted in the first version of the Dutch PG-SGA.

Step 4 Back translation. Two English native-speaking professional translators, of which one of United States origin and one of New Zealand origin, with no special knowledge on the subject of cancer or nutritional status, performed two independent conceptual back translations of the Dutch PG-SGA version that was the result of Step 3 into English.

Step 5, 6 Back translation review and harmonization. These steps were combined in a single panel meeting. The purpose of the back translation review and harmonization was to ensure conceptual and semantic equivalence, and to design a prototype version of the Dutch PG-SGA. All differences between the original English version and the two back translations were discussed in a meeting that was prepared and led by the project coordinator and further attended by the key country person and the corresponding author. Additionally, the Dutch version that resulted from Step 3 (Reconciliation) was adapted if needed, to harmonize with the original English version.

Step 7 Exploration of content validity and cognitive debriefing. In May 2013, two samples, one consisting of Dutch patients and one consisting of Dutch healthcare professionals, were informed about the project, and gave their written consent before participating in the study. Both patients and healthcare professionals had no experience with the PG-SGA. Dietitians, nurse practitioners and medical interns working in the oncology setting and who were inexperienced with the PG-SGA were asked to recruit one of their patients to complete the patient-generated component of the PG-SGA, and to have the patients complete a questionnaire. This 55-item questionnaire included 47 four-point scale items regarding

perceived comprehensibility and difficulty of the items of the patient-generated component of the PG-SGA (Boxes 1 to 4). The remaining eight items of the questionnaire concerned facultative open ended questions to identify potential barriers regarding comprehensibility, difficulty and operational aspects of the PG-SGA.

Subsequently, the healthcare professionals were asked to carefully study the full PG-SGA and complete the professional component (Worksheet 1-5 and numerical score) of the PG-SGA. The professionals were then asked to complete a 134-item questionnaire, consisting of 124 four-point scale items regarding content validity of the items of the full PG-SGA, as well as perceived comprehensibility and difficulty of the items of the professional component of the PG-SGA. The remaining ten items posed to the healthcare professionals concerned facultative open ended questions, to identify potential barriers concerning content validity, comprehensibility, difficulty and operational aspects of the PG-SGA. The distribution of items per concept and component of the PG-SGA is presented in Table 1. For the exploration of content validity, a sample of three to eight healthcare professionals was considered adequate.[40,42] For the cognitive debriefing, a sample of five to eight patients, and a sample of five to eight healthcare professionals was considered adequate.[41]

Step 8 Review of exploration of content validity and cognitive debriefing results. The results of the questionnaire posed to patients and the questionnaire posed to the professionals were reviewed by the project coordinator and the corresponding author.

Table 1. Distribution of questionnaire items related to concepts and PG-SGA components

Concept	Items Patient-generated component	Items Professional component
Content validity	38	26
Comprehensibility	38	34
Difficulty	9	26
Open ended questions	8	10

Step 9 Proofreading and finalization. The key country person and the key developer of the original PG-SGA performed elaborate proofreading on 10 December 2013 and 4 June 2014. During these sessions, operational differences that may influence clarity of the format on scale and item level were discussed and solved.

Step 10 Report on development of translation.

Operationalization of perceived content validity, comprehensibility and difficulty

A widely used approach to quantifying content validity, i.e. perceived relevance, is by reporting the content validity index (CVI).[40,42,43] In this approach, a sample of professionals rates each item of a scale or instrument to be relevant or not, for the construct to be measured. From these ratings, an item content validity index (I-CVI) is calculated that can be averaged into scale content validity indices (S-CVI). The S-CVI of the full PG-SGA reflects overall relevance of the instrument to the construct of malnutrition as perceived by healthcare professionals. The higher the S-CVI, the more consensus on the nature of the construct can be assumed.[40,42] To be able to quantify the concepts of comprehensibility and difficulty, the CVI-approach was

adapted for this study. Indices for item comprehensibility (I-CI)[44] and item difficulty (I-DI) were calculated and averaged into scale comprehensibility indices (S-CI) and scale difficulty indices (S-DI).

The following procedure was used to calculate all item and scale indices: A four point scale (1= very irrelevant/very unclear/very difficult; 2= irrelevant/ unclear/difficult; 3=relevant/clear/easy; 4=very relevant/very clear/very easy) was implemented, to avoid having a neutral and ambivalent midpoint and to dichotomize the results of each item.[40,45] This enabled us to decide whether content validity, comprehensibility and knowledge could be considered present or not for each item. Scores 1 and 2 were considered 'not present', scores 3 and 4 were considered 'present'. The I-CVI, I-CI and I-DI are proportional scores ranging from 0-1, calculated by dividing the number of respondents that considered the item to be 'present' by the total number of respondents. The S-CVI was calculated by averaging the I-CVI scores for the full PG-SGA. S-CI and S-DI of the patient-generated component of the PG-SGA were calculated by averaging I-CI scores and I-DI scores of Boxes 1 to 4. S-CI and S-DI of the professional component of the PG-SGA were calculated by averaging I-CI scores and I-DI scores of Worksheets 1 to 5. The scale indices S-CI and S-DI reflect overall comprehensibility and difficulty, as perceived by patients for the patient-generated component and as perceived by professionals for the professional component.

As predefined, an I-CVI above 0.78 was considered excellent and an I-CVI <0.78 requires further analysis of the item.[43] An S-CVI≥0.80-0.89 was considered acceptable and an S-CVI≥0.90 was considered excellent.[43,46] In agreement with the content validity approach, the same cutoff standards were applied to I-CI, I-DI, and S-CI and S-DI scores. Transparency of

response was provided by reporting overall item response. Patients and healthcare professionals' non-response to items was excluded from the calculation of the index scores. Respectively I-CI, I-DI and I-CVI per item; and S-CI, S-DI and S-CVI per scale were calculated in SPSS (19.0, IBM Inc.).

Results

The forward translation process provided the first two Dutch translations of the PG-SGA. During the reconciliation phase, consensus was reached on the 91 differences (29 patient-reported items and 62 professional-reported items) that were identified between the two forward translations into Dutch. The Dutch documentation of the reconciliation session can be provided upon request by the corresponding author. The back translation and harmonization process resulted in eight additional adaptations (five patient-reported items and three professional-reported items). Documentation of the back translation review and harmonization process is presented in Table 2. The harmonization process resulted in a five page document as prototype of the Dutch version of the PG-SGA.

Eight Dutch healthcare professionals completed the questionnaire developed for the professionals: six dietitians, one nurse practitioner and one medical intern. Within this sample, six healthcare professionals participated with a patient, resulting in six patients completing the questionnaire developed for the patients. The sample of patients consisted of four women and two men (aged 54-73 years) with cancer (head and neck cancer n=4, pancreas cancer n=1, ovarian cancer n=1). Data on difficulty of items of the professional component of the PG-SGA were missing in one healthcare professional.

TABLE 2. Documentation of adaptations made in the back translation review and harmonization meeting

Box	Reconciliation	Translator 1	Translator 2
Box 3 – Symptoms	moeite met slikken	difficulty swallowing	difficulty with swallowing
Box 4 – Activities and functioning	Van de afgelopen maand beoordeel ik mijn activiteiten als	I would assess my activities of the previous months as	Over the past month I would rate my activities as
Box 4 – Activities and functioning	beperkt in zware lichamelijke activiteit, maar ambulant en tot lichte arbeid in staat	limited heavy physical activity, but ambulant and able to perform light work	cannot do heavy physical activities, but moving about and able to do light work
Box 4 – Activities and functioning	slechts tot beperkte zelfverzorging in staat, meer dan 50% van de dag in bed of op stoel	only limited self-care, more than 50% of the day in bed or chair	unable to look after myself, spend more than half the day in bed or on a chair
Worksheet	**Reconciliation**	**Translator 1**	**Translator 2**
Worksheet 5 – Category – Stage B	licht tot matig ondervoed	mild to moderately malnourished	light to moderately malnourished
Worksheet 5 – Category – Stage B and C	aanwezigheid van symptomen die de voedingsinname kunnen verstoren	presence of symptoms that may disrupt the nutritional intake	presence of symptoms that could influence food intake
Worksheet 5-- Physical exam – stage B	duidelijk milde of matige depletie van vetmassa of spiermassa en/of spiertonus bij palpatie	marked mild or moderate depletion of fat mass or muscle mass and/or muscle tone during palpation	clear mild or moderate deficit in fat stores or muscle mass or tone on palpation

Original	Harmonization	Comments
problems swallowing	problemen met slikken	"problemen" implies the symptom is serious enough not to be able to eat. "moeite" could imply it takes more time but does not affect intake
Over the past month, I would generally rate my activity as	Ik beoordeel mijn activiteiten van de afgelopen maand over het algemeen als	to start with "Ik (I)" fits better in Dutch use of language; generally "over het algemeen" was added
restricted in physically strenuous activity but ambulatory and able to carry out light work	beperkt in zware lichamelijke activiteit, maar niet bedlegerig en tot lichte arbeid in staat	"ambulant" appears to difficult. "niet bedlegerig" is clearer to the patient
capable of only limited self-care; confined to bed or chair more than 50% of waking hours	slechts tot beperkte zelfverzorging in staat; meer dan 50% van de dag in bed of stoel	";"interpunction added to clarify "op" deleted
Original	**Harmonization**	**Comments**
moderately malnourished or suspected malnourished	matig ondervoed of verdenking ondervoeding	"verdenking ondervoeding" was changed to "licht tot matig" in the forward translated and is now changed back again
presence of nutrition impact symptoms (box 3 of PG-SGA)	aanwezigheid van symptomen die de voedingsinname verstoren	"kunnen" deleted, symptoms must have actually hindered intake as stated in box 3
evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	duidelijk milde of matige depletie van vetmassa en/of spiermassa en/of spiertonus bij palpatie	"en/of" added after "vetmassa" because it is different from "of"

TABLE 3. Indices for content validity, comprehensibility and difficulty for the patient-generated component of the Dutch PG-SGA as perceived by professionals and patients with cancer

Sample	professionals	patients	Patients
Item	I-CVI (N=8)[1]	I-CI (N=6)[2]	I-DI (N=6)[3]
Box 1: Weight			
1a. I currently weigh about _____ pounds	1.00	1.00	1.00
1b. I am about _____ feet _____ tall	1.00	1.00	1.00
1c. One month ago I weighed about _ pounds	1.00	1.00	1.00
1d. Six months ago I weighed about __ pounds	1.00	1.00	0.83
1e. During the past two weeks my weight has: decreased/ not changed/ increased	0.88	1.00	1.00
Box 2: Food intake			
2a. As compared to my normal intake. I would rate my food intake during the past month as:	1.00	1.00 (N=5)	0.83 (N=5)
2a1. unchanged	1.00	1.00 (N=5)	
2a2. more than usual	0.88	1.00 (N=5)	
2a3. less than usual	1.00	0.83	
2b. I am now taking:	0.86 (N=7)	1.00 (N=5)	1.00 (N=5)
2b1. *normal food* but less than normal amount	0.75	1.00 (N=5)	
2b2. little solid foods	0.86 (N=7)	1.00 (N=5)	
2b3. only liquids	0.88	1.00 (N=5)	
2b4. only nutritional supplements	0.88	1.00 (N=5)	
2b5. very little of anything	0.86 (N=7)	1.00 (N=5)	
2b6. only tube feedings or only nutrition by vein	0.88	1.00	
Box 3: Symptoms			
3a. I have had the following problems that have kept me from eating enough during the past two weeks:	1.00	1.00	1.00 (N=5)
3a1. no problems eating	0.88	1.00	
3a2. no appetite, just did not feel like eating	1.00	1.00	
3a3. Nausea	1.00	1.00	
3a4. Constipation	1.00	1.00	

TABLE 3. Continued

Sample	**professionals**	**patients**	**patients**
Item	I-CVI (N=8)[1]	I-CI (N=6)[2]	I-DI (N=6)[3]
3a5. mouth sores	1.00	1.00	
3a6. things taste funny or have no taste	0.88	1.00	
3a7. problems swallowing	1.00	1.00	
3a8. pain, where?	1.00	1.00	
3a9. Vomiting	1.00	1.00	
3a10. Diarrhea	0.88	1.00	
3a11. dry mouth	0.88	1.00	
3a12. smells bother me	1.00	1.00	
3a13. feel full quickly	1.00	1.00	
3a14. Fatigue	1.00	1.00	
3a15. other: ……..	0.88	1.00	
Box 4. Activities and Function			
4a. Over the past month, I would generally rate my activity as:	1.00	1.00 (N=5)	1.00 (N=5)
4a1. normal with no limitations	1.00	1.00 (N=5)	
4a2. not my normal self, but able to be up and about with fairly normal activities	1.00	1.00 (N=5)	
4a3. not feeling up to most things, but in bed or chair less than half the day	1.00	1.00 (N=5)	
4a4. able to do little activity and spend most of the day in bed or chair	1.00	1.00 (N=5)	
4a5. pretty much bedridden, rarely out of bed	1.00	1.00 (N=5)	
Scale Indices Patient Generated Component	**S-CVI[4]** = 0.95[7]	**S-CI[5]** =0.99[8]	**S-DI[6]** = 0.96[9]
Overall item response	99%	94%	93%

[1]I-CVI: item-content validity index; [2]I-CI: item-comprehensibility index; [3]I-DI: item-difficulty index

[4]S-CVI: scale-content validity index; [5]S-CI: scale-comprehensibility index; [6]S-DI: scale-difficulty index

[7]incl. non-response: 0.94; [8]incl. non response: 0.93; [9]incl. non response: 0.89

I-CVI /I-CI/I-DI>0.78 excellent; S-CVI/S-CI/S-DI>0.80 acceptable; S-CVI/S-CI/ S-DI>0.90 excellent

TABLE 4. Indices for content validity, comprehensibility and difficulty for the professional component of the Dutch PG-SGA as perceived by professionals

Sample	professionals	professionals	professionals
Item	I-CVI (N=8)[1]	I-CI (N=8)[2]	I-DI (N=7)[3]
Worksheet 1: Scoring Weight Loss	0.88	1.00	0.83 (N=6)
Worksheet 2: Disease and its relation to nutritional requirements	1.00	0.88	0.83 (N=6)
2a. All relevant diagnoses	1.00	0.75	0.71
2b. Primary disease stage	1.00 (N= 6)	0.75	0.71
2c. Age	0.86 (N=7)	1.00	1.00
Worksheet 3: Metabolic Demand			
3a. Fever	0.88	0.88	0.71
3b. Fever duration	0.88	0.88	0.71
3c. Corticosteroids	1.00	0.88	0.86
Worksheet 4: Physical Exam	0.29 (N=7)	0.75	0.20 (N=5)
4a. Muscle Status			
4a1. Temples (temporalis muscle)	0.71 (N=7)	0.75	0.40 (N=5)
4a2. Clavicles (pectoralis & deltoids)	0.71 (N=7)	0.75	0.40 (N=5)
4a3. Shoulders (deltoids)	0.86 (N=7)	0.75	0.40 (N=5)
4a4. Interosseous muscles	0.43 (N=7)	0.50	0.17 (N=6)
4a5. Scapula	0.57 (N=7)	0.75	0.40 (N=5)
4a6. Thigh (quadriceps)	0.86 (N=7)	0.75	0.20 (N=5)
4a7. Calf (gastrocnemius)	0.67 (N=6)	0.75	0.20 (N=5)
4b. Fat stores	0.86 (N=7)	0.75	0.20 (N=5)
4b1. Orbital fat pads	0.71 (N=7)	0.75	0.60 (N=5)
4b2. Triceps skinfold	0.86 (N=7)	0.88	0.60 (N=5)
4b3. Fat overlying lower ribs	0.86 (N=7)	0.75	0.20 (N=5)
4c. Fluid status	1.00 (N=7)	0.88	0.60 (N=5)
4c1. Ankle edema	0.57 (N=7)	1.00	0.80 (N=5)

Table 4. Continued

Sample	**professionals**	**professionals**	**professionals**
Item	I-CVI (N=8)[1]	I-CI (N=8)[2]	I-DI (N=7)[3]
4c2. Sacral edema	0.63	0.75	0.60 (N=5)
4c3. Ascites	0.88	0.88	0.60 (N=5)
Worksheet 5 Global Assessment Categories	1.00 (N=6)		0.60 (N=5)
5a. Weight		0.88	
5b. Nutrient intake		0.88	
5c. Nutrition Impact Symptoms		0.88	
5d. Functioning		0.75	
5e. Physical exam		0.88	
Global PG-SGA Rating	1.00 (N=7)	0.75	0.71
Triage 0-1: No intervention required at this time		0.88	
Triage 2-3: Patient & family education		0.75	
Triage 4-8: intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms.		0.88	
Triage ≥9: critical need for improved symptom management and/or nutrient intervention options		0.63	
Scale Indices Professional Component	**S-CVI[4] =** 0.81[7]	**S-CI[5] =** 0.81	**S-DI[6] =** 0.55[8]
Item response Professional Component	90%	100%	81%
Scale Indices Full PG-SGA	**S-CVI[4] =**0.89[9]		
Overall item response	95%		

[1]I-CVI: item-content validity index; [2]I-CI: item-comprehensibility index; [3]I-DI: item-difficulty index; [4]S-CVI: scale-content validity index; [5]S-CI: scale-comprehensibility index; [6]S-DI: scale-difficulty index; [7]incl. non-response: 0.72; [8]incl. non-response: 0.46; [9]incl. non-response: 0.86; I-CVI /I-CI/I-DI>0.78 excellent ; S-CVI/S-CI/S-DI>0.80 acceptable; S-CVI/S-CI/ S-DI>0.90 excellent

The indices for content validity, comprehensibility and difficulty for the patient-generated component and the professional component of the Dutch PG-SGA are presented in Table 3 and Table 4. Content validity of the overall PG-SGA was perceived sufficient for the assessment of malnutrition on scale level (S-CVI: 0.89 [overall item response 95%]). Professionals' individual S-CVI scores ranged from 0.81 to 1.00 for content validity. Cancer patients perceived comprehensibility and level of difficulty of the patient-generated component of the Dutch translation of the PG-GSA as excellent (S-CI: 0.99 [overall item response 94%]; S-DI: 0.96 [overall item response 93%]). Patients' individual S-CI scores ranged from 0.95 to 1.00 for comprehensibility and individual S-DI scores ranged from 0.88 to 1.00 for difficulty. Comprehensibility of the professional component of the PG-SGA was experienced as acceptable on scale level (S-CI: 0.81 [overall item response 100%]). Professionals' individual S-CI scores ranged from 0.44 to 1.00 for comprehensibility. Difficulty of the professional component of the PG-SGA was graded under the predefined cutoff for acceptability on scale level (S-DI: 0.55 [overall item response 81%]). Professionals' individual S-DI scores ranged from 0.39 to 0.89.

The patients' answers to the open ended questions showed that one out of six patients perceived question 2a, “As compared to my normal intake, I would rate my food intake during the past month as: unchanged; more than usual; less than usual” from Box 2 (Food intake) as difficult to answer. Two out of six patients missed answering possibilities that were relevant to them in question 2b, “I am now taking …”. One patient reported that he would have liked to add the following answer: “more food than usual”, and the other patient reported he would have liked to add the option of: “a little solid food and nutritional supplements”. One out of six patients was in frail condition and preferred the dietitian to read the questions and answering possibilities and complete the patient’s answers.

The healthcare professionals' answers to the open ended questions did not reveal any additional aspects of malnutrition that were not measured by the PG-SGA. Six out of eight healthcare professionals had difficulties completing the items concerning the physical examination, because they lacked experience and training regarding the physical exam. Two of these six stated they would need additional training in order to perform this section of the PG-SGA. Six out of eight healthcare professionals considered the elaborateness of the five page template prototype and the time needed to complete the instrument a barrier for them for applying the Dutch PG-SGA in daily practice. Six out of eight healthcare professionals felt that the PG-SGA offers a complete malnutrition assessment.

The proofreading mainly resulted in adaptations of the template of the PG-SGA. The five-page layout was considered a barrier. It should be noted that this format was not consistent with the original template of the PG-SGA, thus the size was confined to two pages A4 size, conforming to the template of the original large print version of the PG-SGA (©2005), using a landscape orientation. Because of these adaptations, on the front page a larger print could be used for the patient-generated component, to improve readability. Professional-generated items and summarized scoring were placed on the back page, conform the template of the 2005 PG-SGA version. The final appropriately formatted version of the Dutch PG-SGA, which has been authorized by the key developer and officially published on www.pt-global.org on 12 August 2014, is presented in Figure 2.[47]

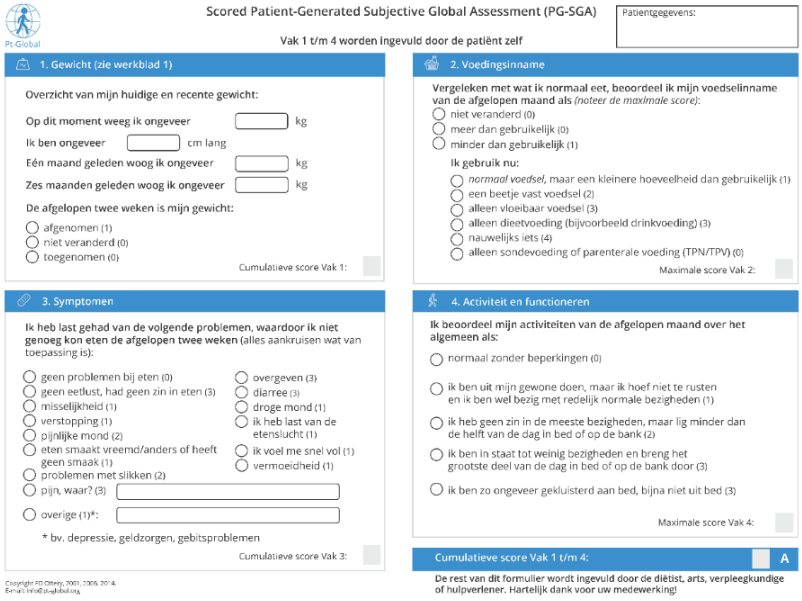

FIGURE 2a. Final Version of the Dutch PG-SGA 12 August 2014: patient component

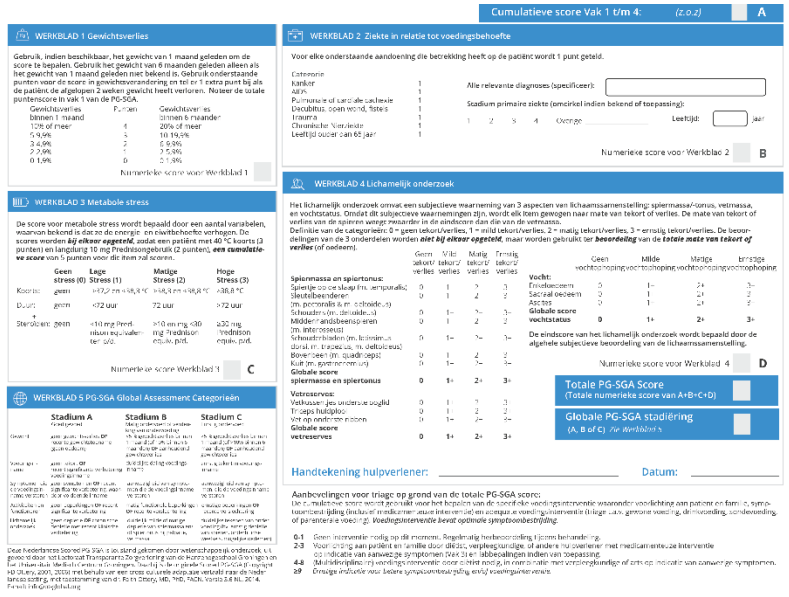

FIGURE 2b. Final Version of the Dutch PG-SGA 12 August 2014: professional component

Discussion

Translation and cultural adaptation of the English PG-SGA (© 2005) according to ISPOR principles resulted in a Dutch version that maintained purpose, meaning and format and has acceptable content validity. Forward and back translation by multiple independent translators, cognitive debriefing in patients and healthcare professionals, and consulting the key developer during the developmental phase enabled safeguarding of conceptual, semantic and operational equivalence.

During the cognitive debriefing, the sample of patients with cancer perceived both comprehensibility and difficulty of the patient-reported component of the prototype version of the Dutch PG-SGA as excellent. This high level of perceived comprehensibility and difficulty suggests feasibility of completion of the patient-generated component, i.e. Boxes 1 to 4, of the PG-SGA or PG-SGA SF by Dutch patients without further instruction. The feasibility of completion of Boxes 1 to 4 by the patient is supported by results from a translation and cultural adaptation study of the PG-SGA that was previously performed for the Brazilian Portuguese setting. In that study in a sample of patients in which 65% had a low education level, a high score for comprehensibility (S-CI >0.80) was reported for all patient-reported items.[44] In our study, two patients suggested additional choices for the item "I am now taking …" in Box 2 (Food intake) in reply to the open ended questions, implying that not all possible alternatives are fully covered in this Box. Although this important observation is noted, adding answering possibilities in the Dutch version at this time is not desirable, as this may affect the PG-SGA score, and thus operational equivalence with the original instrument.

During the exploration of content validity and cognitive debriefing, the sample of PG-SGA naive healthcare professionals perceived content validity, i.e., relevance of the full PG-SGA

(patient-generated plus professional component) to the construct of malnutrition, acceptable on scale level. The healthcare professionals also perceived comprehensibility of the professional component acceptable on scale level. However, the items on the physical examination scored lower for both content validity and comprehensibility. The healthcare professionals scored difficulty of the professional component below acceptable on scale level, of which the items on the physical examination scored lowest. These results for the items of the physical examination suggest that an item perceived as difficult is also at risk to be considered less important, e.g. when knowledge on the subject of the item is lacking, it is also harder to decide whether the item is relevant to the construct. The results for comprehensibility of the physical examination also indicate that if an item is regarded difficult by a respondent, the item is also at risk of being considered harder to comprehend. This may be due to use of vocabulary not suitable to the level of the respondent.[48]

Customized approaches may be appropriate to solve problems related to content validity, comprehensibility, or difficulty of the PG-SGA. Items with low content validity may be improved by adapting the item to adequately represent the construct of malnutrition as perceived in the target culture.[35] Items that lack comprehensibility may be improved by clarifying the formulation of the description of the item, to make this item more understandable. Problems regarding difficulty may be prevented by providing instruction or training, to improve knowledge of the respondent regarding the item.[48] In this study, two items from Worksheet 2: “relevant diagnoses” and “stage of disease” were scored slightly below the cutoff for acceptability by healthcare professionals. Because the problem concerns the concept of comprehensibility, this implies the level of comprehensibility can be improved by clarifying the formulation. To improve comprehensibility for professionals

such as nurses, dietitians and physicians, an additional instruction including further explanation of Worksheet 2 is currently being developed.

The I-DI scores for the physical examination were the most striking, with scores ranging from 0.17 to 0.80, and an average of 0.41. The answers to the open ended questions also suggest the physical exam was perceived difficult by the sample of healthcare professionals that were inexperienced with the PG-SGA. The nature of the concept difficulty implies the level of perceived difficulty can be influenced by improving the level of skill or knowledge. This agrees with the need for further instruction and training regarding the physical examination that was expressed by the healthcare professionals. Since a lack of experience with the physical examination may explain the scores for difficulty, additional training may have a positive effect on professionals' competence to perform the physical examination. The Subjective Global Assessment (SGA)[30] contains the same type of items concerning the physical examination as the PG-SGA. In a study on interrater reliability (IRR) of the SGA, more experienced healthcare professionals (>5 years after graduation) showed an IRR of 89-100% when compared to a well- trained and experienced dietitian (>20 years after graduation), whereas less trained and experienced healthcare professionals (1-2 years after graduation) showed an IRR of 56-100%.[49] To test whether additional instruction improves the level of perceived difficulty and consequently also comprehensibility of the PG-SGA, we developed a training course. The training was tailored to the needs reported by professionals, with emphasis on the physical examination. The effect of this training on perceived comprehensibility and difficulty of the Dutch PG-SGA by healthcare professionals will be reported in a separate article.

Implications for research and practice

The data from this study suggest that translation and cultural adaptation of the PG-SGA according to ISPOR Principles is an effective strategy to maintain purpose, meaning and format of the original PG-SGA. A similar systematic approach for future translations of the PG-SGA into other languages is recommended, to safeguard cultural equivalence of the instrument. Although good concurrent and predictive validity of the original English PG-SGA for assessment of malnutrition and its risk factors have been shown,[18,21,23] further research is needed to explore psychometric characteristics of the Dutch PG-SGA in the Dutch setting. In addition, generalizability of the results to patient groups that were beyond our scope needs to be explored.

The translated and culturally adapted PG-SGA is now available for the Dutch setting and may help facilitate to an efficient, interdisciplinary, and collaborative nutrition care process. Enabling patients to complete the PG-SGA SF at home or in the waiting room addresses in a non-stressful, time flexible but standardized manner a way to address issues that are relevant to the patient and carer, provides an opportunity to save time for the professional, and provides the full interdisciplinary team with information on malnutrition and underlying risk factors. As a result, this may facilitate personalized identification and treatment of impediments and may lead to an improved nutritional care approach with the objective to improve nutritional and other related outcomes. In addition to the PG-SGA SF, the professional component of the PG-SGA can be completed by, for instance, a dietitian, nurse or physician to collect more detailed information. Subsequently, the identification of specific impediments combined with specific nutritional triage

recommendations may help initiating personalized symptom management and/or nutrition intervention.

Strengths and limitations

The strengths of the research include that, in addition to the patient-reported items, the professional-reported items of the PG-SGA were translated and culturally adapted. The ISPOR Principles have been developed and deployed for instruments that contain patient-reported items.[41] However, the PG-SGA additionally contains professional-reported items. By using the ISPOR Principles within the professional-reported section, we came across 62 differences resulting from the two forward translations, and three differences resulting from the two back translations. These differences would not have been noticed with a single forward translation. Cultural equivalence of the professional component of the original instrument might have been affected if these differences had remained unnoticed. Additionally, exploring comprehensibility and difficulty of the professional-reported items of the PG-SGA during the cognitive debriefing resulted in clear information on professionals perceiving difficulty with the physical examination. Hence, following the steps of the ISPOR Principles contributed to the quality of the translated instrument, for both the patient-generated component and the professional component of the PG-SGA.

To the best of our knowledge, this study is the first translation and cultural adaptation study to explore the three concepts content validity, comprehensibility, and difficulty concomitantly, using indices. We were not able to explore conceptual and semantic equivalence with a sample from the source culture, for instance by comparing results of semi-structured interviews with a representative set of patients from the target culture to results of similar interviews with a representative set of patients from the source culture.

Still, an acceptable level of content validity, comprehensibility and difficulty is needed for the instrument to be able to perform accurate measurements.[48] Thus, we decided to quantify perceived content validity, comprehensibility and difficulty, and compare the results to a predefined cutoff value. We found it useful to distinguish between content validity, comprehensibility and difficulty, because the different concepts imply customized approaches to solve problems.

We included healthcare professionals that had no previous experience with the PG-SGA to safeguard unbiased cultural perception of content validity, comprehensibility and difficulty of the instrument. Since healthcare professionals did not receive any instruction prior to the completion of the PG-SGA, lack of experience may have affected the results of this study. For instance, healthcare professionals reported the time needed for completion of the PG-SGA as a barrier, while their own unfamiliarity with the instrument has probably extended the time needed for completion.

The study has some limitations. First, the sample size used to explore content validity, comprehensibility and difficulty was small. Although according to ISPOR Principles the number of six patients can be considered an adequate sample size,[41] the population of patients with cancer is rather heterogeneous, which may call for a somewhat larger sample of patients to cover the breath of the population. However, we attempted to acquire sufficient data density by employing an extensive questionnaire of 47 items and eight open ended questions regarding comprehensibility and difficulty of the patient-generated component of the PG-SGA. In addition, patients and their health care professionals were included in the translation and cultural adaptation process together, which allowed simulating a situation of daily practice. Second, some selection bias in this cognitive debriefing cannot be excluded, as healthcare professionals might have selected motivated

patients or patients with adequate cognitive function to participate in the pilot test. Additionally, level of education was not regarded in this study and underestimation or overestimation of the patients' results due to a lower or higher than average education level in our study cannot be excluded. To confirm the patient-generated results, further testing of the PG-SGA SF in a larger set of randomly selected patients is recommended. Finally, the lay out of the prototype version of the PG-SGA that was used during the cognitive debriefing, was not according the lay out of the 2005 landscape version of the PG-SGA. Importantly, this prototype version of the PG-SGA consisted of five pages and this elaborateness likely extended the time needed for completion.

Conclusion

Translation and cultural adaptation of the PG-SGA according to ISPOR Principles resulted in a Dutch version that maintained purpose, meaning and format and has acceptable content validity. Now a Dutch version of an instrument is available that assesses malnutrition, identifies nutrition impact symptoms and guides interdisciplinary planning of the nutrition care process. The Dutch version of the PG-SGA is considered comprehensible and easy by patients, and comprehensible and relevant by professionals. However, the professional component was considered difficult by the PG-SGA naive professionals, which indicates a need for appropriate training of healthcare professionals. A similar systematic approach for future translations of the PG-SGA is recommended, to safeguard cultural equivalence. Further studies related to the validity and reliability of the Dutch PG-SGA (SF) can now be initiated.

References

1. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren,M.A., et al. A rational approach to nutritional assessment. *Clin Nutr*. 2008;27(5):706-716.

2. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior tochemotherapy in cancer patients. *Am J Med*. 1980;69(4):491-497.

3. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. *Nutr J*. 2012;11:27-2891-11-27.

4. Pressoir M, Desne S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in french comprehensive cancer centres. *Br J Cancer*. 2010;102(6):966-971.

5. Tian J, Chen ZC, Hang LF. Effects of nutritional and psychological status in gastrointestinal cancer patients on tolerance of treatment. *World J Gastroenterol*. 2007;13(30):4136-4140.

6. Capra S, Ferguson M, Ried K. Cancer: Impact of nutrition intervention outcome--nutrition issues for patients. *Nutrition*. 2001;17(9):769-772.

7. Tong H, Isenring E, Yates P. The prevalence of nutrition impact symptoms and their relationship to quality of life and clinical outcomes in medical oncology patients. *Support Care Cancer*. 2009;17(1):83-90.

8. Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the national cancer center in korea. *Nutrition*. 2010;26(3):263-268.

9. Segura A, Pardo J, Jara C, et al. An epidemiological evaluation of the prevalence of malnutrition in spanish patients with locally advanced or metastatic cancer. *Clin Nutr*. 2005;24(5):801-814.

10. Correia MI, Hegazi RA, Higashiguchi T, et al. Evidence-based recommendations for addressing malnutrition in health care: An updated strategy from the feedM.E. global study group. *J Am Med Dir Assoc*. 2014;15(8):544-550.

11. Singh H, Watt K, Veitch R, Cantor M, Duerksen DR. Malnutrition is prevalent in hospitalized medical patients: Are housestaff identifying the malnourished patient? *Nutrition*. 2006;22(4):350-354.

12. Kirkland LL, Kashiwagi DT, Brantley S, Scheurer D, Varkey P. Nutrition in the hospitalized patient. *J Hosp Med*. 2013;8(1):52-58.

13. Holyday M, Daniells S, Bare M, Caplan GA, Petocz P, Bolin T. Malnutrition screening and early nutrition intervention in hospitalised patients in acute aged care: A randomised controlled trial. *J Nutr Health Aging*. 2012;16(6):562-568.

14. Platek ME, Popp JV, Possinger CS, Denysschen CA, Horvath P, Brown JK. Comparison of the prevalence of malnutrition diagnosis in head and neck, gastrointestinal, and lung cancer patients by 3 classification methods. *Cancer Nurs*. 2011;34(5):410-416.

15. Kubrak C, Jensen L. Critical evaluation of nutrition screening tools recommended for oncology patients. *Cancer Nurs*. 2007;30(5):E1-6.

16. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. *Am J Clin Nutr*. 2008;87(6):1678-1685.

17. Abbott J, Teleni L, McKavanagh D, Watson J, McCarthy AL, Isenring E. Patient-generated subjective global assessment short form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients. *Support Care Cancer*. 2016.

18. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr*. 2002;56(8):779-785.

19. Sealy MJ, Nijholt W, Stuiver MM, et al. Content validity across methods of malnutrition assessment in patients with cancer is limited. *J Clin Epidemiol*. 2016.

20. Kubrak C, Olson K, Jha N, et al. Nutrition impact symptoms: Key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck*. 2010;32(3):290-300.

21. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition*. 1996;12(1 Suppl):S15-9.

22. Ottery FD. Patient-generated subjective global assessment. In: McCallum PA, Elliot L, Molseed LL, Grant B, eds. *The clinical guide to oncology nutrition.* Chicago, Il: The American Dietetic Association; 2006:44-53.

23. Thoresen L, Fjeldstad I, Krogstad K, Kaasa S, Falkmer UG. Nutritional status of patients with advanced cancer: The value of using the subjective global assessment of nutritional status as a screening tool. *Palliat Med*. 2002;16(1):33-42.

24. Desbrow B, Bauer J, Blum C, Kandasamy A, McDonald A, Montgomery K. Assessment of nutritional status in hemodialysis patients using patient-generated subjective global assessment. *J Ren Nutr*. 2005;15(2):211-216.

25. Marshall S, Young A, Bauer J, Isenring E. Malnutrition in geriatric rehabilitation: Prevalence, patient outcomes, and criterion validity of the scored patient-generated subjective global assessment and the mini nutritional assessment. *J Acad Nutr Diet*. 2016;116(5):785-794.

26. Boleo-Tome C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the malnutrition universal screening tool (MUST) in cancer. *Br J Nutr*. 2012;108(2):343-348.

27. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: The role of disease and diet. *Clin Oncol*. 2003;15(8):443-450.

28. Read JA, Crockett N, Volker DH, et al. Nutritional assessment in cancer: Comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). *Nutr Cancer*. 2005;53(1):51-56.

29. Term "PG-SGA". The National Center for Biotechnology Information (NCBI) PubMed Web site. http://www.ncbi.nlm.nih.gov/pubmed/?term=pg-sga. Published September 2016. Updated 2016. Accessed September/21, 2016.

30. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr*. 1987;11(1):8-13.

31. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. 1982;5(6):649-655.

32. Gabrielson DK, Scaffidi D, Leung E, et al. Use of an abridged scored patient-generated subjective global assessment (abPG-SGA) as a nutritional screening tool for cancer patients in an outpatient setting. *Nutr Cancer*. 2013;65(2):234-239.

33. Weekes CE, Elia M, Emery PW. The development, validation and reliability of a nutrition screening tool based on the recommendations of the british association for parenteral and enteral nutrition (BAPEN). *Clin Nutr*. 2004;23(5):1104-1112.

34. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren,M.A. Development and validation of a hospital screening tool for malnutrition: The short nutritional assessment questionnaire (SNAQ). *Clin Nutr*. 2005;24(1):75-82.

35. Acquadro C, Conway K, Hareendran A, Aaronson N, European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value Health*. 2008;11(3):509-521.

36. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)*. 2000;25(24):3186-3191.

37. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: Literature review and proposed guidelines. *J Clin Epidemiol*. 1993;46(12):1417-1432.

38. Sartorius N, Kuyken W. Translation of health status instruments. In: Orley J, Kuyken W, eds. *Quality of life assessment: International perspectives.* Berlin Heidelberg: Springer Verlag; 1994:3-18.

39. Stewart AL, Napoles-Springer A. Health-related quality-of-life assessments in diverse population groups in the united states. *Med Care*. 2000;38(9 Suppl):II102-24.

40. Polit DF, Beck CT. The content validity index: Are you sure you know what's being reported? critique and recommendations. *Res Nurs Health*. 2006;29(5):489-497.

41. Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: Report of the ISPOR task force for translation and cultural adaptation. *Value Health*. 2005;8(2):94-104.

42. Lynn MR. Determination and quantification of content validity. *Nurs Res*. 1986;35(6):382-385.

43. Polit DF, Beck CT, Owen SV. Is the CVI an acceptable indicator of content validity? appraisal and recommendations. *Res Nurs Health*. 2007;30(4):459-467.

44. Duarte Bonini Campos JA, Dias do Prado C. Cross-cultural adaptation of the portuguese version of the patient-generated subjective global assessment. *Nutr Hosp*. 2012;27(2):583-589.

45. Davis LL. Instrument review: Getting the most from a panel of experts. *Applied Nursing Research*. 1992;5(4):194-197.

46. Waltz CF, Strickland OL, Lenz ER, eds. *Measurement in nursing and health research.* New York, NY: Springer Publishing Company; 2010.

47. Ottery FD. Patient-generated subjective global assessment [PDF]. PG-SGA/Pt-global Platform website Web site. http://pt-global.org/?page_id=6098. Published Aug 2014. Accessed May, 2015.

48. Acquadro C, Bayles A, Juniper E. Translating patient-reported outcome measures: A multi-step process is essential. *J Bras Pneumol*. 2014;40(3):211-212.

49. Steenson J, Vivianti A, Isenring E. New clinicians require ongoing training to ensure high inter-rater reliability of the subjective global assessment. *Nutrition*. 2013;29(1):361-362.

Chapter 4. Evaluation of change in dietitians' perceived comprehensibility and difficulty of the Patient-Generated Subjective Global Assessment (PG-SGA) after a single training in the use of the instrument

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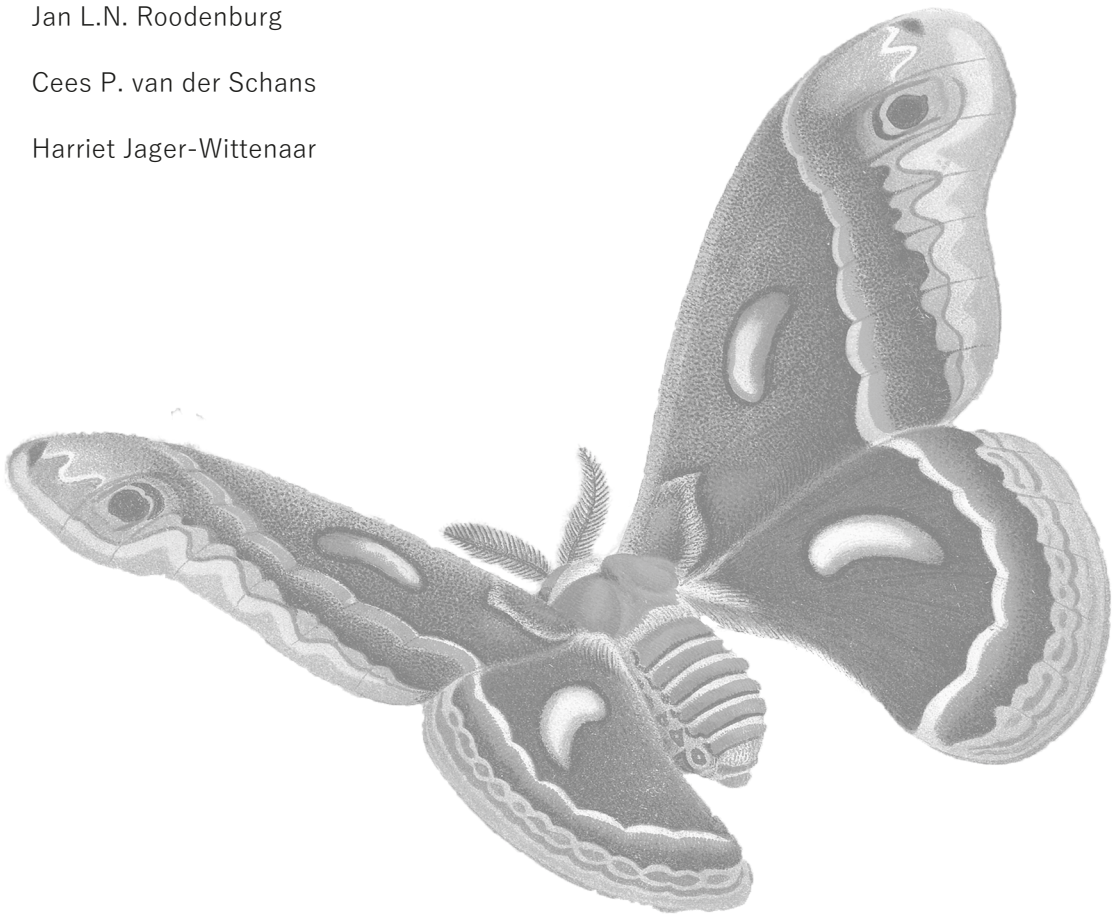

Abstract

Background: The Patient-Generated Subjective Global Assessment (PG-SGA) is an instrument to assess malnutrition and its risk factors. Some items of the PG-SGA may be perceived as hard to comprehend or difficult by healthcare professionals. The objective was to evaluate if and how dietitians' perceptions of comprehensibility and difficulty of the PG-SGA change after a single training in PG-SGA use.

Methods: In this prospective evaluation study, Dutch PG-SGA-naïve dietitians completed a questionnaire regarding perceived comprehensibility and difficulty of the PG-SGA before (T0) and after (T1) receiving a single training in instrument use. Perceived comprehensibility and difficulty were operationalized by calculating item and scale indices for comprehensibility (I-CI, S-CI) and difficulty (I-DI, S-DI) at T0 and T1. An item index of 0.78 was considered acceptable, a scale index of 0.80 was considered acceptable, and a scale index of 0.90 was considered excellent.

Results: A total of 35 participants completed the questionnaire both at T0 and T1. All item indices related to comprehensibility and difficulty improved, although I-DI for the items regarding food intake and physical exam remained below 0.78. Scale indices for difficulty and comprehensibility of the PG-SGA significantly changed ($p<0.001$) from not acceptable at T0 (S-CI=0.69; S-DI=0.57), to excellent for comprehensibility (S-CI=0.95) and acceptable for difficulty (S-DI=0.86) at T1.

Conclusions: The findings of this study suggest that significant improvement in PG-SGA-naïve dietitians' perception of comprehensibility and difficulty of the PG-SGA can be achieved quickly by providing a one day training in the use of the PG-SGA.

Introduction

The Scored Patient-Generated Subjective Global assessment (PG-SGA; Copyright FD Ottery, 1996, 2001, 2006) was developed as a modification of the Subjective Global Assessment[1] and can be used to assess malnutrition in the sense of undernutrition, and its underlying risk factors.[2,3] The PG-SGA includes a patient-generated component and a professional component, thus providing cumulative insight from both perspectives in the nutritional status of the patient. The PG-SGA was first validated in the oncology setting[3-6], and has subsequently been validated in other settings, such as nephrology and geriatric settings.[7,8]

Recently the PG-SGA has been translated and culturally adapted for the Dutch setting.[9] During the pilot testing of the prototype of the Dutch version, the perceived level of difficulty and comprehensibility of the PG-SGA were explored. Whereas patients perceived the patient-generated component of the PG-SGA as sufficiently easy and comprehensible, healthcare professionals perceived comprehensibility of the professional component as acceptable, but the level of difficulty as not acceptable. The concept of comprehensibility reflects the level of clarity of an instrument, as perceived by the user. The related concept of difficulty reflects the level of both knowledge and skills of the user of the instrument. Perceived lack of comprehensibility of an item, e.g., due to use of vocabulary that does not correspond with the respondents' education level, reduces understandability and may increase perceived difficulty of this item.[10-12]

We hypothesized that perception of comprehensibility may change positively by providing explanation of the meaning of each item of the PG-SGA and perception of difficulty may change positively by providing background information, instruction and/or training regarding the PG-SGA.[12] Since in daily practice dietitians are healthcare professionals that

often work with the PG-SGA, in this study we aimed to evaluate if and how perceived comprehensibility and difficulty changes after a training providing lectures (rationale and evidence base), as well as hands-on practice with the PG-SGA, in an omnifarious sample of dietitians.

Materials and methods

Sample and data collection

In this prospective evaluation study, characteristics of perceived difficulty and comprehensibility of version 3.6 of the Dutch PG-SGA at baseline and after receiving a full day training in the use of the PG-SGA were evaluated in a convenience sample of dietitians. Dietitians located at The Netherlands were informed about the training through social media and email. The training was developed in collaboration with the originator of the PG-SGA, and accredited for dietitians by the Dutch Foundation on Accreditation of Competence Stimulating Activities for healthcare workers. Because the PG-SGA had only recently become available in the Dutch language, professionals had little to no experience with the Dutch version of the instrument. All 79 persons that registered for the training were approached to participate in the study. Participants that were not trained at bachelor or higher level as a dietitian were excluded from the study. A lecture that explained the rationale behind the PG-SGA and a lecture demonstrating use of the PG-SGA and its electronic version were provided in the morning. In a workshop in the afternoon, attendees practiced with the PG-SGA, including the physical exam, and discussed the use and interpretation of the PG-SGA.

Three weeks prior to the training, registered professionals were invited to complete a home assignment and were informed about the project. Professionals gave their written consent before participating in the study. At baseline (T0), participants were asked to first complete both the patient and professional component of the PG-SGA, preferably with a patient, and subsequently to complete the online questionnaire. The second measurement (T1) followed directly after the training, at the training site. At T1, attendees were asked to complete a paper version of the questionnaire to stimulate immediate completion of the questionnaire, to prevent loss to follow-up. To further prevent loss to follow-up, five days after the training a reminder was sent to participants who did not complete the questionnaire at the training site. These participants were asked to complete an online version of the questionnaire.

The Medical Ethics Committee of the University Medical Center Groningen ruled that no permission was needed to perform the study (reference M14.165328), because the study was not under regulation of the 'Medical Research Involving Human Subjects Act' (WMO).

PG-SGA

The PG-SGA (*Online supplement 1*) consists of a patient-generated and a professional component. First, the patient-generated component includes four topic-specific Boxes designed to be completed by the patient. Box 1 addresses weight history. Box 2 addresses food intake. Box 3 addresses nutrition impact symptoms and other factors hindering food intake. Box 4 includes activity and function, and is based on the Eastern Cooperative Oncology Group (ECOG) performance status.[13] Second, the professional component includes five Worksheets and is completed by the healthcare professional. Worksheet 1

instructs on how to score the percentage weight loss. Worksheet 2 addresses conditions that may increase nutritional risk. Worksheet 3 addresses metabolic stress. Worksheet 4 includes a nutrition-focused physical examination. Worksheet 5 categorizes the overall global assessment of the patient. Categories include Stage A = Well nourished; Stage B = Moderately malnourished or suspected malnutrition; and Stage C = Severely malnourished.[4] Finally, a score is generated that guides triage recommendations for interdisciplinary interventions.

Comprehensibility and Difficulty

Comprehensibility and difficulty were measured using a questionnaire, which is available upon request. The questionnaire was pretested for clarity in three final year Bachelor Students Nutrition and Dietetics. The questionnaire opened with four items on demographics. Furthermore, it included 14 items regarding perceived comprehensibility and 14 items on difficulty of the PG-SGA. For both comprehensibility and difficulty, questionnaire items 1-4 referred to Box 1-4 of the PG-SGA. Questionnaire items 5-8 referred to Worksheet 1-3. In our preceding study we found that Worksheet 4 (Physical Exam) may be perceived difficult by professionals.[9] Therefore, more questions (item 9-12) were posed on Worksheet 4 as compared to other Boxes and Worksheets. Item 13 and 14 related to Worksheet 5 (Global Assessment Categories) and the nutritional triage recommendations, respectively.

To be able to differentiate between the level of comprehensibility and difficulty, both concepts were included in the questionnaire in this study. As proposed by Lynn and others, a four-point scale (1= very unclear/very difficult; 2= unclear/difficult; 3= clear/easy; 4= very clear/very easy) was used to avoid having a neutral and ambivalent midpoint.[14-16]

Scores 1 and 2 were considered 'not present', and scores 3 and 4 were considered 'present'.[14-16] For each item, an item comprehensibility index (I-CI) and an item difficulty index (I-DI) were calculated at T0 and T1. The I-CI and I-DI indicate the level of knowledge and level of clarity of each item as perceived by the respondents, respectively. I-CI and I-DI scores can range from 0-1, and were calculated by dividing the number of respondents that considered the item to be 'present' by the total number of respondents. In accordance with our previous study, I-CI and I-DI≥0.78 were considered acceptable.[9] An item score <0.78 requires further analysis of the item.[17] I-CI and I-DI scores of all items were averaged into a weighted summarized scale comprehensibility index (S-CI) and a scale difficulty index (S-DI) for the full PG-SGA. The S-CI and S-DI reflect respondents' perceived overall knowledge and overall comprehensibility level of the instrument, respectively. S-CI≥0.80 and S-DI≥0.80 were considered acceptable scores, S-CI≥0.90 and S-DI≥0.90 were considered excellent scores.[17,18] Item non-response was excluded from calculation of the index scores. Transparency of response was provided by reporting item response and overall response percentages.

Data management and statistical analyses

We performed power analysis for S-DI because in a pilot study S-DI was rated 0.55 by healthcare professionals, i.e. not acceptable, whereas S-CI was rated 0.81, which is already acceptable.[9] A minimal sample of 8 dietitians was considered sufficiently powered to detect a change of S-DI from 0.55 to S-DI 0.80 (cutoff for acceptable), with estimated variability 0.25 (allowing a type I error α=0.05, and a type II error β=0.20).[19]

Although S-CI and S-DI scores can range from 0 to 1, they can be considered nominal scores, transformed to weighted average scores. Therefore, the non-parametric Wilcoxon signed rank test was used to test significance of differences in distribution of participants' comprehensibility and difficulty indices at T0 and T1. The Mann-Whitney U test was used to compare distribution of T0 results of participants that completed the questionnaire both at T0 and T1 to distribution of T0 results of participants that were lost to follow up. Participants that were lost to follow-up were not included in the analysis. However, to test robustness of the results, T0 scores of the missing participants were imputed to the T1 scores, and the Wilcoxon signed rank test was used in a sensitivity analysis. All statistical tests were performed using SPSS24 (IBM) and significance level was set at p=0.05.

Results

In total, 56/79 (79%) professionals responded at T0, of which 47 (60%) were considered eligible and gave their consent. Of these 47 professionals, 35 (75%) completed the questionnaire both at T0 and T1 and were included in the analysis. Reasons for not completing the post-training questionnaire were lack of time and absence during the training. Two out of 35 participants were not currently practicing as dietitians. Characteristics of the participants that completed the questionnaire both at T0 and T1 are presented in Table 1. Indices and response rates for comprehensibility and difficulty of the PG-SGA are reported in Table 2. Online supplement II presents summarized frequency of scores 1,2,3 and 4 at both T0 and T1. Overall, comprehensibility and difficulty indices significantly improved after the training ($p<0.01$). At T0, comprehensibility and difficulty of the PG-SGA were not perceived acceptable on scale level (S-CI=0.69; overall response 93%; S-DI=0.57, overall response 92%). After the training, comprehensibility was

perceived as excellent on scale level (S-CI=0.95; overall response 97%) and difficulty of the PG-SGA was perceived as acceptable (S-DI=0.86, overall response 96%). S-CI improved in 30 participants and remained stable in 5 participants. S-DI improved in 29 participants, remained stable in 2 participants and decreased in 4 participants.

At T0, the lowest I-CI was found on the item concerning Worksheet 2 (Disease and relation to nutritional requirements; I-CI=0.38), and the highest I-CI were found for the items regarding Worksheet 1 (Scoring Weight Loss; I-CI=0.94). At T0, lowest I-DI scores were found on the items regarding Worksheet 4 (Physical Exam; I-DI=0.13-0.35). Furthermore, the highest I-DI score was found on the item concerning Box 3 (Symptoms; I-DI=0.80) and the items regarding Worksheet 1 (Scoring Weight Loss; I-DI=0.84-0.88).

At T1, all items had I-CI scores above the threshold of 0.78. Furthermore, maximum I-CI score of 1.0 was reached in Worksheet 1 items (Scoring Weight Loss), Worksheet 5 (Global Assessment Categories), and Total PG-SGA Score. At T1, the I-DI for items concerning Box 2 (Food intake [I-DI=0.76]) and Worksheet 4 (Physical Exam [I-DI=0.53-0.71]) still scored below the threshold of 0.78. Moreover, maximum I-DI score of 1.0 was reached on items concerning Box 4 (Activity and Function), Worksheet 1 (Scoring Weight Loss), Worksheet 5 (Global Assessment Categories), and Total PG-SGA Score.

Distribution of T0 indices for comprehensibility and difficulty of participants that were lost to follow up was not significantly different from those of participants that completed the questionnaire both at T0 and T1 ($p=0.15$, resp. $p=0.21$). After the T0 scores of the missing participants were imputed to the T1 scores, median improvement of comprehensibility and difficulty indices remained significant between T0 and T1 ($p<0.01$).

TABLE 1: Characteristics of dietitians that participated in exploration of perceived comprehensibility and difficulty of the PG-SGA before and after training in its use

Characteristics	n	%
Participants	35	100
Dietitian	33	94
Other[a]	2	6
Working setting[b]	45	100
General Hospital	17	38
Geriatrics/Nursing home/Rehabilitation	10	22
Primary Care	7	16
Academic Hospital	4	9
Tertiary Care Health Centre	4	9
Other	3	7
Field of interest[b]	75	100
Oncology	14	19
Gastroenterology/Diabetes	13	17
Malnutrition	9	12
Lung disease	7	9
Nephrology	6	8
Geriatrics	6	8
Pediatrics	5	7
Other	15	20
Reason for registering for the PG-SGA training[b]	38	100
Interest in PG-SGA	9	24
Interest in malnutrition assessment	8	21
The opportunity was provided	6	16
Interest in malnutrition screening	5	13
Interest in the electronic version of the PG-SGA (PG-SGA app)	4	11
Interest in improving nutrition care	3	8
Professional development	2	5
Interest in PG-SGA SF	1	3
	Median	Min-Max
Years of work experience	14	0-38

[a] 1 teacher in Program Nutrition and Dietetics, 1 junior researcher with background in dietetics

[b] More than 1 setting, and/or field of interest, and/or reason for registering possible per participant

TABLE 2. Comprehensibility and Difficulty Indices and Response Rates Scored by Dietitians for Items of the PG-SGA at T0 and T1

	Comprehensibility T0 (N=35)	**Comprehensibility T1 (N=35)**	**Difficulty T0 (N=35)**	**Difficulty T1 (N=35)**
Items	I-CI[a] T0 (N response)	I-CI[a] T1 (N response)	I-DI[b] T0 (N response)	I-DI[b] T1 (N response)
Box 1	0.86 (N=35)	0.97 (N=33)	*0.74* (N=35)	0.88 (N=34)
Box 2	*0.69* (N=35)	0.79 (N=33)	*0.57* (N=35)	*0.76* (N=34)
Box 3	0.89 (N=35)	0.94 (N=33)	0.80 (N=35)	0.94 (N=33)
Box 4	0.80 (N=35)	0.97 (N=33)	*0.76* (N=33)	1.00 (N=31)
Worksheet 1 explanation	0.94 (N=32)	0.97 (N=35)	0.88 (N=32)	0.94 (N=34)
Worksheet 1 items	0.94 (N=32)	1.00 (N=34)	0.84 (N=32)	1.00 (N=35)
Worksheet 2	*0.38* (N=32)	0.97 (N=35)	*0.50* (N=32)	0.97 (N=35)
Worksheet 3	*0.77* (N=31)	0.94 (N=35)	*0.72* (N=32)	0.97 (N=35)
Worksheet 4 explanation	*0.50* (N=32)	0.94 (N=32)	*0.35* (N=31)	*0.70* (N=33)
Worksheet 4 muscle	*0.41* (N=32)	0.91 (N=35)	*0.16* (N=32)	*0.53* (N=32)
Worksheet 4 fat	*0.44* (N=32)	0.94 (N=35)	*0.13* (N=32)	*0.59* (N=32)
Worksheet 4 fluids	*0.50* (N=32)	0.97 (N=35)	*0.19* (N=32)	*0.71* (N=35)
Worksheet 5	*0.75* (N=32)	1.00 (N=34)	*0.60* (N=30)	1.00 (N=34)
PG-SGA point score	0.81 (N=32)	1.00 (N=35)	*0.69* (N=29)	1.00 (N=35)
	S-CI[c] *0.69*	**S-CI[c] 0.95**	**S-DI[d] *0.57***	**S-DI[d] 0.86**
Overall item response	93%	97%	92%	96%

[a]I-CI=Item Comprehensibility Index; [b]I- DI=Item Difficulty Index; [c]S-CI=Scale Comprehensibility Index; [d]S-DI=Scale Difficulty Index

Italics: below acceptable level of 0.78 for I-CI and I-DI respectively, and 0.80 for S-CI and S-DI respectively

Discussion

The results of this study show that perceived comprehensibility and difficulty of the PG-SGA improved significantly in a sample of PG-SGA-naïve dietitians, after providing information and hands-on training in the use of the PG-SGA. While perceived comprehensibility improved to an acceptable level for all components of the PG-SGA, perceived difficulty for the physical examination and food intake remained under the predefined cut-off for acceptability. Overall scores for comprehensibility improved from

not acceptable at baseline to excellent after the training. Overall scores for difficulty improved from not acceptable at baseline to acceptable after the training.

The items related to the physical examination were perceived the most difficult component of the PG-SGA, in accordance with the findings of the pre-testing of the Dutch version of the PG-SGA.[9] Scores on difficulty improved after a single training, but not to an acceptable level, implying perceived difficulty of the physical examination could still improve. Scores on comprehensibility for items related to the physical examination did improve to an acceptable level, implying that the explanation of the physical examination was helpful to clarify Worksheet 4 (Physical examination). It is unclear why participating dietitians regarded the physical examination of the PG-SGA clear but difficult. A possible explanation would be that some dietitians did not feel confident to examine and interpret signs of loss or deficit of muscle and/or fat in their own patients after a single training. These dietitians may need repeated hands-on training and practice. It is not reported how often professionals actually receive training in the use of nutritional assessment tools such as PG-SGA or the SGA, and how lack of training may influence the results of the physical exam. We hypothesize that sufficient knowledge and experience could improve perceived difficulty of the physical exam and additionally may lead to more reliable results. A recent study showed that dietitians that received training in the use of the PG-SGA presented good reliability in assessment (intraclass correlation of 0.90 [$p<0.001$]).[20] Results from a study on interrater reliability (IRR) utilizing the SGA indicate in the same direction.[21] In that study, more experienced professionals (>5 years after graduation) utilizing the SGA showed similar results (IRR range of 89-100%) when compared to a well-trained and experienced dietitian (>20 years after graduation), whereas less experienced professionals

(1-2 years after graduation) showed an IRR range of 56-100% when compared to the same dietitian.[21]

Notably, dietitians experienced some difficulty in interpreting an item from the patient-generated component. Although scores for item comprehensibility for Box 2 (Food intake) improved to an acceptable level after training, scores on difficulty remained slightly below an acceptable level, with an I-DI of 0.76. Box 2 is one of the four Boxes designed to be completed by patients. Difficulty of these items may be perceived differently when tested in a patient population as compared to a sample of professionals. During the pilot testing of the prototype of the Dutch version in a small sample of patients, the level of difficulty and comprehensibility of Box 2 was perceived acceptable.[9] Additionally, a different study reported that patients with cancer found the patient-generated component of the PG-SGA not difficult and not hard to understand.[22] We suggest to test the patient-generated component of the PG-SGA in a larger sample of patients, representing different patient populations, to evaluate whether adjustment or further explanation is needed.

Interestingly, some participants perceived the PG-SGA as more difficult after the training, despite improvement in perceived comprehensibility. These participants may have been unaware of a lack of knowledge or experience in performing the PG-SGA assessment prior to the training. After the training, they may have improved their understanding of the PG-SGA and consequently may be more conscious of a possible lack of knowledge or experience. In that case, dietitians may also profit from repeated practice and hands on training with the PG-SGA.

This is the first study that evaluated changes in perception of difficulty and comprehensibility of the PG-SGA after training in an omnifarious sample of dietitians. The results are of interest because a single training can be done quickly and at low expenses.

The study has some limitations. First, due to the design of the study, we did not have access to a control group. The effects of the training may have been positively influenced, and some improvements may have resulted from increased familiarity of participants with the PG-SGA at T1, when compared to T0, due to repetition. However, we attempted to temper the potential positive effect of repetition by incorporating an interval of three weeks between inviting participants to complete the questionnaire at T0 and repetition at T1.[23] Second, in this study we assessed only short term effects of the training. As a result of the "single training" design, we did not acquire data on longer term effects of the training and thus it is unclear how the level of perceived comprehensibility and difficulty changes over time. Third, the training subject was the PG-SGA, and about 40% of participants reported to have registered for the training because of an interest in the (electronic version of the) PG-SGA or PG-SGA SF. These dietitians may be more interested in the PG-SGA than average, and subsequently have a more positive view of the PG-SGA than average. Therefore, some response bias cannot be ruled out. However, we tried to encourage all types of dietitians to enroll by limiting the registration fee and by awarding accreditation points. Moreover, scale difficulty and scale comprehensibility were well under acceptable scores at T0 (S-CI=0.69, S-DI=0.57), not indicating the results were influenced by a positive attitude prior to the training. Fourth, participants were almost exclusively dietitians, which makes it difficult to generalize the results to other healthcare professionals. However, dietitians are amongst the professionals most likely to work with the PG-SGA in practice. Finally, 25% of participants were lost to follow up. However, distribution of baseline results for comprehensibility and difficulty of respondents that were lost to follow up did not significantly differ from those of respondents that completed the questionnaire both times, thus loss to follow up appears random. If the baseline scores of the missing

participants are imputed to the T1 scores, perceived level of comprehensibility and difficulty would still significantly have improved between T0 and T1 (α <0.001).

Perceived comprehensibility and difficulty are concepts related to each other.[11,12] We hypothesize that providing sufficient clarity is conditional to be able to accurately identify and overcome concerns with difficulty of the PG-SGA. A dual approach towards improving clarity and knowledge and skills may lead to greater confidence in the use of the PG-SGA among dietitians, which in turn could further stimulate implementation of the PG-SGA in practice. To further improve perceived level of difficulty, supplemental information such as online materials or instruction videos for dietitians may be helpful. Furthermore, we suggest to independently start training the skills to adequately perform a nutrition-focused physical assessment during the education of dietitians, preferably with practice sessions involving actual patients. In The Netherlands, several Programs on Nutrition and Dietetics have incorporated training in the use of the PG-SGA in their curriculum already.

Conclusion

The findings suggest that significant improvement in PG-SGA-naïve dietitians' perception of difficulty and comprehensibility of the PG-SGA can be achieved quickly by providing training in the use of the PG-SGA. While perceived comprehensibility improved to an acceptable level for all components of the PG-SGA, perceived difficulty for the physical examination still required further improvement after a single training, suggesting supplemental information and/or more training may be needed for PG-SGA-naïve dietitians to ensure an acceptable level of perceived difficulty of all components of the PG-SGA, including the physical exam.

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References

1. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren,M.A., et al. A rational approach to nutritional assessment. Clin Nutr. 2008;27(5):706-716.

2. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior tochemotherapy in cancer patients. Am J Med. 1980;69(4):491-497.

3. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. Nutr J. 2012;11:27-2891-11-27.

4. Pressoir M, Desne S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in french comprehensive cancer centres. Br J Cancer. 2010;102(6):966-971.

5. Tian J, Chen ZC, Hang LF. Effects of nutritional and psychological status in gastrointestinal cancer patients on tolerance of treatment. World J Gastroenterol. 2007;13(30):4136-4140.

6. Capra S, Ferguson M, Ried K. Cancer: Impact of nutrition intervention outcome--nutrition issues for patients. Nutrition. 2001;17(9):769-772.

7. Tong H, Isenring E, Yates P. The prevalence of nutrition impact symptoms and their relationship to quality of life and clinical outcomes in medical oncology patients. Support Care Cancer. 2009;17(1):83-90.

8. Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the national cancer center in korea. Nutrition. 2010;26(3):263-268.

9. Segura A, Pardo J, Jara C, et al. An epidemiological evaluation of the prevalence of malnutrition in spanish patients with locally advanced or metastatic cancer. Clin Nutr. 2005;24(5):801-814.

10. Correia MI, Hegazi RA, Higashiguchi T, et al. Evidence-based recommendations for addressing malnutrition in health care: An updated strategy from the feedM.E. global study group. J Am Med Dir Assoc. 2014;15(8):544-550.

11. Singh H, Watt K, Veitch R, Cantor M, Duerksen DR. Malnutrition is prevalent in hospitalized medical patients: Are housestaff identifying the malnourished patient? Nutrition. 2006;22(4):350-354.

12. Kirkland LL, Kashiwagi DT, Brantley S, Scheurer D, Varkey P. Nutrition in the hospitalized patient. J Hosp Med. 2013;8(1):52-58.

13. Holyday M, Daniells S, Bare M, Caplan GA, Petocz P, Bolin T. Malnutrition screening and early nutrition intervention in hospitalised patients in acute aged care: A randomised controlled trial. J Nutr Health Aging. 2012;16(6):562-568.

14. Platek ME, Popp JV, Possinger CS, Denysschen CA, Horvath P, Brown JK. Comparison of the prevalence of malnutrition diagnosis in head and neck, gastrointestinal, and lung cancer patients by 3 classification methods. Cancer Nurs. 2011;34(5):410-416.

15. Kubrak C, Jensen L. Critical evaluation of nutrition screening tools recommended for oncology patients. Cancer Nurs. 2007;30(5):E1-6.

16. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. Am J Clin Nutr. 2008;87(6):1678-1685.

17. Abbott J, Teleni L, McKavanagh D, Watson J, McCarthy AL, Isenring E. Patient-generated subjective global assessment short form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients. Support Care Cancer. 2016.

18. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr. 2002;56(8):779-785.

19. Sealy MJ, Nijholt W, Stuiver MM, et al. Content validity across methods of malnutrition assessment in patients with cancer is limited. J Clin Epidemiol. 2016.

20. Kubrak C, Olson K, Jha N, et al. Nutrition impact symptoms: Key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. Head Neck. 2010;32(3):290-300.

21. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.

22. Ottery FD. Patient-generated subjective global assessment. In: McCallum PA, Elliot L, Molseed LL, Grant B, eds. The clinical guide to oncology nutrition. Chicago, Il: The American Dietetic Association; 2006:44-53.

23. Thoresen L, Fjeldstad I, Krogstad K, Kaasa S, Falkmer UG. Nutritional status of patients with advanced cancer: The value of using the subjective global assessment of nutritional status as a screening tool. Palliat Med. 2002;16(1):33-42.

24. Desbrow B, Bauer J, Blum C, Kandasamy A, McDonald A, Montgomery K. Assessment of nutritional status in hemodialysis patients using patient-generated subjective global assessment. J Ren Nutr. 2005;15(2):211-216.

25. Marshall S, Young A, Bauer J, Isenring E. Malnutrition in geriatric rehabilitation: Prevalence, patient outcomes, and criterion validity of the scored patient-generated subjective global assessment and the mini nutritional assessment. J Acad Nutr Diet. 2016;116(5):785-794.

26. Boleo-Tome C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the malnutrition universal screening tool (MUST) in cancer. Br J Nutr. 2012;108(2):343-348.

27. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: The role of disease and diet. Clin Oncol. 2003;15(8):443-450.

28. Read JA, Crockett N, Volker DH, et al. Nutritional assessment in cancer: Comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). Nutr Cancer. 2005;53(1):51-56.

29. Term "PG-SGA". The National Center for Biotechnology Information (NCBI) PubMed Web site. http://www.ncbi.nlm.nih.gov/pubmed/?term=pg-sga. Published September 2016. Updated 2016. Accessed September/21, 2016.

30. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.

31. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982;5(6):649-655.

32. Gabrielson DK, Scaffidi D, Leung E, et al. Use of an abridged scored patient-generated subjective global assessment (abPG-SGA) as a nutritional screening tool for cancer patients in an outpatient setting. Nutr Cancer. 2013;65(2):234-239.

33. Weekes CE, Elia M, Emery PW. The development, validation and reliability of a nutrition screening tool based on the recommendations of the british association for parenteral and enteral nutrition (BAPEN). Clin Nutr. 2004;23(5):1104-1112.

34. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren,M.A. Development and validation of a hospital screening tool for malnutrition: The short nutritional assessment questionnaire (SNAQ). Clin Nutr. 2005;24(1):75-82.

35. Acquadro C, Conway K, Hareendran A, Aaronson N, European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. Value Health. 2008;11(3):509-521.

36. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-3191.

37. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: Literature review and proposed guidelines. J Clin Epidemiol. 1993;46(12):1417-1432.

38. Sartorius N, Kuyken W. Translation of health status instruments. In: Orley J, Kuyken W, eds. Quality of life assessment: International perspectives. Berlin Heidelberg: Springer Verlag; 1994:3-18.

39. Stewart AL, Napoles-Springer A. Health-related quality-of-life assessments in diverse population groups in the united states. Med Care. 2000;38(9 Suppl):II102-24.

40. Polit DF, Beck CT. The content validity index: Are you sure you know what's being reported? critique and recommendations. Res Nurs Health. 2006;29(5):489-497.

41. Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: Report of the ISPOR task force for translation and cultural adaptation. Value Health. 2005;8(2):94-104.

42. Lynn MR. Determination and quantification of content validity. Nurs Res. 1986;35(6):382-385.

43. Polit DF, Beck CT, Owen SV. Is the CVI an acceptable indicator of content validity? appraisal and recommendations. Res Nurs Health. 2007;30(4):459-467.

44. Duarte Bonini Campos JA, Dias do Prado C. Cross-cultural adaptation of the portuguese version of the patient-generated subjective global assessment. Nutr Hosp. 2012;27(2):583-589.

45. Davis LL. Instrument review: Getting the most from a panel of experts. Applied Nursing Research. 1992;5(4):194-197.

46. Waltz CF, Strickland OL, Lenz ER, eds. Measurement in nursing and health research. New York, NY: Springer Publishing Company; 2010.

47. Ottery FD. Patient-generated subjective global assessment [PDF]. PG-SGA/Pt-global Platform website Web site. http://pt-global.org/?page_id=6098. Published Aug 2014. Accessed May, 2015.

48. Acquadro C, Bayles A, Juniper E. Translating patient-reported outcome measures: A multi-step process is essential. J Bras Pneumol. 2014;40(3):211-212.

49. Steenson J, Vivianti A, Isenring E. New clinicians require ongoing training to ensure high inter-rater reliability of the subjective global assessment. Nutrition. 2013;29(1):361-362.

Chapter 5. Low muscle mass is associated with early termination of chemotherapy related to toxicity in patients with head and neck cancer

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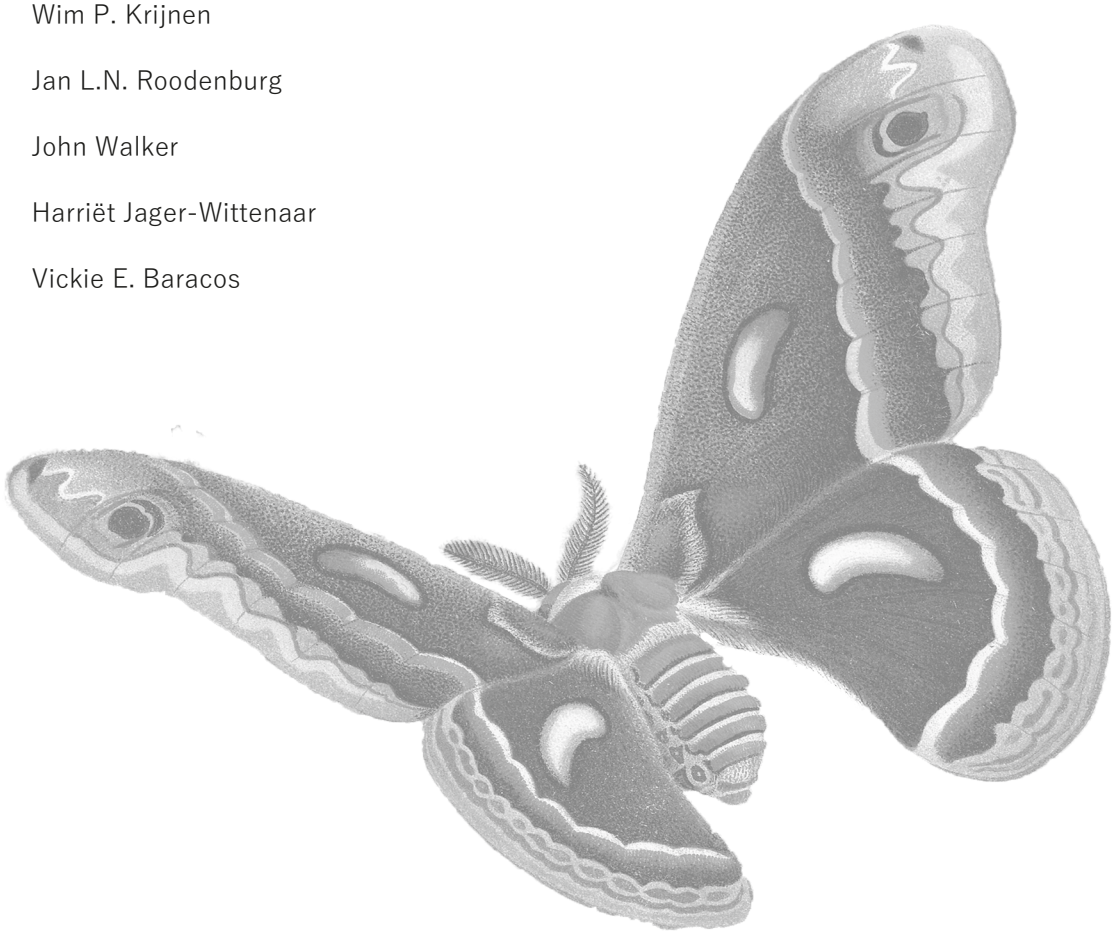


Abstract

Background and aims: We studied whether low pre-treatment muscle mass, measured with CT at thoracic (T4) or lumbar level (L3) associates with early termination of chemotherapy related to toxicity in head and neck cancer (HNC) patients.

Methods: This was a retrospective chart and image review. Adult HNC patients treated with (surgery and) platinum-based chemo-radiotherapy were included if a pre-treatment CT scan at T4 or L3 level was available. Muscle mass was evaluated by assessment of skeletal muscle index (SMI; cm^2/m^2). T4 and L3 SMI measurements were corrected for deviation from their respective means and were merged into one score for SMI difference (cm^2/m^2). All cases were assessed for presence of toxicity-related unplanned early termination of chemotherapy ('early termination'). Univariate and multivariate logistic regression models were used to investigate associations between pooled SMI and early termination.

Results: 213 patients (age: 57.9±10.3 y, male: 77%, T4 image: 45%) were included. A significant association between SMI as a continuous variable and early termination was found, both in the univariate analysis (p=0.007, OR=0.96 [0.94-0.99]) and the multivariate analysis (p=0.021, OR 0.96 [0.92-0.99]). The multivariate models identified potential associations with type of chemotherapy, presence of co-morbidity, a combination of (former) smoking and alcohol consumption, and sex.

Conclusion: Lower muscle mass was robustly associated with higher odds of early termination of chemotherapy in HNC patients. CT-based muscle mass assessment may allow clinicians to optimize care in HNC patients at risk of complications related to low muscle mass.

Introduction

Decreased oral intake due to tumor location cancer treatment, and/or cachexia is common in patients with head and neck cancer (HNC) and may induce loss of skeletal muscle.[1-4] In turn, low muscle mass has a negative impact on overall function and survival in patients with HNC.[5-9] However, the treatment approach in patients with locally advanced HNC can be aggressive and may consist of surgery followed by radiotherapy, with or without concomitant chemotherapy. In patients not eligible for surgery or when the anticipated functional outcome with surgery is poor, radiotherapy with concomitant chemotherapy is preferred.[10-12] Although prognosis improves when patients are capable of completing their therapy, early termination of treatment related to toxicity is observed more often in cancer patients with low muscle mass, and thus such benefit may be limited.[7,13,14]

The development of chemotherapy toxicity may be partially explained by variation in body composition in patients with cancer.[15] The overall weight is comprised mostly of fat tissue and non-fat tissue. In turn, non-fat tissue is comprised of bone tissue and lean tissue such as organ tissues (e.g., liver and kidneys) and muscle tissue.[16,17] Distribution and metabolism of water soluble chemotherapy agents, such as cisplatin, mainly takes place in the lean tissue.[18] Therefore, patients with low muscle mass may have a smaller amount of area available for distribution of chemotherapy agents due the limited amount of lean tissue. Recent studies have revealed there is considerable variation in the proportions of lean and fat tissues in patients with cancer, and patients with solid tumors may present as overweight or obese, while simultaneously showing severe loss of skeletal muscle mass.[8,13,19] Body area estimates based on body mass and stature are used for dose calculation of chemotherapy agents such as cisplatin.[20] Thus, if a chemotherapy agent distributes well in lean tissue, patients with relatively low muscle mass may be at risk of receiving a higher dose of

chemotherapy agent relative to the actual amount of lean tissue, due to overestimation of lean tissue. This relatively high dose of chemotherapy may increase risk of chemotherapy toxicity.[7,14,17,21]

Chemotherapy toxicity may result in early termination of chemotherapy.[22] Accurate identification of patients with low muscle mass is currently possible, since muscle mass has become identifiable and quantifiable with image-based approaches, such as computed tomography (CT). CT analysis of the lumbar muscle area has been thoroughly validated for the evaluation of human body composition and correlates well with lean body mass.[23-25] In some patient populations, CT images of the lumbar muscle area are not generally available, and CT analysis of thoracic muscle area may serve as an alternative.[26] However, although it is now possible to accurately identify patients with low muscle mass, it is still unclear to what extent toxicity of chemotherapy treatment correlates with muscle area identified with lumbar or thoracic CT cross-sections in HNC patients. Therefore, we aimed to study whether low pre-treatment lumbar or thoracic muscle area as measured with CT is associated with toxicity-related early termination of chemotherapy treatment, in patients with HNC treated with concomitant radiotherapy and chemotherapy.

Materials and methods

Patients and study design

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics board. Data were collected in consecutive adult patients diagnosed with HNC during their initial visit to the outpatient medical oncology clinic at the tertiary cancer treatment center serving northern Alberta. Demographic information,

and cancer site and stage were obtained from the Alberta Cancer Registry, certified by the North American Association for Central Cancer Registries. Cancer stage was based on the American Joint Committee on Cancer (7th Edition) stage groupings for HNC.[27] HNC tumor sites were based on the International Classification of Diseases for Oncology (ICD)-O-3 site codes. Cohorts were sampled from March 2004 until July 2010 (Sample I) and from May 2012 until May 2016 (Sample II). Adult patients diagnosed with HNC, mainly presenting cancer of the lip, oral cavity, nose, paranasal sinus, larynx, and pharynx, were considered for inclusion if they received concomitant radiotherapy and platinum-based chemotherapy treatment (CRT) with curative intent, with or without prior surgery (Sx). To be considered for inclusion, a routine diagnostic CT image taken before start of CRT including the 4th thoracic vertebra (T4; sample I) or the 3th lumbar vertebra (L3; sample II) needed to be available.

The primary treatment for advanced stages of HNC was CRT; in addition, approximately half of the patients in our cohort had prior HNC surgery, with tumor resection, bilateral neck dissection, and free flap reconstruction. Radiotherapy treatment included conventional or tomotherapy 66-76 cGy. The main treatment plans for chemotherapy were cisplatin 100 mg/m^2, three weekly (3 cycles), cisplatin 40 mg/ m^2, weekly (7 cycles), or, if cisplatin could not be tolerated, carboplatin 1.5 area under the curve (AUC) weekly (6-7 cycles). For each patient, chemotherapy type and dose were selected by the treating oncologist. If patients had a contraindication to high dose cisplatin such as poor renal function or pre-existing hearing problems, carboplatin was used in the first instance.

Measures

Data collected from medical charts included: number of days between CT scan and start of chemotherapy and radiotherapy; type of treatment; presence of co-morbidities; performance status was recorded as Eastern Cooperative Oncology Group (ECOG);[28] alcohol intake; history of smoking, treatment plan of platinum-based chemotherapy and chemotherapy toxicities.

Body composition

Weight and height were recorded according to standard procedures by hospital staff. Weight (kg) was measured with a medical balance beam scale and height (m) with a stadiometer. Body mass index (BMI) was calculated [weight (kg)/height (m^2)]. Percentage of weight loss in the last month before starting CRT was retrieved from Patient-Generated Subjective Global Assessment Short Form data,[29] as collected in routine care. Body composition was assessed by evaluating CT images that were taken for diagnostic purposes. Most studies using this approach have adopted the convention of quantifying muscle cross-sectional area in a single image landmarked at L3.[22-24,30] However in HNC routine diagnostic imaging does not always include the abdominal region, thus we selected T4 as an alternative vertebral landmark for Sample I, as this region represents large and diverse muscle areas and was included in staging studies in the majority of patients. For Sample II, routine imaging included L3 in the majority of patients.

One axial image at T4 or L3 was selected for analysis of total muscle cross-sectional area (cm^2).[23,31] CT image parameters included: contrast-enhanced, 5 mm slice thickness, 120 kVp, and ~290 mA. Observers were blinded to the patients' treatment and toxicity status.

Muscles were quantified within a Hounsfield unit range of −29 to +150 HU using Slice-O–Matic software (v.5.0; Tomovision, Magog, Canada). Total muscle cross-sectional area (SMA) was computed for each image. The directly determined unit for SMA was cm^2 of total T4 or L3 skeletal muscle. Cross-sectional area of total muscle at T4 or L3 were normalized for stature, and skeletal muscle index (SMI; cm^2/m^2) was calculated. Correction for deviation of the mean enables pooling of the SMI results of sample I and sample II, and could be performed because standard deviations of T4 and L3 measurements were similar (12.6 cm^2/m^2 and 10.3 cm^2/m^2, respectively). The mean SMI of Sample I was subtracted from all SMI measurements in Sample I (T4 measurements) and the mean SMI of Sample II was subtracted from all SMI measurements in Sample II (L3 measurements). After correction for deviation from the mean, the scores were combined in one pooled SMI variable representing the SMI deviation to the mean (cm^2/m^2).

Outcome measures

In this study, early termination of chemotherapy related to toxicity ('early termination') was considered the primary outcome measure and was defined as completion of at least one cycle of chemotherapy less than planned. If the initial chemotherapy treatment plan was altered from cisplatin to carboplatin (often due to ototoxicity), and cycles were completed, this was not considered an early termination. Otherwise, if early termination was specifically attributed to toxicity, early termination was considered present. Reduction of the dose of cisplatin or carboplatin provided all cycles where completed, was not considered early termination.

Statistical analysis

Mean (standard deviation; SD) or median scores (interquartile range; IQR) are reported for all continuous variables. Absolute numbers (percentages) are reported for ordinal and dichotomous variables. Differences between Sample I and Sample II were explored with Pearson Chi square, Mann-Whitney U test, or independent samples t-test.

Univariate analysis was used to test the association between pooled SMI and early termination. Multivariate binary logistic regression analyses were used to investigate possible effects of sex, age, BMI, presence of co-morbidities (present, not present); ECOG performance status (ECOG ≤1, ECOG>1), smoking (yes, no), alcohol consumption (yes, no), tumor site (oropharynx, other), treatment plan (CRT, SxCRT), and type of platin-based chemotherapy (cisplatin, carboplatin) on early termination. A p-level of <0.05 was considered significant and Odds Ratios (OR) [95% CI] were presented.

Due to the large number of explanatory variables, model selection procedures were explored to identify associations. The penalized regression approach according to the Smoothly Clipped Absolute Deviation (SCAD)[32] penalty was used, as it performs well in variable selection without creating bias.[33,34] For selecting the explanatory variables, the value of the penalty parameter is determined by repeating the cross-validation procedure 200 times and taking the mean from these repeats. To test the robustness of the results, the model resulting from SCAD was compared with that obtained from minimum Akaike Information Criterion (AIC)[35] and minimizing Bayesian Information Criterion (BIC)[36] approaches. To allow for analysis of all included patients, missing data were imputed by the Multivariate Imputation by Chained Equations procedure for the variables alcohol intake (n=2) and ECOG performance status (n=13).[37,38] Toxicity profiles of cisplatin-based

chemotherapy treatment may differ from carboplatin-based treatment. Therefore, difference in distribution of SMI (cm2/m2) stratified for early termination being absent or present was tested for cisplatin and carboplatin separately with an independent samples Mann-Whitney U test. Furthermore, the association between muscle mass and early termination was explored with univariate binary logistic regression, for subgroups treated with cisplatin or carboplatin separately.

Descriptive, univariate and explorative analyses were performed with SPSS (version 24.0 2016, IBM Inc., Chicago, Il). Multivariate analysis was performed with R (R version 3.4.1, R Core Team Vienna, 2017).

Results

In total, 213 patients met the inclusion criteria and could be included in the analysis (Sample I: n=93; Sample II: n=120). Characteristics of the included HNC patients prior to CRT are reported in Table 1. All patients received at least one cycle of chemotherapy. Of these 213 patients, 61 (29%) terminated chemotherapy prematurely. In one patient that terminated chemotherapy early, the initial chemotherapy treatment plan was altered from cisplatin tot carboplatin. In 28 patients, the initial chemotherapy treatment plan was altered from cisplatin to carboplatin, and treatment was considered completed. The following reasons for early termination of chemotherapy treatment were not considered toxicity-related: non-completion due to non-compliance (n=4); further chemotherapy treatment not indicated (n=2); non-completion of CRT due to reported radiation-related side effects (n=2); postponement of treatment due to surgical infections (n=1) or personal circumstances (n=1). Dose reduction of chemotherapy treatment ranged from 25% to 90%

and occurred in 19 patients. Seven of these patients had toxicity-related dose reductions preceding early termination, and early termination was considered present. In eight patients the reason for dose reduction was not described and all cycles were completed, and early termination was not considered present. Finally, in four patients dose reductions were related to chemotherapy toxicity, but all cycles were completed, and early termination was not considered present.

Body composition measurements

In Sample I, CT images at T4 level of 93 eligible patients were analyzed. In sample II, CT images at L3 level were available in 120 of 124 (94.4%) eligible HNC patients. All selected images could be analyzed and SMI was calculated. Pre-treatment anthropometrical measurements and indices of body composition of the participants are presented in Table 2. Patients that altered their treatment from cisplatin to carboplatin did not have a significantly different pooled SMI when compared to patients continuously treated with cisplatin ($p=0.823$), or when compared to all other patients ($p=0.541$). Frequency of early termination did not significantly differ between patients treated with cisplatin 100 mg/m^2 and cisplatin 40 mg/m^2 ($p=0.864$). The univariate and multivariate modeling analysis of pooled SMI and early termination corrected for possible confounding variables in HNC patients is presented in Table 3. In addition to pooled SMI, variables that emerged associated with early termination were sex, type of chemotherapy, co-morbidity and (former) smoking combined with alcohol consumption. The time interval between CT and CRT was significantly different for Sample I and Sample II ($p<0.001$). To rule out possible effect modification, the time interval between CT and CRT (days) was therefore added to

the statistical modeling analyses. However, time interval between CT and CRT was not identified as effect modifier of pooled SMI on early termination in the AIC, BIC, or SCAT model. Associated odds of early termination of chemotherapy treatment across the distribution of pooled SMI in HNC patients are presented in Figure 1.

Figure 2 illustrates the distribution of SMI stratified by absence or presence of early termination of chemotherapy for cisplatin-based and carboplatin-based treatment in patients with head and neck cancer. To further explore the association between muscle mass and early termination for the different types of chemotherapy agents, a sub-analysis was performed for the cisplatin and the carboplatin subgroup, respectively. The sub-analysis showed that in the cisplatin subgroup, a higher SMI was significantly associated with a lower incidence of early termination (p=0.025; OR 0.96 [95% CI: 0.93-1.00]). This indicates that if SMI is 1 cm2/m2 higher, the odds of early termination decrease with 4% in the patients treated with cisplatin. Also in the carboplatin subgroup, a higher SMI was significantly associated with a lower incidence of early termination (p=0.041; OR 0.93 [95% CI: 0.86-1.00]). This indicates that if SMI is 1 cm2/m2 higher, the odds of early termination decrease with 7% in the patients treated with carboplatin.

TABLE 1. Characteristics of patients with head and neck cancer prior to chemo-radiotherapy treatment reported for the whole study sample and separately for Sample I and II

Basic characteristic	Total (n=213)	Sample I (n=93)	Sample II (n=120)	(Mean) diff p value
Age (years) Mean ± SD	57.9±10.3	58.0 (10.7)	57.8 (10.1)	0.842
Sex Male (%)	164 (77.0)	71 (76.3)	93 (77.5)	0.858
Tumor site				
Oral cavity	31 (14.6)	9 (9.7)	22 (18.3)	0.155
Pharynx	144 (67.6)	67 (72.1)	77 (64.2)	
Larynx	22 (10.3)	12 (12.9)	10 (8.3)	
Other	16 (7.5)	5 (5.4)	11 (9.2)	
Stage (%)				
1	2 (0.9)	0	2 (1.7)	0.602
2	6 (2.8)	2 (2.2)	4 (3.3)	
3	27 (12.7)	12 (12.9)	15 (12.5)	
4	171 (80.3)	76 (81.7)	95 (79.2)	
X	7 (3.3)	3 (3.2)	4 (3.3)	
Tumor classification				
T1	32 (15.0)	12 (12.9)	20 (16.7)	0.158
T2	53 (24.9)	22 (23.7)	31 (25.8)	
T3	58 (27.2)	28 (30.1)	30 (25.0)	
T4	54 (25.4)	28 (30.1)	26 (21.7)	
Tx	16 (7.5)	3 (3.2)	13 (10.8)	
Mode of treatment				
Primary chemo-radiotherapy (CRT)	105 (49.3)	49 (52.7)	56 (46.7)	0.383
Surgery plus post-operative chemo-radiotherapy (Sx-CRT)	108 (50.7)	44 (47.3)	64 (53.3)	
Time between CT and CRT (days)				
Median (interquartile range)	55.0 (27.0-93.0)	32.0 (15.0-82.5)	70.0 (42.5-103.0)	<0.001*
Type and dose of chemotherapy				
- Cisplatin 100 mg/m2	133 (62.4)	59 (63.4)	74 (61.7)	<0.001*
- Cisplatin 40 mg/m2	34 (16.0)	3 (3.2)	31 (25.8)	
- Carboplatin 1.5 AUC	46 (21.6)	31 (33.3)	15 (12.5)	
ECOG performance status (%)				
Normal	99 (46.5)	48 (56.1)	51 (42.5)	0.148
Not normal self	71 (33.3)	25 (26.9)	46 (38.3)	
Not feeling up to most	19 (8.9)	7 (7.5)	12 (10.0)	
Little activity	11 (5.2)	5 (5.4)	6 (5.0)	
Missing	13 (6.1)	8 (8.6)	5 (4.2)	
Presence of co-morbidity				
Yes (%)	126 (59.2)	53 (57.0)	73 (60.3)	0.571
Smoking				
Never (%)	49 (23.0)	19 (20.2)	30 (25.4)	0.509
Former (%)	86 (40.4)	37 (39.4)	48 (40.7)	
Current (%)	77 (36.2)	38 (40.4)	39 (33.1)	
Unknown (%)	1 (0.5)		1 (0.8)	
History of alcohol drinking				
Yes (%)	140 (65.7)	61 (65.6)	79 (65.8)	0.836
No (%)	71 (33.3)	32 (34.4)	39 (32.5)	
Unknown (%)	2 (0.9)		2 (1.7)	
Early termination of chemotherapy				
Present (%)	61 (28.6)	23 (24.7)	38 (31.7)	0.267

Significance set at a 0.05 leve

TABLE 2. Anthropometrics and indices of body composition of head and neck cancer patients prior to chemo-radiotherapy treatment

Body composition measurements	Total N=213	Sample I[a] N=93	Sample II[b] N=120	(mean) diff Sample I and II, p-value
Body weight Mean ± SD				
Overall kg	77.8±18.5	75.3±17.8	79.7±18.8	0.083
Male kg	81.3±17.6	78.9±17.9	83.1±17.3	
Female kg	65.9±16.3	63.4±11.2	68.0±19.5	
(mean) difference male and female, p-value	<0.001*	<0.001*	<0.001*	
Weight loss in 1 month[c] Mean ± SD				
Overall %	1.46±3.56	1.06±3.72	1.76±3.42	0.159
Male %	1.37±3.39	1.19±3.76	1.50±3.09	
Female %	1.78±4.12	0.65±3.65	2.65±4.32	
(mean) difference male and female, p-value	0.489	0.565	0.126	
Body mass index Mean ± SD				
Overall (m^2)	26.3±5.4	25.9±5.0	26.6±5.7	0.315
Male (m^2)	26.6±5.2	26.9±5.3	26.2±5.1	
Female (m^2)	25.5±5.9	25.8±6.9	25.0±4.7	
(mean) difference male and female, p-value	0.209	0.353	0.397	
Skeletal muscle area Mean ± SD				
Overall (cm^2)		191.27 (46.36)	155.44 (36.86)	
Male (cm^2)		208.92 (36.50)	168.2 (30.6)	
Female (cm^2)		134.32 (22.91)	111.07 (23.23)	
(mean) difference male and female, p-value		<0.001*	<0.001*	
Skeletal muscle index Mean ± SD		65.53 (12.60)	51.62 (10.16)	
Overall (cm2/m2)		69.45 (11.02)	53.4 (9.4)	
Male (cm^2/m^2)		52.88 (8.41)	42.23 (7.79)	
Female (cm^2/m^2)		<0.001*	<0.001*	
(mean) difference male and female, p-value				

*Significance set at a 0.05 level

[a] Sample I: 4th thoracic vertebra (T4) as vertebral landmark.

[b] Sample II: 3th lumbar vertebra (L3) as vertebral landmark.

[c] Percentage of weight loss in one month reported at intake for chemo-radiotherapy.

TABLE 3. Univariate and multivariate modeling analysis of skeletal muscle index and confounding variables in HNC patients

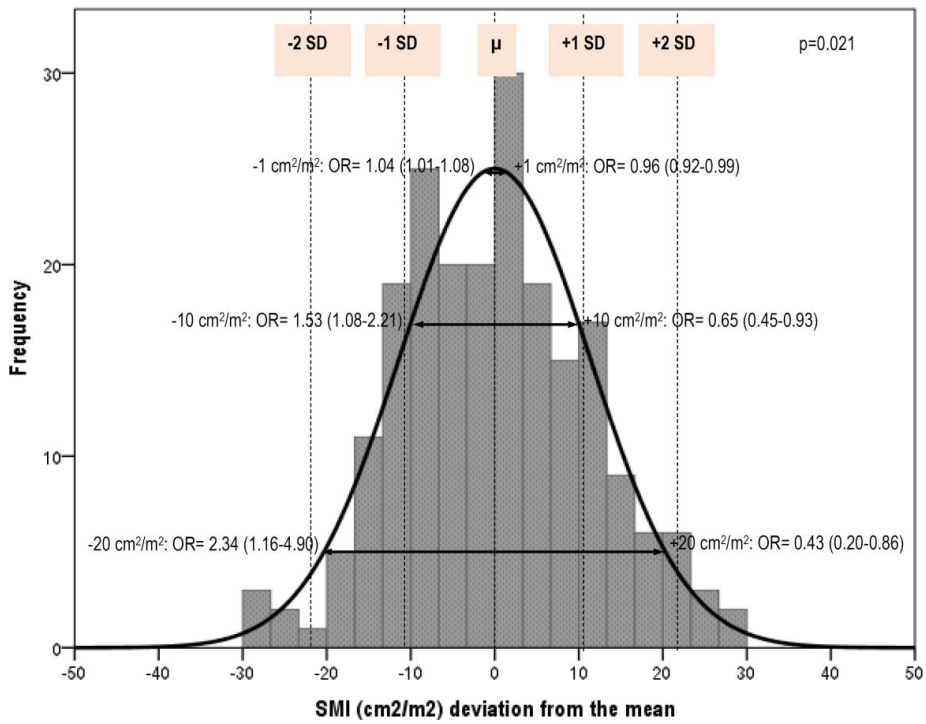
Covariables	Early termination of chemotherapy related to toxicity	
	Univariate (n=213)	
	OR [95%CI]	p-value
Skeletal muscle index (cm^2/m^2)[a]	0.96 [0.94-0.99]	0.007[b]
Body mass index (BMI; kg/m^2)	0.97 [0.92-1.03]	0.277
Age (years)	1.02 [0.99-1.06]	0.126
Sex (Male)		
Female	2.33 [1.19-4.54]	0.013[b]
Stage (I&II)		
III&IV	1.21 [0.24-6.19]	0.817
Tumor site (Others)		
Oropharynx	0.67 [0.36-1.24]	0.203
Treatment (CRT)		
Sx+CRT	1.33 [0.73-2.41]	0.353
Chemotherapy (Cisplatin)		
Carboplatin	0.54 [0.24-1.20]	0.128
Time between CT and CRT (days)	1.00 [0.99-1.01]	0.598
ECOG performance status (0-1)		
2-4	1.12 [0.48-2.62]	0.791
Co-morbidity (No)		
Yes	2.21 [1.16-4.21]	0.016[b]
Alcohol drinking (No)		
Yes	0.69 [0.38-1.27]	0.235
Smoking (No)		
Yes	0.92 [0.49-1.72]	0.802
Alcohol AND smoking (No)		
Yes	0.69 [0.48-1.01]	0.055

[a] Pooled T4 and L3 skeletal muscle index corrected for deviation from the mean; [b] Significance set at a 0.05 level

toxicity-related early termination of chemotherapy treatment corrected for possible

Early termination of chemotherapy related to toxicity					
Multivariate (n=213)					
AIC OR [95% CI]	p-value	BIC OR [95%CI]	p-value	SCAD OR [95%]	p-value
0.95 [0.92-0.98]	0.001[b]	0.96 [0.93-0.99]	0.004[b]	0.96 [0.92-0.99]	0.021[b]
				1.36 [0.59-3.08]	0.469
0.36 [0.14-0.84]	0.023[b]	0.35 [0.14-0.79]	0.017[b]	0.38 [0.15-0.87]	0.029[b]
2.38 [1.21-4.87]	0.015[b]	2.52 [1.30-5.07]	0.008[b]	2.49 [1.27-5.08]	0.010[b]
1.80 [0.58-5.80]	0.314				
1.50 [0.77-3.01]	0.243				
0.41 [0.17-0.97]	0.044[b]			0.66 [0.44-0.98]	0.044[b]

Magnitude of toxicity related unplanned early termination of chemotherapy is assessed with SCAD analysis of skeletal muscle index (SMI; cm2/m2). Positive deviation from the group mean is associated with decrease of the odds of early termination: an SMI that is 1 cm2/m2 higher indicates a decrease in odds of early termination of 4% (OR=0.96). An SMI that is 20 cm2/m2 higher indicates a decrease in odds of early termination of 57% (OR=0.43). Accordingly, negative deviation from the group mean is associated with an increase of the odds for early termination: an SMI that is 1 cm2/m2 lower indicates an increase of odds of early termination of 4% (OR=1.04). An SMI that is 20 cm2/m2 lower indicates an increase of odds of early termination of 134% (OR=2.34).



SMI deviation to the mean		-20 (cm²/m²)	-10 (cm²/m²)	-1 (cm²/m²)	0	1 (cm²/m²)	10 (cm²/m²)	20 (cm²/m²)
Corresponding lumbar or thoracic SMI (cm²/m²)	lumbar	31.6	41.6	50.6	51.6	52.6	61.6	71.6
	thoracic	45.5	55.5	64.5	65.5	66.5	75.5	85.5
OR of early termination of chemotherapy (95% CI)		2.34 (1.16-4.90)	1.53 (1.08-2.21)	1.04 (1.01-1.08)	1.00	0.96 (0.92-0.99)	0.65 (0.45-0.93)	0.43 (0.20-0.86)

Figure 1. Associated odds of early termination of chemotherapy treatment for skeletal muscle index (SMI; cm^2/m^2) in patients with head and neck cancer

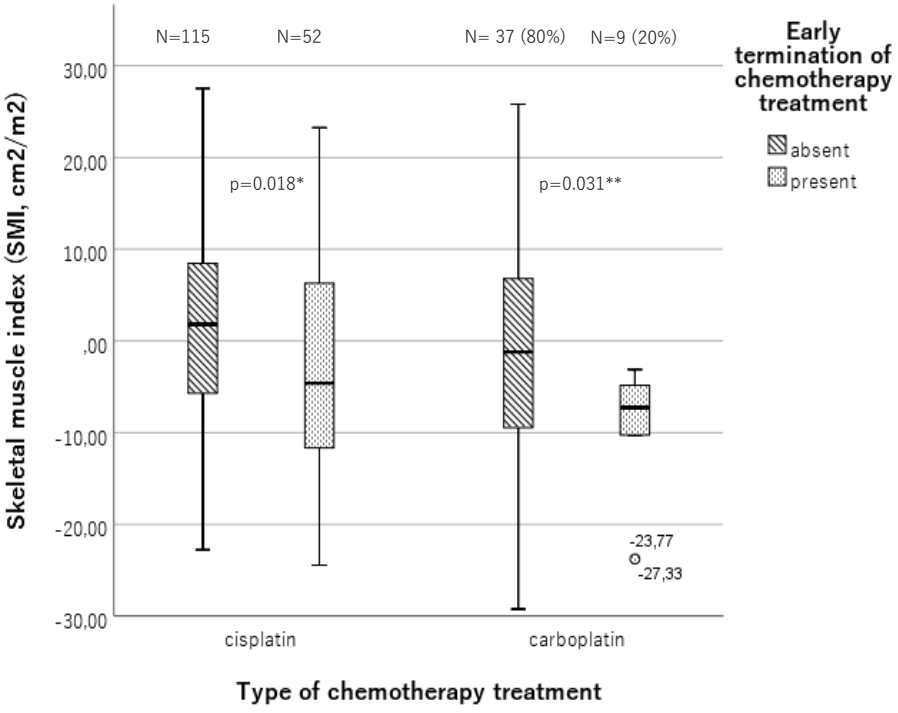


Figure 2. Distribution of skeletal muscle index corrected for deviation from the mean (SMI: cm^2/m^2) across absence (green) or presence (red) of early termination of chemotherapy for cisplatin-based and carboplatin-based treatment in patients with head and neck cancer.

* Number (%) of patients with early termination absent or present. ** Difference in distribution of SMI (cm^2/m^2) across early termination absent or present for cisplatin and carboplatin was tested with an independent samples Mann-Whitney U test. Significance was set at 0.05.

Discussion

The results of our study indicate that cross-sectional measurements of large and representative muscle areas are significantly associated with incidence of toxicity-related early termination of chemotherapy in patients with HNC. A lower level of lumbar and thoracic SMI of 1 cm2/m2 was firmly associated with 4 to 5% higher odds of early termination of chemotherapy. Other variables associated with early termination were type of chemotherapy, presence of co-morbidity, a combination of smoking and alcohol consumption, and sex. The results of this study agree with other studies that have shown that cancer patients with low muscle mass generally are vulnerable to chemotherapy toxicity.[6,15,21,41] We speculate that this could be partially explained by higher concentrations of water soluble chemotherapy agents such as cisplatin and, to a lesser extent, carboplatin in lean tissues in patients with low muscle mass [18]. Our exploratory results also indicate that for both cisplatin-based and carboplatin-based chemotherapy, lower muscle mass was associated with a significantly higher incidence of early termination. Alternatively, complications of chemotherapy may also be explained by reduced overall function as a result of low muscle mass. Studies show that cancer patients with low muscle mass are also vulnerable to a range of other problems, such as slower recovery, complications from surgery, and shorter survival.[5,42,44]

Availability of abdominal CT images was better than reported in other studies in HNC patients.[45,46] In our study, a 94% availability of L3 level CT measurements was encountered in Sample II, which was the more recent cohort of patients with HNC. This broad availability of abdominal CT images is explained by routine imaging with whole body PET-CT scans. Although in recent years a growing number of HNC patients have whole body PET-CT scans for staging purposes, routine abdominal imaging is currently not part of

NCCN guidelines, and clinical practice varies per country and institution.[32] As long as not all CT cross-sectional areas are as well-validated as L3, before deciding on analyzing thoracic or cervical muscle areas in HNC patients, we recommend to first explore the availability of whole body PET-CT scans, and thus L3 images.

To our knowledge, our study is the first to include CT cross-sections of large and representative lumbar and thoracic muscle areas in head and neck cancer patients. The results of our advanced statistical analysis confirmed the results of a study that explored the association between CT cross-sections of smaller cervical muscle areas and toxicity-related early termination in HNC patients.[46] Additionally, our study identified possible interactions of early termination with type of chemotherapy regimen, sex, presence of co-morbidity, and combined smoking and alcohol consumption.

Our study also had some limitations. Firstly, we were not able to acquire CT images that included cross-sections of L3 vertebra for all patients. Currently, a validated formula is available for cross-sectional muscle area at L3 level,[25] but not for T4 level. Therefore, lean body mass on the whole body level could not be estimated. However, we were able to pool and interpret results by correcting T4 and L3 measurements for deviation to their means. Secondly, type and dose of chemotherapy were significantly different between Sample I (2004-2010) and Sample II (2012-2016). This difference resulted from adaptations in head and neck cancer treatment guidelines, in which use of carboplatin is nowadays less often recommended and use of the lower dose of cisplatin is more often recommended. As a result, the subgroup of patients treated with weekly cisplatin (40 mg/m^2) in our sample was limited (n=34). However, toxicity-related early termination did not significantly differ between the subgroup of patients treated with high dose cisplatin 100 mg/m^2 and those treated with weekly cisplatin 40 mg/m^2. Also, studies indicate that high-dose cisplatin at

100 mg/m^2 and weekly cisplatin at 40 mg/m^2 have similar toxicity profiles.[47-49] Hence, we considered it justified to dichotomize type of chemotherapy treatment into cisplatin versus carboplatin in the multivariate analysis. Finally, we combined the data of patients with CRT and surgery prior to CRT. Patients with surgery prior to CRT may have a different disease profile than patients that did not have surgery prior to CRT.[12] Therefore, we included presence or absence of surgery as a co-variable in our statistical analysis. This statistical analysis showed no significant difference in early termination of treatment for both groups.

Our results suggest that CT-based muscle mass assessment may allow clinicians to optimize and tailor care in patients with HNC. Since incidence of early termination is higher in patients with lower muscle mass, the odds of treatment completion may improve if patients receive chemotherapy treatment that is tailored to their muscle mass or lean body mass instead of whole body area estimates. However, adjusting chemotherapy dosage to prevent toxicity should not be considered without testing possible effects of adjustments on disease control. Additionally, in future studies on muscle mass and chemotherapy toxicity in patients with HNC, we recommend taking into account co-variables such as type of chemotherapy, presence of co-morbidity, combined smoking and alcohol consumption and sex, since these variables may possibly interact with chemotherapy toxicity.

In conclusion, in this study we found that a lower muscle mass is associated with higher odds of toxicity-related early termination of chemotherapy treatment in patients with HNC. CT-based muscle mass assessment may allow clinicians to optimize care in HNC patients at risk of complications related to low muscle mass.

References

1. Jager-Wittenaar H, Dijkstra PU, Vissink A, van Oort RP, van der Laan, B F, Roodenburg JL. Malnutrition in patients treated for oral or oropharyngeal cancer--prevalence and relationship with oral symptoms: An explorative study. Support Care Cancer. 2011;19(10):1675-1683.
2. Baracos VE. Cancer-associated cachexia and underlying biological mechanisms. Annu Rev Nutr. 2006;26:435-461.
3. Baracos VE. Skeletal muscle anabolism in patients with advanced cancer. Lancet Oncol. 2015;16(1):13-14.
4. Jager-Wittenaar H, Dijkstra PU, Dijkstra G, Bijzet J, Langendijk JA, van der Laan BF, et al. High prevalence of cachexia in newly diagnosed head and neck cancer patients: An exploratory study. Nutrition. 2017;35(22 Pt 1):114-118.
5. Nishikawa Daisuke D. The impact of skeletal muscle depletion on head and neck squamous cell carcinoma. ORL J Otorhinolaryngol Relat Spec. 2018;80(1):1-9.
6. Baracos V, Kazemi-Bajestani SM. Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses. Int J Biochem Cell Biol. 2013;45(10):2302-2308.
7. Antoun Sami S. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. Current opinion in supportive and palliative care. 2013;7(4):383-9.
8. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, 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. 2013;31(12):1539-1547.
9. Bahig H, Fortin B, Alizadeh M, Lambert L, Filion E, Guertin L, et al. Predictive factors of survival and treatment tolerance in older patients treated with chemotherapy and radiotherapy for locally advanced head and neck cancer. Oral Oncol. 2016;51(5):521-528.
10. Bernier J, Cooper JS, Pajak TF, Van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative

radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843-850.

11. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945-1952.
12. Licitra L, Felip E, ESMO Guidelines Working Group. Squamous cell carcinoma of the head and neck: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20 Suppl 4:121-122.
13. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15(8):2920-2926.
14. Sjøblom B, Grønberg BH, Benth JŠ, Baracos VE, Fløtten Ø, Hjermstad MJ et al. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. Lung Cancer. 2015;90(1):85-91.
15. Baker S D SD. Should anticancer drug doses be adjusted in the obese patient? J Natl Cancer Inst. 1995;87(5):333-4.
16. Ali R, Baracos VE, Sawyer MB, Bianchi L, Roberts S, Assenat E, et al. Lean body mass as an independent determinant of dose - limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. Cancer medicine. 2016;5(4):607-616.
17. Prado CM, Maia YL, Ormsbee M, Sawyer MB, Baracos VE. Assessment of nutritional status in cancer--the relationship between body composition and pharmacokinetics. Anticancer Agents Med Chem. 2013;13(8):1197-1203.
18. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: Molecular mechanisms of action. Eur J Pharmacol. 2014;0:364-378.
19. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: Clinical and nutritional impact. Proc Nutr Soc. 2016:1-11.

20. Chamchod S, Fuller CD, Mohamed AS, Grossberg A, Messer JA, Heukelom J, et al. Quantitative body mass characterization before and after head and neck cancer radiotherapy: A challenge of height-weight formulae using computed tomography measurement. Oral Oncol. 2016;61:62-69.

21. Prado CM, Lima IS, Baracos VE, Bies RR, McCargar LJ, Reiman T, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. Cancer Chemother Pharmacol. 2011;67(1):93-101.

22. Silber JH, Fridman M, DiPaola RS, Erder MH, Pauly MV, Fox KR. First-cycle blood counts and subsequent neutropenia, dose reduction, or delay in early-stage breast cancer therapy. J Clin Oncol. 1998;16(7):2392-2400.

23. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: Advances in models and methods. Annu Rev Nutr. 1997;17:527-558.

24. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

25. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85(1):115-122.

26. Popuri K, Cobzas D, Esfandiari N, Baracos V, Jägersand M. Body composition assessment in axial CT images using FEM-based automatic segmentation of skeletal muscle. IEEE Trans Med Imaging. 2016;35(2):512-520.

27. Edge SB, Compton CC. The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology. 2010;17(6):1471-1474.

28. Zubrod C, Scheiderman M, Frei Iii E, Brindley C, Gold GL, Shnider B, et al. Cancer appraisal of methods for the study of chemotherapy of cancer in men: Thiophosphoramide. Journal of Chronic Disorders. 1960;11:7-33.

29. Ottery F. Patient-generated subjective global assessment. In: McCallum PA EL, ed. The clinical guide to oncology nutrition. Chicago Il: The American Dietetic Association; 2006:44-53.

30. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. Curr Opin Support Palliat Care. 2009;3(4):269-275.

31. Shen W, Punyanitya M, Wang Z, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97(6):2333-2338.

32. Breheny P, Huang J. Coordinate descent algorithms for nonconvex penalized regression, with applications to biological feature selection. Ann Appl Stat. 2011;5(1):232-253.

33. Fan J, Li R. Variable selection via nonconcave penalized likelihood and its oracle properties. Journal of the American statistical Association. 2001;96(456):1348-1360.

34. Fan J, Peng H. Nonconcave penalized likelihood with a diverging number of parameters. The Annals of Statistics. 2004;32(3):928-961.

35. Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974;19(6):716-723.

36. Burnham KP, Anderson DR. Multimodel inference: Understanding AIC and BIC in model selection. Sociological methods & research. 2004;33(2):261-304.

37. Buuren van S, Groothuis-Oudshoorn K. No title. Mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.

38. Buuren van S, Brand JP, Groothuis-Oudshoorn CG, Rubin DB. Fully conditional specification in multivariate imputation. Journal of statistical computation and simulation. 2006;76(12):1049-1064.

39. Hope AC. A simplified monte carlo significance test procedure. Journal of the Royal Statistical Society.Series B (Methodological). 1968:582-598.

40. Patefield W. Algorithm AS 159: An efficient method of generating random R× C tables with given row and column totals. Journal of the Royal Statistical Society.Series C (Applied Statistics). 1981;30(1):91-97.

41. Bahig Houda H. Predictive factors of survival and treatment tolerance in older patients treated with chemotherapy and radiotherapy for locally advanced head and neck cancer. Oral Oncol. 2015;51(5):521-528.

42. Grossberg AJ, Chamchod S, Fuller CD, Mohamed AS, Heukelom J, Eichelberger H, et al. Association of body composition with survival and locoregional control of radiotherapy-treated head and neck squamous cell carcinoma. JAMA Oncol. 2016;2(6):782-789.

43. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol. 2015.

44. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107(6):931-936.

45. Veiga C, McClelland J, Moinuddin S, Lourenço A, Ricketts K. Annkah,J, et al. Toward adaptive radiotherapy for head and neck patients: Feasibility study on using CT - to - CBCT deformable registration for "dose of the day" calculations. Med Phys. 2014;41(3).

46. Wendrich AW, Swartz JE, Bril SI, et al. Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. Oral Oncol. 2017;71:26-33.

47. Lee JY, Sun JM, Oh DR, et al. Comparison of weekly versus triweekly cisplatin delivered concurrently with radiation therapy in patients with locally advanced nasopharyngeal cancer: A multicenter randomized phase II trial (KCSG-HN10-02). Radiother Oncol. 2016;118(2):244-250.

48. Perez CA, Wu X, Amsbaugh MJ, et al. High-dose versus weekly cisplatin definitive chemoradiotherapy for HPV-related oropharyngeal squamous cell carcinoma of the head and neck. Oral Oncol. 2017;67:24-28.

49. Jacinto, JK, Co, J, Mejia, MB, Regala, EE. The evidence on effectiveness of weekly vs triweekly cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell carcinoma (HNSCC): a systematic review and meta-analysis. The British journal of radiology. 2017;90:1079.

Chapter 6. Perception and performance of physical activity behavior after head and neck cancer treatment: exploration and integration of qualitative and quantitative findings

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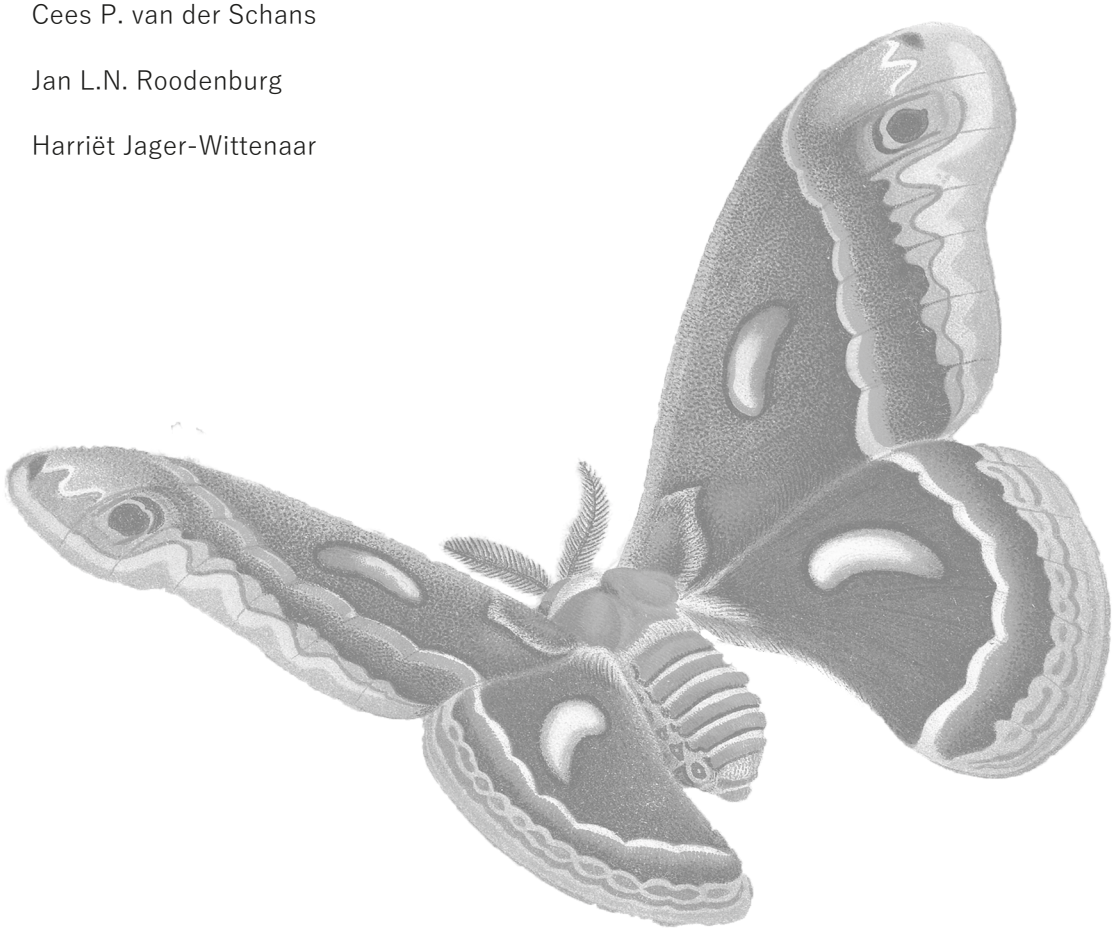

Abstract

Objective: To explore head and neck cancer (HNC) survivors' views on physical activity (PA), their report of PA, and to compare these with objectively measured PA.

Methods: Combined qualitative and quantitative data of HNC survivors were explored post treatment. Data from semi-structured interviews, questionnaires and objective measurements of PA were collected, analysed and integrated.

Results: Five themes were identified (barriers and problems prioritizing, perception and interpretation of PA, no need to increase PA, association of PA with positive feelings or effects, and social support and persuasion) in 9 HNC survivors (male: n=5; age: 52-67 y). Objectively measured PA levels were sedentary to low.

Conclusions: Physical limitations constitute important barriers for PA.PA is considered as a habitual activity and associated with positive feelings or benefits. The lack of intention to increase PA may be related to HNC survivors' perception that their current activity level is sufficient, although the levels of measured PA were low. While some participants feel they need no help with PA, others are insecure about possible harms of PA. A tailored approach that reduces fear of harm and helps to incorporate higher intensity PA in daily activities may help to improve PA in HNC survivors.

Introduction

Survivors of head and neck cancer (HNC) often experience adverse changes in body composition, which are characterized by loss of muscle mass.[1,2] Low muscle mass is associated with lower survival and higher local-regional cancer recurrence after treatment for HNC [3]. Recent findings suggest that maintaining physical activity (PA) may prevent loss of muscle mass and strength during HNC treatment.[4,5,6] Moreover, resistance training after completion of treatment improves muscle mass and strength.[7] However, patients with HNC often show suboptimal lifestyle behavior prior to their diagnosis, which likely includes physical inactivity, although little is known about the average pre-diagnosis level of PA.[8] Also, even though resistance training may be feasible during and after treatment,[5,6] HNC treatment may result in long-term barriers for PA, including fatigue, problems swallowing, and pain.[9] As a result, attaining and maintaining an adequate level of PA after treatment may pose a challenge for post-treatment HNC survivors.

Theory-based interventions tailored to perception and understanding of PA of HNC survivors could potentially contribute to increased PA behavior. However, development and implementation of such interventions require insight into HNC survivors' PA motivation and insight into associations between PA perception and PA performance post treatment. Motivational aspects of PA behavior can be framed using known behavioral theories, such as the Theory of Planned Behavior (TPB) [10] or the Attitude-Social influence-self-Efficacy (ASE) model [11]. These theories have been used with some success to explain physical activity behavior in HNC cancer populations, but could not fully explain variation in PA behavior.[9,12]

To gain better insight into the psychological mechanisms that can influence PA behavior in HNC survivors recovering from anti-cancer treatment, we conducted an explorative study with qualitative and quantitative aspects and a high level of information density per individual. With this information, we intended to increase our understanding of HNC survivors' PA behavior and identify possibilities for PA promotion interventions. Thus, the objectives of this study were to explore HNC survivors' views on PA, including their self-perceived PA-level, and to compare these with objectively measured PA.

Methods

Design

In this study, a two-phase parallel mixed data analysis design was applied. Thus, in parallel but independently, both qualitative and qualitative data were collected and analyzed. The qualitative and quantitative data were combined during the overall interpretation of the results.13 Concepts from the ASE model served to explore subjective PA behavioral mechanisms on two levels: PA beliefs as described in interviews, and PA level as reported by using questionnaires. The data consisted of a predominantly qualitative analysis of semi-structured interviews framed within the ASE model, descriptive analysis of questionnaires regarding PA behavior, and actual measurements of PA with pedometers and accelerometers, in a sample of individuals that were treated for HNC in the University Medical Center Groningen, The Netherlands. This study was a sub-study of a prospective observational study on PA in patients with head and neck cancer; the 'PA in Patients with head and neck cancer' (PAP) study.

Parent study

The Medical Ethical Committee of the University Medical Center Groningen (UMCG) approved the parent (PAP)study: , under regulation of the Medical Research Involving Human Subjects Act (reference METc 2012/063). We obtained permission to add the semi-structured interviews to the original research protocol for the purpose of the current sub-study. The PAP study was registered in the Netherlands Trial Register, reference NTR4828. The primary outcome of the PAP study was PA as assessed by daily step count and PA level as measured by an accelerometer. Secondary outcomes included self-reported physical performance, self-reported PA level, and PA self-efficacy. The UMCG mainly serves patients from the north-east region of The Netherlands. Dutch speaking adult patients with a new primary oral or oropharynx tumor to be treated with surgery with curative intent, with or without adjuvant radiotherapy or concomitant chemo-radiotherapy, were considered eligible. Patients with limited mobility or cognitive impairment were not included. Measurements for the PAP study were performed at three time points: one or two days before surgery (T0), six to eight weeks after completion of HNC treatment (T1), and three months after completion of HNC treatment (T2).

Participants

The sample for the current study was recruited at T1, i.e. six to eight weeks after treatment. All PAP participants who were scheduled for a T1 measurement in the spring of 2013 or in the spring of 2014 were approached for the interviews. The interviewers informed the participants about the purpose and nature of the semi-structured interviews by telephone and asked for additional consent prior to the interviews. Nine out of ten patients who were

considered eligible agreed to participate. The patient who declined participation reported personal circumstances as reason. Participants of neither the PAP study nor the current sub-study were financially compensated for their participation.

Qualitative study component

The qualitative component of the study aimed to explore the subjects' experience of PA, with use of the ASE model as a theoretical framework.

ASE model

The ASE behavioral model is an adaptation from the TPB that integrates the concepts of the TPB with the concept of self-efficacy from the Social Cognitive Theory.[11] The TPB is based on the assumption that the intention of persons to perform certain behavior, such as being physically active, can be predicted from their attitude towards the behavior, from their subjective norms, and from their perceived behavioral control.[14] The ASE model is very similar in the assumption that the intention to perform certain behavior is the central determinant of behavior. However, in the ASE model perceived behavioral control is adapted into self-efficacy, and subjective norm is adapted into social influence. The adaptation from subjective norm into social influence allows to include role modeling, and social support in addition to social norms.[15] Finally, the ASE model includes the concepts 'barriers and stimuli' and 'knowledge and skills'.[11]

Semi-structured interviews

Nine semi-structured interviews, guided by the ASE model, took place at the home of the participants or, if preferred, in a quiet room at the UMCG. The interviews lasted 30-50 minutes. The interviews were performed by two final-year students (one male and one female) from the bachelor Program of Applied Psychology of the Hanze University of Applied Sciences. The interviewers were supervised by researchers with extensive experience in qualitative research and behavioral research in cancer survivors.

Data collection

The interviewers performed the interviews independently and used an interview guide based on a topic list related to concepts of the ASE model. We had additional interests in the participants' view of the role of healthcare professionals in promoting PA. Therefore, this topic was added to the interview guide. All interviews began by asking the participants to describe "What is PA from your point of view?". A sample of the questions that were used, is provided as Online supplement I (Dutch language).

Quantitative component

We enriched the qualitative data with quantitative data from the same nine participants, which were obtained in the parent study. The aim was to explore participants' self-reported PA, self-efficacy and intention, and measurements of objectively measured PA as measured at T1, and to integrate these findings with the findings from the semi-structured interviews.

Measures

Age, sex, cancer diagnosis, cancer stage, and type of treatment, surgery with or without adjuvant radiotherapy or concomitant chemo-radiotherapy, were obtained from the medical records. Weight and height were measured using a platform balance (Seca, Hamburg, Germany) and a stadiometer, calibrated to the nearest 0.2 kg and 0.1 cm, respectively.

The key concepts self-efficacy and intention from both the TPB and the ASE model also provide the basis for validated questionnaires, which can provide insight into various aspects of lifestyle behavior motives to perform PA. The Exercise Self-Efficacy Scale (ESES) [16] and the Stage of Change-Exercise screening instrument (SoC-E)[17] are based on the key concepts of cognitive theory. The ESES was used to explore participants' self-efficacy in performing physical exercise. The score of each item ranges from 0 to 100. A score of 0 indicates the participant has no confidence in his/her skills of performing physical exercise at all, a score of 50 indicates moderate confidence, and a score of 100 indicates the participants has highest confidence in his/her skills of performing physical exercise.[16] The SoC-E instrument, was used to explore self-perceived stage of change of participants regarding PA.[18] In the SoC-E, 'physically active' is defined as doing activities such as walking, playing sports, bicycling or dancing for at least 20 minutes, 3 to 5 times a week. The SoC-E is a single-item scale with a score ranging from 1-5 indicating: pre-contemplation, contemplation, preparation, action, and maintenance, respectively. The Exercise Self-Regulation Questionnaire (SRQ-E) was used to explore participants' self-perceived regulation of regular exercise behavior and is based on the Self-Determination Theory (SDT).[19,20] SDT differentiates behavioral mechanisms in terms of the degree to which they represent autonomous or self-determined functioning versus less autonomous

or controlled functioning. The SRQ-E includes four domains: external regulation, introjected regulation, identified regulation, and intrinsic motivation. All items are stated as assertions and scored on a 1 to 7 Likert scale. The Relative Autonomy Index (RAI) can be calculated from the four domain scores. A predominantly autonomous style will yield a positive RAI score, a predominantly controlled style will yield a negative RAI score.[21]

To assess daily step count, each participant wore a Yamax pedometer for three consecutive days, including one weekend day, in the week before or after T1 measurements were planned. Average steps per day were calculated from the three days of wearing the Yamax device. We classified the PA based on steps counts using the following thresholds: 7500-9999 steps/day = somewhat active; 5000-7499 steps/day = low active; 2500 to 4999 steps/day = limited activity/mostly sedentary; and < 2500 steps/day = basal activity/sedentary.[22] A SenseWearPro3 (SWP3) accelerometer was worn day and night, during the same timeframe as the Yamax pedometer. Average daily PA level (PAL) was calculated from the minute-by-minute SenseWear data as the average MET value during the measured days. PAL was classified as follows: PAL 1.00–1.39 = sedentary; PAL 1.40–1.59 = low active; PAL 1.60–1.89 = active.[23] Average daily time spent in PA with a moderate intensity of at least 3 metabolic equivalents (MET), in minutes, was also calculated for the measured days.[24] A minimum level of 360 minutes per week of moderate intensive PA was associated with better survival in a mixed population of cancer patients,[25] therefore a minimum of 51 minutes of PA at the level of 3 MET per day was used as a threshold for sufficient PA.

Qualitative component

The recorded interviews were transcribed verbatim by the interviewers or the project coordinator.[26] The transcripts were uploaded in Atlas.ti for text coding. The interviews were analyzed by means of directed content analysis[27] using the seven concepts of the ASE model i.e., attitude, social influence, self-efficacy, intention, behavior, barriers and motivators, and knowledge and skills) to generate a template for the coding scheme. Subsequently, the research coordinator coded all text relevant to perception of PA and all codes were placed into one of the seven concepts. This process was repeated by a research assistant with a bachelor's degree in Applied Psychology. The independently coded transcripts from Atlas.ti were compared in harmonization sessions and discussed until consensus for coding was reached. Finally, new overarching themes were allowed to emerge from the codes.

Quantitative component

Data related to participant characteristics and data resulting from ESES, SoC-E, SRQ-E, and PA measurements were reported in a descriptive manner. Summarized results were reported as median (minimum-maximum). SPSS 23.0 (IBM) was used for all quantitative data analyses.

TABLE 1. Characteristics of participants

ID	Sex	Age (y)	Treatment	Tumor class.	Height (m)	Body weight (kg)	Education level	Currently smoking	Currenly using alcohol
P28	female	67	Surgery and chemoradiation	T2	1.74	67	Not reported	no	No
P29	male	65	Surgery and radiotherapy	T2	1.78	68	Vocational higher education	no	No
P30	male	52	Surgery and chemoradiation	T4	1.76	91	Preparatory vocational education	Not reported	Not reported
P31	female	56	Surgery	T1	1.70	56	Vocational secondary education	no	No
P32	female	67	Surgery	T1	1.66	75	Junior general secondary education	no	Yes
P33	male	59	Surgery and radiotherapy	T2	1.93	92	Preparatory vocational education	no	No
P34	female	56	Surgery	T2	1.68	63	Vocational higher education	Not reported	Not reported
P35	male	65	Surgery	T4	1.83	99	Vocational secondary education	yes	No
P36	male	65	Surgery and radiotherapy	T2	1.67	87	Junior general secondary education	yes	No

Results

Participants

Characteristics of the nine participants are reported in Table 1.

Qualitative component

Within the seven concepts of the ASE model that provided the analytical framework, a total of 24 codes were identified. Five overarching themes of PA perception emerged from the

codes: 1) Barriers and problems prioritizing; 2) Perception and interpretation of PA; 3) No need to increase PA (lack of intention); 4) PA is associated with positive feelings or effects; and 5) Social support and persuasion. The codes and themes are presented with ASE concepts and signature quotes in Table 2.

Quantitative component

An overview of the results of the questionnaires and the objective measurements regarding PA are presented in Table 3.

Questionnaires

The median average ESES score was 68 (min 45, max 100; n=7). The scores in the three domains were mostly balanced, although in most participants scores for competing demands tended to be slightly higher than scores for internal feelings and situational/interpersonal. The individual scores indicate a moderate to very high confidence in self-efficacy to exercise. The median SoC-E score in these participants was 5 (min. 2, max. 5). Five out of seven participants reported that they had been physically active for at least 20 minutes per day, 3 to 5 times a week, for more than 6 months, and thus were in a state of exercise maintenance based on the SoC-E.

Overall, participants reported a low level of internalized regulation of PA. The regulatory style represented by the subscales was predominantly controlling, and resulted in negative RAI score for all participants (median -11.3 ; range -15.8 to -5.0), which indicates a limited level of autonomous behavior with regard to PA.

Objective measurements

Step count data were available for eight participants. The median step count was 4094 (min. 807, max. 9852; n=8). Based on step count, two participants were considered somewhat active and four mostly sedentary. Median measured PAL/day was 1.2 (min. 1.0, max. 1.6; n=8). Based on PAL/day, 6 of 8 participants were considered mostly sedentary (PAL ≤1.4). Three individuals met the minimum sufficient level of 51 minutes of PA at 3 MET intensity.

Integrated analysis

Combined qualitative and quantitative data on participant level are presented in Table 4. Five participants reported the highest scores ('I have been physically active for more than 6 months on a regular basis for at least 2.5 hours a week') on the cognitive theory based SoC-E questionnaire. Four of these five participants also reported they had no intention for increasing their PA level. This confidence in maintaining an adequate level of PA appears to conflict with the fact that in four out of these five participants, objectively measured PA level was classified as sedentary. All SRQ-E scores for exercise self-regulation indicate a limited level of autonomous behavior regarding PA. These results appear inconsistent with the ESES scores in which 8 participants reported (high) confidence in their skills to perform PA. Overall, self-perceived PA level is higher than actually measured PA. Only one participant met the recommended guideline for PA. This participant did not report a need for PA improvement and also scored the highest score for self-efficacy and intention. Participants who were committed to PA or motivated for PA and who felt stimulated by their social network tended to have more PA than participants who worried about PA harm.

TABLE 2. Overarching themes of PA perception presented with related codes, ASE

Theme	Code	Concepts ASE	P28	P29	P30	P31
Barriers and problems prioritizing	Physical barriers Physical limitations may include pre-existing problems, for instance knee injuries or lung disease, or limitations resulting from cancer and cancer treatment.	Barriers/Stimuli	●	●	●	●
	Psychological impact of having cancer	Barriers/Stimuli	●	●	●	●
	Fear or insecurities as a result of PA harm	Barriers/Stimuli	●	●		
	External Barriers for PA related to prioritizing. Participants mentioned not being able to have additional PA due to work, social obligations, weather conditions, financial problems/constraints or travel distance	Barriers/Stimuli	●	●	●	●
	Conditional Intention Waiting for physical function to improve. Prepared to increase PA after physical barriers are reduced.	Intention	●	●		
Perception and interpretation of PA	Low intensity activities are serving as examples of typical PA behavior Typical PA: activities in and around the house, volunteer work or informal work, walking or hiking and riding the bicycle.	Knowledge/Skills	●	●	●	●
Perception and interpretation of PA	Poor awareness of limited capacity to perform higher intensity PA activities	Behaviour	●	●	●	●
	PA is a habit/automatism/natural	Self-efficacy	●	●	●	●
	PA is important/ a duty	Behavior			●	●
	Work are important source for PA	Attitude	●			
	PA is different because of not working	Knowledge/Skills		●		●
	Sports as example of PA behavior Jogging and gym-based fitness exercise.	Behaviour		●		
No need to increase PA (lack of intention)	No interest or aversion towards more PA Increase of PA considered irrelevant, because of the amount of PA at work, because of pre-existing PA habits or due to age .	Attitude	●		●	●

concepts and signature quotes

P32	P33	P34	P35	P36	N	Signature Quote
●	●	●	●	●	9	P34: *"And making my bed, well in the summer it is easier, because I don't have a heavy duvet blanket on it. But in the winter, I have a woolen duvet, those are very heavy. I really can't do that".*
				●	5	P36*: I just let it (treatment) happen, but that is pretty much all I do."*
			●	●	4	P29*: I'm not going to do things without thinking it over. I would like to know first whether it is safe"*
●	●	●			7	P34*: "Badminton; that is what I'd like to do most. But then you need a partner, or join a club. And I can't afford to join a club"*
				●	3	P28: *"After that (the cancer) is gone, well, you know, talking and eating is a challenge as well. Still... (hesitates) I think I'll manage then (PA).*
●	●	●	●	●	9	P31: *"Well, just vacuuming, cleaning the house, clipping something in the garden, mowing the lawn. ... [further explanation]...It's not always to do with attitude, you just do things. .. going upstairs, changing the bed linen... always busy".*
●	●	●	●	●	9	
●	●	●			7	P29: *"...when I go to town for groceries, I do take my bike, actually that's something I simply do as part of normal day to day activities"*
	●	●	●	●	6	P34: "*I just think it (PA) is very important."*
	●	●	●	●	5	P33: *"I work in the mornings. I work in the metal industry. That's pretty hard work, in fact; walking all the time and handling heavy things. I am working with my arms, I am working with my hands and I'm working with my head.*
				●	3	P31: *"PA is now different. [...] The inevitability of being physically active (for work), that has now changed into needing to plan when you are going to do something.*
●					2	
●	●	●	●	●	8	P33: *"I will just continue moving the way I do now. And not with something like that ⋯ [sports]. I think this is sufficient. [...] As long as we keep busy, we're good, I think. No need to add anything much. I'm also physically active at work."*

TABLE 2. Continued

Theme	Code	Concepts ASE	P28	P29	P30	P31
No need to increase PA (lack of intention)	Lack of intention	Intention	●		●	●
PA is associated with positive feelings or effects	Positive feelings effects as stimuli for PA	Barriers/Stimuli	●	●	●	●
	Relating PA to positive feelings/effects	Attitude		●	●	●
	Committed to (restoring) PA habits	Intention		●		
	Understanding the health benefits of PA	Knowledge/Skills		●		
	Intrinsically motivated for PA	Self-efficacy				●
Social support and persuasion	PA advise by docters/nurses little, none or no recalling by participant	Social norm	●		●	●
Social support and persuasion	Social network stimulates PA and/or shows some fear of harm P28, P29, P31, P32, P34 felt stimulated, but also mentioned that their social network advised them to be careful.	Social norm	●	●		●
	Physiotherapist is needed or involved	Social norm		●	●	
	Need to do it yourself/to have control	Attitude	●	●		●
	No need for professional help with PA	Self-efficacy	●			●

P32	P33	P34	P35	P36	N	Signature Quote
		●	●	●	6	P35: *"I just don't take the time for it (PA), or don't want to make time. After I have done my work - I think that's enough obligatory physical activity - then I'd rather read a book … or watch something on television that interests me."*
●	●	●	●		8	partner P32: *" Yes, you enjoy doing it (PA). If you like doing something, you keep doing it"*
●	●	●	●		7	P33: *"But it is also pleasant to be outside, to take a stroll. My wife spends the whole day in the hospital, but then we say 'let's catch some fresh air"*
●	●	●			4	P32: *"I was first operated on in September, in October a second time, and in November a third time and then my husband wouldn't let me go work out any sooner than January. So I started on January 2nd, right away."*
	●	●		●	4	P34: *"For example, this morning I washed the dishes and mopped the kitchen; and just by getting moving, the pain [in my knees] is less bad".*
●		●			3	
	●	●	●	●	7	P33: *"Well wait a minute - I believe they did tell me once to 'keep moving'. But I think I mentioned it first. That I'm usually active. Yes, and then they told me that I should keep moving."*
●	●	●			6	P29: *"But when I'm with colleagues - these people are very much into exercising, and someone will ask you at some point. "What time did you run?"…that can be very stimulating".* P32*: "I would have liked to start [working out] a little sooner, but he [points at partner] wouldn't let me that is why. But otherwise nothing has changed".*
	●		●	●	5	
		●	●		5	P35: "*I would prefer to build myself a (PA) schedule".*
		●	●		4	P31: *"But, look, I have always done that [PA] myself. I was a single mom, so I took all my decisions myself. I know very well what I can do and what is good for me. I really need no help with that.*

Table 3. Quantitative results of questionnaires and measurements on participant level

		Questionnaires				
ID	Sex	**ESES[a]** (n=7)	**SoC-E[b] (n=8)**	SRQ-E[c] ER (n=7)	SRQ-E[c] IR (n=7)	SRQ-E[c] ID (n=7)
P28	Female	NA	5	NA	NA	NA
P29	Male	73	3	7.0	5.5	1.8
P30	Male	NA	NA	NA	NA	NA
P31	Female	68	5	6.3	5.3	1.5
P32	Female	100	4	7.0	7.0	4.8
P33	Male	61	5	6.0	5.8	2.8
P34	Female	70	5	7.0	6.3	1.5
P35	Male	54	5	7.0	7.0	2.5
P36	Male	45	2	5.3	5.8	2.8
Median		**68**	**5**	7.0	5.8	2.5
(min-max)		**(45-100)**	**(2-5)**	(5.3-7.0)	(5.3-7.0)	(1.5-4.8)

Summarized scores of multidimensional instruments ESES and SRQ-E are printed in bold print.

[a] Exercise Self-Efficacy Scale (ESES). ESES = average ESES score. ESES scores range from 0 to 100. 0 = no skills of performing physical exercise.

[b] Exercise Stages of Change (SoC-E): 1 = pre-contemplation; 2 = contemplation; 3 = preparation; 4 = action; 5 = maintenance.

[c] Exercise Self-Regulation Questionnaire [SRQ-E; Deci and Ryan]. ER = external regulation; IR = introjected regulation; ID = identified regulation; IM = intrinsic motivation. Scores:1 = regulation or motivation very untrue for participant; 4 = regulation or motivation somewhat true for participant; 7 = regulation or motivation very true for participant.

		Measures		
SRQ-E[c] IM (n=7)	**SRQ-E[c] RAI[d]** (n=7)	steps/ day[e] (n=8)	PAL/ day[f] (n=8)	Minutes of MET level 3/ day[g]
NA	NA	807	1.2	20
3.8	-10.3	5439	1.5	113
NA	NA	NA	NA	NA
2.0	-12.3	9852	1.6	205
2.5	-11.3	5998	1.2	83
3.5	-8.0	7763	1.3	47
1.5	-15.8	2750	1.0	27
2.0	-14.5	1314	1.0	8
4.3	-5.0	1383	1.1	12
2.5	**-11.3**	4094	1.2	37
(1.5-4.3)	**(-15.8 - -5.0)**	(807-9852)	(1.0-1.6)	(8-205)

[d] Relative Autonomy Index (RAI): 2 X Intrinsic + Identified - Introjected - 2 X External. A predominantly controlled style will yield a negative RAI and a predominantly autonomous style will yield a positive RAI.

[e] Steps/day: 7500-9999 steps/day = somewhat active; 5000-7499 steps/day = low active; 2,500 to 4,999 steps/day = limited activity/ mostly sedentary; and < 2,500 steps/day = basal activity/ sedentary

[f] PAL/day: PA level/day. PAL 1.00–1.39 = sedentary; PAL 1.40–1.59=low active; PAL 1.60–1.89=active

[g] Metabolic equivalents minutes of MET 3 medium intensive activity > 360 minutes/week = < 51 minutes/day

NA = not available

Table 4. Combined qualitative and quantitative results on participant level

Participant **Selected codes from interviews**	**Activity level measured by steps, PAL and minutes spend in 3 MET PA per day**	**Self-reported PA self-efficacy according to ESES**
Fear of harm/inactivity/lack of motivation/ lack of support = … At least one or two themes positive for PA =⋯. Reports sports/motivated/ feels supported = ⋯.	Basal, sedentary or insufficient activity score = … Limited to low activity score = ⋯. Ssomewhat active, active or sufficiently active PA score = ⋯	Low confidence in PA skills = … (moderate) Confidence in PA skills = ⋯ Highest confidence in PA skills = ⋯
P32 female Reported PA sports Committed to or motivated for PA Feels stimulated by social network	Steps: low active PAL: sedentary 3 MET minutes sufficient	Highest confidence in skills to perform PA
P31 female Reported PA low intensity No intention to improve PA Feels stimulated by social network	Steps: somewhat active PAL: active 3 MET minutes sufficient	Confidence in skills to perform PA
P33 male Reported PA low intensity Committed to or motivated for PA Feels stimulated by social network	Steps: somewhat active PAL: sedentary 3 MET minutes not sufficient	Confidence in skills to perform PA
P34 female Reported low PA intensity No intention to improve PA Committed to or motivated for PA Feels stimulated by social network	Steps: limited activity PAL: sedentary 3 MET minutes not sufficient	Confidence in skills to perform PA
P29 male Worries about harm from PA Reported PA sports Committed to or motivated for PA Feels stimulated by social network	Steps: low active PAL: low active 3 MET minutes: sufficient	Confidence in skills to perform PA
P28 female Worries about harm PA Reported PA low intensity No intention to improve PA Feels stimulated by social network	Steps: basal activity PAL: sedentary 3 MET minutes not sufficient	Not Available

Self-reported PA intention according to SoC-E low PA intention = ⋯ (preparing) PA action = ⋯ maintaining PA = ⋯	**Self-reported autonomous PA behavior according to SRQ-E** little autonomous PA behavior = ⋯ low to moderate autonomous PA behavior = ⋯ predominantly autonomous PA behavior ⋯	**Signature quotation**
Action regarding reaching a sufficient level of PA	Little autonomous behavior regarding PA	*I was first operated on in September, in October for the second time, and in November for the third time and then my husband would not allow me to work out any sooner that January. So I started on January 2nd, right away.*
Maintaining a sufficient level of PA	Little autonomous behavior regarding PA	*Your body has let you down a little bit, so that is a difference[⋯] PA is now different. [...] The inevitability of being physically active (for work), has now changed into needing to plan when you are going to do something.*
Maintaining a sufficient level of PA	Little autonomous behavior regarding PA	*Look, PA is always good, right? But you need to enjoy PA. If you get no pleasure from it, then it kind of becomes an obligation. [⋯.] On the other hand, let's say [you need PA] to accomplish certain health goals ⋯ By combining both, fun and obligation, you do get results.*
Maintaining a sufficient level of PA	Little autonomous behavior regarding PA	*Look, it is not like: "cancer has happened to me, let us just get on with it". But before, [cancer] I was already physically active, so that did not change a lot in itself. Now I'm a little more aware of it (PA) sometimes. But I'm not thinking 'I should have more PA because I had cancer'.*
Preparing for actions regarding reaching a sufficient level of PA	Little autonomous behavior regarding PA	*I am not looking for an easy way. In my old work building, I still go there a lot so to speak... there is an elevator, but I always take the stairs and stuff, like I always used to do*
Maintaining a sufficient level of PA	Not Available	*Well, I would not start with biking. I think that I sway somewhat⋯ that [is why] I don't dare [to do] it that well. But, walking I would do. In the afternoon an hour's walk,⋯, but I haven't done that yet, you know, I haven't come that far yet.*

TABLE 4. Continued

Participant **Selected codes from interviews**	**Activity level measured by steps, PAL and minutes spend in 3 MET PA per day**	**Self-reported PA self-efficacy according to ESES**
Fear of harm/inactivity/lack of motivation/ lack of support = … At least one or two themes positive for PA =…. Reports sports/motivated/ feels supported = ….	Basal, sedentary or insufficient activity score = … Limited to low activity score = …. somewhat active, active or Sufficiently active PA score = …	Low confidence in PA skills = … (moderate) confidence in PA skills = … highest confidence in PA skills = …
P35 male Worries about harm from PA Reported PA low intensity No intention to improve PA	Steps: basal activity PAL: sedentary 3 MET minutes not sufficient	Moderate confidence in skills to perform PA
P30 male Reported PA low intensity No intention to improve PA	Not Available	Not Available
P36 male Worries about harm from PA Reported PA low intensity No intention to improve PA	Steps: basal activity PAL: sedentary 3 MET minutes not sufficient	Lower to moderate confidence in skills to perform PA

Self-reported PA intention according to SoC-E low PA intention = ⋯ (preparing) PA action = ⋯ maintaining PA = ⋯	**Self-reported autonomous PA behavior according to SRQ-E** little autonomous PA behavior = ⋯ low to moderate autonomous PA behavior = ⋯ predominantly autonomous PA behavior ⋯	**Signature quotation**
Maintaining a sufficient level of PA	Little autonomous behavior regarding PA	*No, it [feeling fit and sleeping well] does not motivate me, but I am PA because it has to be done. It is my work. The PA is something [⋯] that I just must do, dutifully. If I don't, I will forsake.*
Not Available	Little autonomous behavior regarding PA	*It (PA) is not a thing that actually appeals to me. You do it automatically for work. It is an automatism, you are physically active because it is necessary ⋯ (to carry out work). But I wouldn't say "Boys, let's go for a nice jog, or workout."*
Contemplating actions regarding PA	Little autonomous behavior regarding PA	*Well, it was the same before the treatment, but I was a little more active and showed a little more enthusiasm. Now I'm constantly up against myself and have great difficulty with swallowing. And I uhm, I don't feel at home in my body. [⋯] Everything takes great effort⋯*

Discussion

This study added quantitative data to a qualitative design to explore HNC survivor's views on PA, their report of PA and to compare these with objectively measured PA. The qualitative exploration led to identification of five major themes that may contribute to a more nuanced understanding of behavioral patterns. While participants reported a relatively high level of self-efficacy and intention in the cognitive theory-based questionnaires, the reported level of autonomous behavior with regard to PA was limited in the self-determination driven questionnaire. Overall, objectively measured PA was low to mostly sedentary. Participants identified physical limitations, either pre-existing or caused by cancer or its treatment, as an important barrier for PA. Barriers also often appeared to be related to problems with prioritizing PA. All participants reported examples of PA characterized by low intensity. Most participants considered daily activities and occupational activities to be synonymous with PA in general. Participants generally saw no need to increase PA, and most participants viewed PA as associated with positive feelings or effects, regardless of their actual PA performance. Finally, social support and persuasion came up as an important theme. While some participants found they do not need help with PA, others were insecure about possible harms of PA and indicated that they would appreciate help of a physiotherapist. The fear of harm resulting from PA aligns with findings in other studies.[9,28]

The combined interview and questionnaire results suggest that the high scores for self-efficacy are congruent with the lack of intention to further increase PA as reported in the interviews. However, the limited level of autonomous behavior reported in the SDT questionnaire appears to conflict with the high confidence in self-efficacy reported by the

participants. On the other hand, this limited level of autonomous behavior seems in agreement with the limited motivation and the lack of intention to increase PA expressed during the interviews. The persons that explicitly expressed a need for professional help with PA in the interviews were among the participants with the least low SRQ-E RAI scores. These persons also scored highest for the SRQ-E domain Intrinsic Motivation. We speculate that these individuals perhaps were aware of their need for support and thought that they could improve their PA level with professional help.

The apparent contradiction between the high self-perceived self-efficacy and intention and the objective measurements that indicate mainly sedentary PA behavior, may be partially explained by the fact that almost all participants described PA as a habit, an automatism, and also something that comes naturally as a result from their work. These results may indicate that participants may overestimate their PA performance as a result from unawareness of how much PA is needed and what intensity of PA is needed to achieve active PA performance. If PA performance is overestimated, and judged to be at a sufficient level, participants may have little incentive to prioritize PA.

Our results partially agree with other studies of PA behavior in HNC survivors. In a survey on physical activity barriers and social cognitive theory correlates of exercise behavior in HNC survivors, physical symptoms resulting from HNC and its treatment were significantly correlated with PA barriers and low self-efficacy.[9] Our results also indicate that physical limitations are an important barrier for PA, but the physical problems in our participants were not always related to cancer and its treatment. In our interviews, the association between codes related to intention and codes related to other social cognitive concepts did not appear very clear. This impression is similar to the results of another, more recent survey on social cognitive correlates of exercise in a large sample of HNC survivors.

Although that study found statistically significant associations between intention and most other TPB concepts, less than a quarter of the variance in intention and only one-sixth of exercise behavior could be explained by the TPB.[12]

Strengths and limitations

Our study provides unique in-depth insights regarding PA in HNC survivors, due to the design that allowed for exploring and combining data from interviews, questionnaires and measurements. However, our study also had some limitations. Firstly, the number of participants in the current study was limited, and within the small sample there is some missing data for the quantitative measurements. On the other hand, we present a high level of data density per participant. Secondly, the recruitment for this study was limited to the participants included in the parent study. Patients that participated in the parent study may have had a higher than average interest in the subject of PA when compared to the average HNC population. If the PA results are above average in our participants, due to a higher than average interest in PA, PA intention and behavior in a less motivated group of HNC survivors may be even less pronounced.

Recommendations for research and practice

Since physical limitations may constitute important barriers for additional PA, this is an important target for HNC rehabilitation. Because many HNC survivors experience physical issues, improving coping with impairments while being physical active may help improve PA. In addition, some HNC survivors may have a need for behavioral support, i.e. professional guidance to help them prioritize PA and make them feel safe while exercising.

A recent study reported that participation in an exercise program increased priority of exercise and improved lack of interes.[29] Additionally, a tailored approach that reduces fear of harm and emphasizes safety of PA may improve exercise self-efficacy.[30] Also, helping HNC survivors to understand how they can incorporate more intensive forms of PA in daily activities and work may help them to improve their PA level.[31,32] However, survivors may overestimate their current level of PA and thus may not be intrinsically motivated to improve PA. In those cases, a necessary first step is to improve awareness of actual PA level with use of instruments such as step counters or accelerometers.[33] These measurement results may also provide a base for setting PA goals.

For survivors who have an intention to not become more physically active, TPB-based counseling strategies which target intention may provide a suitable approach. However, our results indicate that, for some HNC survivors, PA does not follow from a conscious intention to be physically active. Rather, it is the result of engaging in other meaningful activities (e.g. work). In such cases, using only TPB-based strategies might be less useful. For this reason, for future research aimed at understanding PA and development of tailored interventions in HNC survivors, we recommend to critically review the appropriateness of the theoretical framework that is used. If not all patients have an explicit intention for PA, it might be valuable to explore the applicability of theories that focus more on assuming that individuals operate on different levels of motivation and autonomy (such as Self Determination Theory). The higher scores found in our study for external regulation and introjected regulation could indicate that PA behavior is mostly employed if rewards or external approval can be gained.[21] To encourage PA at higher intensity levels in HNC survivors, it may be helpful if physical exercise is individually monitored, progression is applauded, and benefits of progression are made explicit and match the patient's interest.

Conclusion

Physical limitations, either pre-existing or caused by cancer or its treatment, constitute important barriers for PA in our sample of recent HNC survivors. HNC survivors in our sample considered PA to be synonymous with habitual daily activity, which they associated with positive feelings or benefits. The lack of intention to improve PA may be partially explained by the finding that HNC survivors perceive their - mostly low-intensity - activities as already sufficient, even though the median level of measured PA was sedentary. Finally, although some participants feel that they do not need help with PA, others are insecure about possible harms of PA. A tailored approach that reduces fear of harm and helps to incorporate higher intensity PA in daily activities, may help to improve PA in HNC survivors.

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References

1. Jager - Wittenaar H, Dijkstra PU, Vissink A, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head Neck*. 2011;33(6):863-870.

2. Chamchod S, Fuller CD, Mohamed AS, et al. Quantitative body mass characterization before and after head and neck cancer radiotherapy: A challenge of height-weight formulae using computed tomography measurement. *Oral Oncol*. 2016;61:62-69.

3. Grossberg AJ, Chamchod S, Fuller CD, et al. Association of body composition with survival and locoregional control of radiotherapy-treated head and neck squamous cell carcinoma. *JAMA Oncol*. 2016;2(6):782-789.

4. Sandmael JA, Bye A, Solheim TS, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: A pilot randomized trial. *Cancer*. 2017;123(22):4440-4448.

5. Grote M, Maihöfer C, Weigl M, Davies-Knorr P, Belka C. Progressive resistance training in cachectic head and neck cancer patients undergoing radiotherapy: A randomized controlled pilot feasibility trial. *Radiation Oncology*. 2018;13(1):215.

6. Lonkvist CK, Vinther A, Zerahn B, et al. Progressive resistance training in head and neck cancer patients undergoing concomitant chemoradiotherapy. *Laryngoscope investigative otolaryngology*. 2017;2(5):295-306.

7. Lonbro S, Dalgas U, Primdahl H, et al. Progressive resistance training rebuilds lean body mass in head and neck cancer patients after radiotherapy--results from the randomized DAHANCA 25B trial. *Radiother Oncol*. 2013;108(2):314-319.

8. Duffy SA, Ronis DL, McLean S, et al. Pretreatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. *J Clin Oncol*. 2009;27(12):1969-1975.

9. Rogers LQ, Courneya KS, Robbins KT, et al. Physical activity correlates and barriers in head and neck cancer patients. *Support Care Cancer*. 2008;16(1):19-27.

10. Ajzen I, Fishbein M. Theory of reasoned action-theory of planned behavior. *University of South Florida*. 1988.

11. de Vries H, Dijkstra M, Kuhlman P. Self-efficacy: The third factor besides attitude and subjective norm as a predictor of behavioural intentions. *Health Educ Res*. 1988;3(3):273-282.

12. Buffart LM, de Bree R, Altena M, et al. Demographic, clinical, lifestyle-related, and social-cognitive correlates of physical activity in head and neck cancer survivors. *Support Care Cancer*. 2017.

13. Teddlie C, Tashakkori A. *Foundations of mixed methods research: Integrating quantitative and qualitative approaches in the social and behavioral sciences.* Sage; 2009.

14. Ajzen I. From intentions to actions: A theory of planned behavior. J. kuhl, & J. beckman (eds.), action-control: From cognition to behavior (pp. 11-39). *Heidelberg: Springer*. 1985.

15. van Bree RJ, van Stralen MM, Bolman C, Mudde AN, de Vries H, Lechner L. Habit as moderator of the intention–physical activity relationship in older adults: A longitudinal study. *Psychol Health*. 2013;28(5):514-532.

16. Bandura A. *Social foundations of thought and action.* Englewood Cliffs NJ: Prentice Hall; 1986.

17. Marcus BH, Banspach SW, Lefebvre RC, Rossi JS, Carleton RA, Abrams DB. Using the stages of change model to increase the adoption of physical activity among community participants. *Am J Health Promot*. 1992;6(6):424-429.

18. Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. *Res Q Exerc Sport*. 1992;63(1):60-66.

19. Deci EL, Ryan RM. Self-determination theory: A macrotheory of human motivation, development, and health. *Canadian psychology/Psychologie canadienne*. 2008;49(3):182.

20. Deci EL, Ryan RM. The general causality orientations scale: Self-determination in personality. *Journal of research in personality*. 1985;19(2):109-134.

21. Olson BC. Motivation and competition: Their role in sports. *Sports, games, and play: Social and psychological viewpoints*. 1989:83.

22. Tudor-Locke C, Craig CL, Aoyagi Y, et al. How many steps/day are enough? for older adults and special populations. *International Journal of Behavioral Nutrition and Physical Activity*. 2011;8(1):80.

23. Ma G, Luan D, Li Y, et al. Physical activity level and its association with metabolic syndrome among an employed population in china. *Obes Rev*. 2008;9 Suppl 1:113-118.

24. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for health professionals from the american heart association. *Circulation*. 1990;82(6):2286-2322.

25. Gunnell AS, Joyce S, Tomlin S, et al. Physical activity and survival among long-term cancer survivor and non-cancer cohorts. *Front Public Health*. 2017;5:19.

26. Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: Developing best practices based on science and experience. *Quality of Life Research*. 2009;18(9):1263-1278.

27. Potter WJ, Levine‐Donnerstein D. Rethinking validity and reliability in content analysis. . 1999.

28. Wasley D, Gale N, Roberts S, et al. Patients with established cancer cachexia lack the motivation and self-efficacy to undertake regular structured exercise. *Psychooncology*. 2017.

29. Jackson C, Dowd A, Capozzi L, Bridel W, Lau H, Culos‐Reed S. A turning point: Head and neck cancer patients' exercise preferences and barriers before and after participation in an exercise intervention. *European journal of cancer care*. 2018;27(2):e12826.

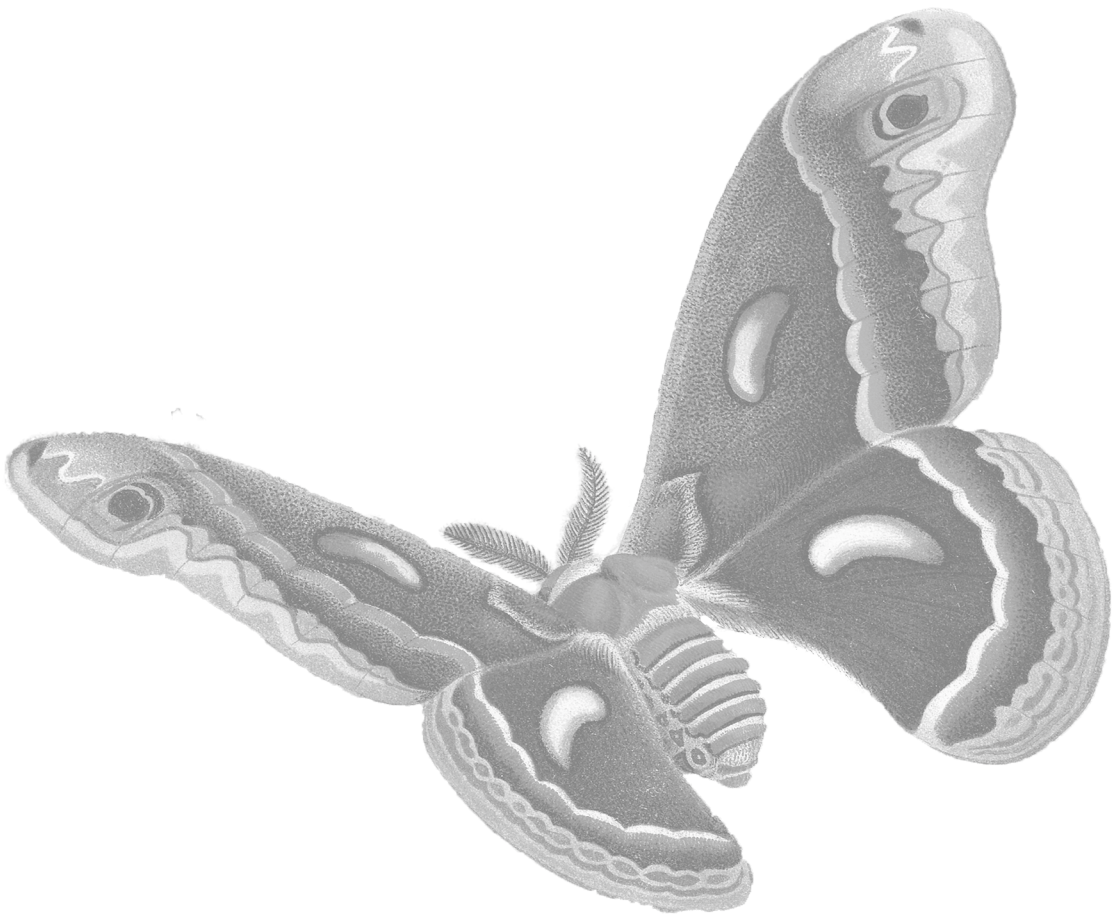
30. Ringash J, Bernstein LJ, Devins G, et al. Head and neck cancer survivorship: Learning the needs, meeting the needs. *Semin Radiat Oncol*. 2018;28(1):64-74.

31. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate-to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. *Journal of Clinical Oncology*. 2015;33(17):1918-1927.

32. Toohey K, Pumpa K, McKune A, Cooke J, Semple S. High-intensity exercise interventions in cancer survivors: A systematic review exploring the impact on health outcomes. .

33. Valle CG, Deal AM, Tate DF. Preventing weight gain in african american breast cancer survivors using smart scales and activity trackers: A randomized controlled pilot study. *J Cancer Surviv*. 2017;11(1):133-148.

Chapter 7. General discussion



Introduction

Malnutrition increases the risk of developing postoperative complications, a decreased tolerance or response to cancer treatment, reduces quality of life and leads to higher mortality in patients with head and neck cancer.[1-5] Even though prevalence of malnutrition and loss of muscle mass and strength have been studied in patients with head and neck cancer for decades now,[6,7] today, patients with head and neck cancer are still at serious risk of becoming malnourished from diagnosis to rehabilitation phase.[8-10]

In this thesis the general aim was threefold. Firstly, to describe diagnostic value of malnutrition assessment methods including body composition assessment with CT analysis. Secondly, to adapt the PG-SGA for Dutch practice. Finally, to explore psychological mechanisms that may influence physical activity behavior in patients with head and neck cancer. There is broad consensus that prevention and treatment of malnutrition is of great importance in patients with head and neck cancer, since an adequate nutritional status is related to improved outcomes.[9,11-13] Nevertheless, there is still discussion about which instrument(s) to use in order to be able to assess the nutritional status. Additionally, it is still not clear how the diagnosis of malnutrition in cancer patients can be employed for design of interventions tailored to the needs of the patient. Therefore, diagnostic value of malnutrition assessment methods in patients with cancer needed to be studied. Furthermore, patients with head and neck cancer may have a sedentary life style. Improved physical activity may improve muscle mass and muscle strength. Improved muscle mass and strength, in turn, improves nutritional status of patients with head and neck cancer. Therefore, promoting an active lifestyle can be part of treatment of malnutrition. However, it is unclear whether patients with head and neck cancer are motivated to improve their physical activity level. Therefore, we needed to study existing

behavioral patterns and perceptions with regard to physical activity that are present in patients with head and neck cancer.

Main findings

Malnutrition

One of the objectives of this thesis was to provide an overview of malnutrition assessment methods used in adult cancer patients in the recent literature, and to determine their content validity based on consensus-based definitions of malnutrition. For this purpose, in the systematic review (Chapter 2), a model was provided for a multidimensional construct based on broadly accepted ESPEN and ASPEN definitions of malnutrition.[14] Four domains were identified within the conceptual definitions of malnutrition: 1. Nutrient balance; 2. Body shape, body size and body composition; 3. Body function; and 4. Inflammatory factors.[15] In addition, this study identified 37 methods that are used to assess malnutrition in research. The operationalization of malnutrition was evaluated as defined, in all methods with proportional scores with use of content validity scores. Content validity scores can range from 0-1 and a predefined cut-off score ≥0.80 was considered acceptable. When measured against the multidimensional construct, the content validity of none of the methods used was acceptable. In almost half of the methods that have been used to assess malnutrition, only one domain of the multidimensional construct of malnutrition was operationalized. This lack of agreement between the conceptual definitions for malnutrition[16,17] and malnutrition operationalization for diagnostic purpose results in low content validity. Low content validity, in its turn, indicates a lack of diagnostic value with regard to malnutrition as defined. Accurate diagnosis of multidimensional aspects of

malnutrition is very important, not only to identify the patients with malnutrition correctly, but also to identify problems within each domain to provide guidance to tailor malnutrition treatment to the specific needs of the patient (Chapter 3).

Assessment of nutritional status

PG-SGA

The systematic review (Chapter 2) indicates that content validity is not acceptable in any methods that were identified to be used for diagnosis of malnutrition in cancer patients. Since there is no cancer-specific definition for malnutrition, the Mini Nutritional Assessment (MNA), the Subjective Global Assessment (SGA) and the Patient-Generated Subjective Global Assessment (PG-SGA) were categorized with the highest content validity and thus best cover the breadth of the definitions for malnutrition in general. The PG-SGA is a versatile instrument that can be used for screening, interventional triage, assessment, and monitoring of nutritional status and risk factors. In addition, the PG-SGA includes both patient- and professional-reported items, thus providing accumulated insight from both perspectives in the nutritional status of the patient.[18] Because of this versatility, in the Netherlands the PG-SGA could provide a valuable addition to the instruments that are currently available. Although dietitians in the Netherlands were aware of the existence of the PG-SGA, it had not been officially translated into the Dutch language. A straightforward translation of the PG-SGA from English to Dutch could have led to loss of the original purpose, meaning and format.[19] Therefore, a objective was to translate and culturally adapt the original English PG-SGA for the Dutch setting. We safeguarded conceptual, semantic and operational equivalence by performing a systematic forward and backward translation and cultural adaptation of the PG-SGA according to a rigorous

international consensus-based approach (the ISPOR Principles).[20] In addition to items regarding relevance to safeguard content validity,[21] extra information was generated by discriminating between comprehensibility and difficulty. By including items regarding comprehensibility and difficulty of the PG-SGA, deeper insight was gained in what items are considered comprehensible, implying the formulation is clear, and what items are considered difficult, implying a need for more knowledge and/or training by the respondent.[19,22,23] The Dutch version of the PG-SGA that was developed is considered comprehensible and easy by our sample of patients (Chapter 3 and 4). However, although the PG-SGA was considered comprehensible and relevant to assess malnutrition by healthcare professionals, the professional component is considered difficult by our sample of professionals. This may be explained by the fact that most of the professionals were not yet familiar to the PG-SGA. Therefore, subsequently change of perceived comprehensibility and difficulty in the use of the PG-SGA in dietitians after a training was evaluated. Perceived comprehensibility and difficulty of the PG-SGA improved significantly in a sample of PG-SGA-naïve dietitians after providing a single day of explanation and hands-on training in the use of the PG-SGA. After training, perceived comprehensibility reached an acceptable level for all components of the PG-SGA and perceived difficulty improved significantly. However, the scores for perceived difficulty of items regarding the physical examination and food intake remained under the predefined cut-off for acceptability (Chapter 4). The lower scores for perceived difficulty of the physical examination may be partially explained by the fact that the physical examination of patients is traditionally not a part of the training of dietitians in the Netherlands. Therefore, Dutch dietitians may have limited knowledge and skills regarding the physical

examination. The full PG-SGA is now available for the Dutch setting, but training is recommended for professionals to feel more comfortable with all elements of the PG-SGA.

Muscle mass and chemotherapy tolerance

Another objective was to study the association between low pre-treatment muscle area measured with CT analysis and toxicity-related early termination of chemotherapy treatment in patients with head and neck cancer. The results of this study indicate that lower lumbar or thoracic skeletal muscle area is firmly related to higher odds of early termination of chemotherapy treatment (Chapter 5). Similar associations between low muscle mass and increase of chemotherapy treatment intolerance were also found in other studies.[24-26] In addition, other CT-based muscle mass analysis studies show an association between low muscle mass and outcomes, such as treatment intolerance and mortality in patients with head and neck cancer.[27,28] Also, cut-off values for low muscle mass have been established, based on large datasets that include patients with head and neck cancer.[28] Importantly, a recent study reported that muscle mass depletion in patients with head and neck cancer can be overlooked with the use of body area estimates that are solely based on body mass and stature.[29] However, in the cancer setting, body area measurements based on body mass and stature, such as body mass index (BMI), are still being used to screen for deviations in body composition.[30] Moreover, body area measurements, such as body surface area (BSA), are used for dose calculation of pharmacological interventions (i.e., chemotherapy agents such as cisplatin). Since patients with low muscle mass can be overlooked with the use of body area estimates, use of body area estimates in these patients may have consequences for their treatment tolerance and, ultimately, outcome. If diagnostic CT images and knowledge of image analysis are present, CT images can be used.

If CT images at L3 level are not available, CT images at other vertebra levels may provide an alternative.

Physical activity

A final objective of this thesis was to explore views on physical activity and reports of physical activity of head and neck cancer survivors, and to compare these views with objectively measured physical activity. Increase of physical activity is an important means to improve body composition and body function, and thus nutritional status in cancer patients.[31-33] However, patients with head and neck cancer showed mostly sedentary behavior (Chapter 6). The lack of intention to improve physical activity may be partially explained by the finding that head and neck cancer survivors perceive their mostly low-intensity activities as already sufficient. In addition, many patients have physical barriers for physical activity and some patients are insecure about possible harms of physical activity (Chapter 6). These findings are supported by findings from another study.[34] A recent study in patients with colorectal cancer reports that many opportunities for promotion of physical activity during the chemotherapy pathway were missed. Similar to our study, in this study, no physical activity promotion was observed, despite patients reporting low physical levels or treatment side effects.[35] Since physical activity promotion is an important component of patient self-management, healthcare professionals need to be more attentive to signs of decline of physical activity and to barriers that may be caused by the illness and the medical treatment, but may also be pre-existing. If these problems are identified, patients can for instance be referred to a physical therapist to help improve physical activity and address physical barriers with interventions tailored to these barriers.

Interpretation of main findings

Content validity of methods used to assess malnutrition was established to be limited and the level of content validity of these methods has not improved in recent years. Recently, the Global Leadership Initiative on Malnutrition (GLIM) has presented criteria for the diagnosis of malnutrition, that includes a simple and broadly applicable set of indicators.[36] GLIM has reached consensus about a two-step model in which malnutrition risk screening with a validated screening instrument is step 1 and assessment for diagnosis and severity grading of malnutrition is step 2. Malnutrition is considered present if at least one phenotypic characteristic (e.g. weight loss, low BMI, reduced muscle mass) and at least one etiologic characteristic (e.g. reduced food intake or assimilation, or disease burden or presence of inflammation). In the systematic review it was established that the ESPEN and ASPEN conceptual definitions describe four domains (nutrient balance, body composition, body function, and inflammatory factors) within the construct of malnutrition. The GLIM includes criteria related to three of those four domains: nutrient balance, body composition, and inflammatory factors. The primary set of GLIM criteria does not include the domain of body function, instead, measurements of muscle function are considered supportive measures. In addition, if the minimum of one etiologic characteristic is included, either nutrient balance or inflammatory factors are not assessed, and only two domains are included, thus affecting content validity. Surprisingly, some of the validated instruments that are being proposed for screening by GLIM, such as SGA, cover more domains than the minimum required set of two diagnostic criteria that is proposed in the same position paper. In theory, results of elaborate malnutrition screening could be counter-acted by results from a malnutrition diagnosis with lower content validity. Furthermore, the new model of malnutrition differentiates several etiology-based types of malnutrition: disease-related

malnutrition with inflammation (chronic and acute), disease-related malnutrition without inflammation, and malnutrition not related to disease.[7,36] The diverse clinical implications of these subtypes of malnutrition indicate that the (interdisciplinary) treatment approach may differ per subtype. For instance, a patient with acute disease-related malnutrition with inflammation may require immediate clinical treatment and a nutritional treatment plan that, for instance, includes enteral feeding. A patient with malnutrition related to social isolation may need a different approach with social assistance in the home setting, in addition to nutritional advice. Therefore, in practice, professionals need to be able to discriminate between the etiology-based types of malnutrition, since this may provide guidance for practice.

From assessment to awareness

The studies in this thesis show that although instruments that identify problems with nutritional status are available, both on multidimensional and on indicator level, this availability does not guarantee that these instruments will be implemented in practice. Clinicians may perceive the instrument as too difficult, and/or sufficient knowledge of the technique may not be available in the local setting. In addition, patients may not have the intention to change their behavior, even when problems such as decline of physical function and physical inactivity have been identified. Although PG-SGA and CT-based body composition analysis are serving as reference standards in cancer patients for malnutrition and muscle mass assessment,[37-40] these methods are not always considered first choice in clinical practice. This lack of use may be partially caused by the perception of clinicians that these instruments are complex (Chapter 3 and 4).[41] If understanding and knowledge are lacking in professionals as with PG-SGA (Chapter 3 and 4) and perhaps also with CT body

composition analysis techniques (Chapter 5), providing explanation and practical training for the professionals can resolve this. If explanation and training are already incorporated in the professional education, these techniques may be viewed as a practical option more easily and more often later in practice. Also, patients with head and neck cancer may not perceive increase of their physical activity level as needed, important, and/or relevant (Chapter 6). If perceived relevance is lacking, it may be helpful to create more awareness of their physical activity with help of practical guidelines and wearable devices. To create awareness, patients need to receive clear and practical guidelines about the level of PA that is needed to improve their wellbeing and their nutritional status. In addition, patients need to be informed about their actual physical activity level. This way the existing gap between actual and required level of physical activity becomes explicit to patients. This explicit information may facilitate patients to make an informed consideration about the relevance of increasing their physical activity level. Perhaps if patients have clear and personalized guidelines of how much (and what type of) extra physical activity is needed to reach a level that may improve their wellbeing, it will be easier to proceed to action.

The chain of care that surrounds patients with head and neck cancer is another aspect that we need to be aware of in treating malnutrition and monitoring nutritional status. There is a dividing line between clinical care and primary care in the Netherlands. Often professionals that work in the clinical setting cannot continue their care in the home setting and patients' care plans will need to be transferred and allocation of costs is different. Especially in high complex, low volume care like in head and neck cancer patients, the continuity of malnutrition treatment is not always secured. Not only the nutritional intake, but also physical activity is important and needs coaching. Specialized physical treatment for head and neck cancer patients is not always available in primary care or may be

considered unaffordable by patients. To improve interdisciplinary care of malnutrition for these vulnerable patients, a secure chain of care is needed, tailored to the needs of the patients.

Methodological considerations

Discrepancy in typifying malnutrition screening

Screening of malnutrition is typified in two different ways: 1) identifying patients at risk of developing malnutrition and 2) screening for patients with malnutrition. These different types of screening may have different implications for practice. Malnutrition screening was used in the sense of identifying patients at risk of developing malnutrition.[42-44] In such cases, medical screening is defined as "the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action" (Oxford Medicine online, http://oxfordmedicine.com), for instance screening for risk of decubitus. If screening is used in this sense, we can assume that the instrument has the capacity to prospectively identify patients that may develop malnutrition. This implies that patients identified can be monitored and interventions can be initiated in order to prevent malnutrition. On the other hand, the term malnutrition screening was also used in the sense of screening for patients with malnutrition.[37,45] In this situation screening can be defined as "tests or examinations to discover if there is anything wrong with something" (Cambridge dictionary, https://dictionary.cambridge.org), for instance screening for breast cancer. If screening is used in this sense, we can assume that the instrument has the capacity to select patients that probably have malnutrition. This implies that further assessment of malnutrition is needed to confirm this initial screening.

Implications for clinical practice are different for risk assessment (monitoring and/or pro-active intervention) than for screening (further assessment). An alternative would be to encourage use of malnutrition screening methods that identify both risk of developing future malnutrition and existing malnutrition. An example of a tool that includes items for identifying risk of malnutrition and that simultaneously includes items that indicate presence of malnutrition, is the PG-SGA Short Form.

The fallacy of affirming the consequent in malnutrition screening

Instruments designed for malnutrition screening need to sensitively identify patients with malnutrition. Thus, the items of the instrument need to reflect the concept of malnutrition as defined. The importance of malnutrition as a concept is emphasized by the increased risk of clinical complications that can occur as a result of malnutrition. However, some validation studies of malnutrition screening instruments appeared to focus on the value of these instruments to predict occurrence of clinical complications that may be related to malnutrition.[42,43] The capacity to predict clinical complications appeared to be interpreted as an indication that this instrument is suitable to screen for malnutrition.[42,43] This type of reasoning can be typified as an example of the fallacy of affirming the consequent. The mechanism of this type of reasoning can be clarified with an example argument: Bella is a horse, therefore Bella's diet is vegetarian. This argument has one premise followed by a conclusion. Within this argument the conditional statement "If you are a horse, then your diet is vegetarian" is an implicit premise, but can be explicated. This conditional statement is a true statement and contains two sentences which are connected through the logical connective "If…, then...". The sentence that follows "if" is called antecedent, the sequence that follows "then" is called consequent. The rule of inference is as following: given "if

antecedent, then consequent" and given "antecedent", then the conclusion "consequent" necessarily follows. The logical form of this type of reasoning is known as "modus ponendo ponens"; the truth of the premises guarantee the truth of the conclusion. The fallacy of affirming the consequent occurs when the consequent is affirmed in the reasoning: "If you are a horse (antecedent), then your diet is vegetarian (consequent). Bella's diet is vegetarian (consequent), therefore Bella is a horse (antecedent)". This reasoning is not valid, which means that if the two premises are true the conclusion is not guaranteed to be true. Furthermore it could imply the conditional "if your diet is vegetarian, then you are a horse." The latter statement is not conclusive since horses are just one example of a large variety of beings with a vegetarian diet. We can apply the same type of reasoning to validation of screening instruments for malnutrition against clinical complications that may arise as a result of malnutrition. The valid statement that can be made is as follows: if a patient has malnutrition (antecedent), then clinical complications may arise (consequent). A patient has malnutrition (antecedent), therefore clinical complications may arise (consequent). However, if we validate a malnutrition screening tool against clinical complications that may arise as a result of malnutrition, the fallacy of affirming the consequent occurs: "If a patient has malnutrition (antecedent), then clinical complications may arise (consequent). Clinical complications may arise (consequent), therefore the patient has malnutrition (antecedent)". This reasoning is not valid. Furthermore it could imply the conditional: "if clinical complications may arise, then this patient has malnutrition". This statement is not conclusive since clinical complications that may arise do not necessarily occur due to malnutrition, complications may also occur due to other reasons.

Screening instruments that have not been validated against the construct of malnutrition itself may not identify patients with malnutrition, but rather patients at risk of the clinical complications that it has been validated against. Therefore, such screening instruments need to be further validated against other instruments that represent the diagnose of malnutrition, to explore how suitable the instrument is for malnutrition screening. If the goal is to identify patients with malnutrition in order to be able to start malnutrition therapy, valid questions that should be asked are:

How well does a malnutrition screening tool explain or describe malnutrition in this patient group?

How much better than other methods is this malnutrition screening tool at explaining malnutrition in this patient group?

If the results of an instrument reflect the nutritional status of the patient more accurately, responsiveness to malnutrition interventions may improve.

Cultural adaptation

Cultural adaptation of the PG-SGA proved to be very helpful, for both the patient-generated component and the professional component. By using a structured consensus-based approach that includes forward translation and reconciliation, backward translation and revision, and cognitive testing and analysis, conceptual, semantic and operational equivalence of the instrument could be safeguarded.[46-48] In addition to safeguarding equivalence we explored comprehensibility and difficulty of the instrument, to gain deeper insight into how the instrument would be perceived in practice. We can illustrate this with an example of a healthcare professional with little training in human muscle anatomy (e.g.

a dietitian). If this professional first reads the following question of the PG-SGA: "How would you rate the status of the interosseous muscles – 0=no loss, 1=mild loss, 2=moderate loss, 3=severe loss", it may be incomprehensible to this professional, because the term "interosseous" is not very common. Once this term is clarified (muscles that arise from and run between the long bones of the hand and foot, extending to and producing movement of the digits), the question becomes comprehensible. However, it can still be difficult to answer it. To answer the question, the professional needs knowledge of the human muscle anatomy and the skills to distinguish between "no loss", "mild loss", "moderate loss" and "severe loss". By discriminating between comprehensibility and difficulty, extra information is generated and deeper insight is gained in what items are considered incomprehensible, implying the formulation is unclear, and what items are considered difficult, implying a need for more knowledge and/or training. If an instrument that is used by patients or professionals is considered partially incomprehensible or difficult, information or training are needed to improve clarity or easiness. Without information and/or training, the instrument will remain partially incomprehensible or difficult to its users, and successful implementation of the instrument may be at risk.

Generalizability in qualitative research

Generalizability is still often approached as a statistical model, in which ideally data are collected from a representative sample within a population. However, other models towards generalizability have been introduced in the last 25 years.[49-51] Case-to-case translation provides an alternative model of generalizability and focuses on transferability of data. Instead of extrapolating findings from a representative sample to a population with statistical procedures, transferability allows readers and researchers to evaluate the extent

to which findings apply to new situations for themselves. To be able to make this evaluation, a rich level of high quality descriptive data is needed. Approaching generalizability from the perspective of data density can be used in instances where the aim is to explore a broad range of structured data more deeply. This approach allows us to understand more about the dynamics of a situation and the beliefs and perceptions of the patients. In qualitative studies, a high level of data density presented per participant in a structured manner adds is valuable, because it allows readers to evaluate transferability of findings for their own situation, regardless of sample size. In studies that aim for uncovering dynamics in beliefs and perceptions of patients that may be generalizable, more focus towards high data density may improve quality and nuance of findings.

Intention-based cognitive behavior models

Prevention or treatment of malnutrition often involves a need for behavioral change in the sense that nutritional status may need to be restored by changing dietary habits and physical activity may need to be improved by altering physical activity patterns. Intention-centered cognitive behavior models, such as the theory of planned behavior and the attitude – social influence – efficacy (ASE) model, are often used as a framework to identify behavioral patterns in physical activity studies.[34,52-54] However, participants were identified who appeared to have a lack of intention for behavioral change (Chapter 6). After deeper analysis of our data, some participants appeared to imply that they are not aware of their physical activity behavior. For these participants physical activity is something that comes naturally while performing other, meaningful, activities such as work. Whereas other participants appeared to imply they have a (strong) intention to not change their physical

activity behavior, because they were convinced they were already at a sufficient level of physical activity. This difference is of interest, because both situations may have different implications for practice. Unawareness of a need for physical activity does not provide any directions for intention-centered strategies to improve physical activity, due to the lack of the central theme that is present. In contrast, an intention to not increase physical activity could be targeted in intention-centered cognitive behavior strategies, since the central theme of physical activity is perceived as an independent concept, and a need for increase of physical activity can be shown to the participant. Use of motivation-centered strategies may provide an alternative for cognitive behavior strategies. For instance, a-motivation is addressed in the self-determination theory.[55] Using instruments for behavioral change that include strategies for lack of intention or motivation may be helpful in providing clearer directions for interventions to positively influence behavior such as dietary habits and physical activity patterns.

Conclusion and recommendations for future research

This study has led to the conclusion that it is still a challenge to find the most suitable and effective method to treat malnutrition in patients with head and neck cancer. However, the PG-SGA appears to be a suitable and available instrument for screening and assessment of malnutrition (risk) and provides information for tailored interventions. Since malnutrition is a highly complicated problem, a multidimensional approach is needed, with attention for nutritional balance, body composition and function, possible influence of inflammatory factors, and a sufficient level of physical activity.

Besides providing answers to the research questions, this thesis raises multiple new questions. Malnutrition is a complex concept, and even if malnutrition assessment is accurate many factors influence the success of the treatment. Future research should address malnutrition assessment from a multidimensional point of view, and needs to be sensitive to the different subtypes of malnutrition: disease-related malnutrition with inflammation (chronic and acute), disease-related malnutrition without inflammation, and malnutrition not related to disease. Furthermore, if malnutrition assessment or screening instruments are used internationally or in different cultural settings, attention needs to be paid to cultural aspects that may influence conceptual, semantic and operational equivalence of these instruments in a new setting. Finally, future research needs to further determine behavioral patterns and provide tools for effective therapeutic interventions in patients with head and neck cancer.

Malnutrition

Since one global conceptual definition has been proposed (i.e. the ESPEN definition),[7] and in addition criteria have been proposed for the diagnosis of malnutrition,[36] development of a generic diagnostic instrument for malnutrition with high content validity is now within reach. The full set of GLIM criteria already covers three of the four domains that can be derived from the conceptual definition malnutrition: nutrient balance, body shape, body size and body composition, and inflammatory factors. Only the domain of body function is lacking in the primary indicators. If this set of criteria is complemented with indicators or criteria from the domain of body function, content validity as compared to the current conceptual definition of malnutrition will improve. Such a diagnostic instrument can be

used to further study prognostic validity of malnutrition as defined for important outcome measures such as clinical complications, quality of life, healthcare costs, and survival.

Cultural adaptation

To safeguard equivalence of research instruments that assess patient-reported outcome measures, when translated to a different language and adapted to a different cultural context, a rigorous approach is needed. Such an approach ideally includes participation of the instrument developer, forward translation and reconciliation, backward translation and revision, and cognitive testing and analysis. Contact with the instrument developers may help understand what was the original aim of the instrument, and how the instrument was originally intended to be used. Forward translations by different translators may reveal different linguistic interpretations that are possible. Backward translations are a comprehensive tool to test if the linguistic and cultural meaning of the instrument in the target culture has remained similar to the original. Cognitive testing provide an instrument to finetune the instrument to its' target population in a new cultural setting. Therefore, if you are translating an instrument to a new cultural setting, it is important to use a transparent methodology for each step of the translation and cultural adaptation process in order to safeguard equality of the instrument to its original version.

CT analysis of body composition and nutritional assessment

With regard to the subject of CT analysis of body composition, some important research questions still need to be answered. Firstly, CT analysis of muscle mass at lumbar vertebrae (L3) level is well validated and L3 muscle mass is strongly associated with overall lean body

mass. However, the association of cross-sections of muscle mass at other vertebrae levels with L3 muscle mass and lean body mass is still relatively unknown. Since not all images of cancer patients include vertebrae at L3 level, CT-based body composition analysis is not available for all cancer patients. For instance, patients with head and neck cancer may have CT scans that mainly include the cervical vertebrae and patients with lung cancer may have CT scans that mainly include the thoracic vertebrae. Still these patients are often at risk of malnutrition. Therefore, it is of great interest to explore the association of muscle mass at cervical or thoracic vertebrae levels with muscle mass at L3 level and overall lean body mass. Secondly, some types of chemotherapy agent are mainly distributed in lean body tissue. However, chemotherapy agent dose is often determined based on body surface area estimates. A dose based on a body surface area estimate may overestimate lean body mass in patients with relatively low muscle mass, thus possibly causing toxicity related chemotherapy intolerance. In the future, tailoring chemotherapy agent dose to lean body mass may prevent chemotherapy intolerance. Although the association between muscle mass and chemotherapy tolerance in patients with head and neck cancer has been studied,[28,56] trials are still needed that compare chemotherapy dose based on lean body mass versus dose based on body area index.

Finally, the GLIM criteria mention muscle mass as a criterion for the diagnosis of malnutrition. If CT images are present, CT analysis of body composition may become a standard procedure in malnutrition assessment. However, to use this method in clinical practice, we need thousands of professionals to be trained to interpret CT images and analyze body composition. This may pose a challenge in practice. Another option would be the use of automated segmentation software to analyze CT images. However, although semi-automated software is available, reliable automated segmentation and analysis

software is not available yet. Development of reliable (and affordable) automated segmentation software could facilitate the use of CT body composition analysis results in practice.

Physical activity

Some research has been initiated with regard to feasibility of increased physical activity to maintain muscle mass and strength in patients with head and neck cancer before, during and after treatment, and some positive effects are reported for improved quality of life and fatigue.[57-60] However, these studies have not shown significant effects of exercise on lean body mass.[57-60] More knowledge is needed on how improved physical activity in patients treated for head and neck cancer affects nutritional status and, more specifically, muscle mass. In addition, we found that not all participants had the intention to improve physical activity or they intended not to improve physical activity. Therefore, we also need more knowledge on how patients can be motivated on an individual level to become more physically active, in the instance that they are not motivated. Further, out patients did not feel encouraged by nurses of doctors to improve their level of physical activity. Thus, an multi- or interdisciplinary approach is needed that targets different disciplines, such as nurses, doctors and dietitians and that assists these disciplines in giving appropriate physical activity advice and that helps them to refer to a physical therapist when indicated.

Behavioral change

For future research aimed at understanding behavioral patterns and development of tailored interventions for behavioral change, it is recommended to critically review the

appropriateness of the theoretical framework that is used. If not all participants are explicitly aware intention to change their behavior, it might be rewarding to explore the applicability of other theories, for instance theories that focus on assuming that individuals operate on different levels of motivation and autonomy (such as the Self Determination Theory).[61]

References

1. 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*. 2013;31(12):1539-1547.

2. Unal D, Eroglu C, Ozsoy SD, Besirli A, Orhan O, Kaplan B. Effect on long-term survival of psychiatric disorder, inflammation, malnutrition, and radiotherapy-related toxicity in patients with locally advanced head and neck cancer. *J BUON*. 2015;20(3):886-893.

3. Gourin CG, Couch ME, Johnson JT. Effect of weight loss on short-term outcomes and costs of care after head and neck cancer surgery. *Ann Otol Rhinol Laryngol*. 2014;123(2):101-110.

4. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. *Nutr J*. 2012;11:27-2891-11-27.

5. Purkey MT, Levine MS, Prendes B, Norman MF, Mirza N. Predictors of aspiration pneumonia following radiotherapy for head and neck cancer. *Ann Otol Rhinol Laryngol*. 2009;118(11):811-816.

6. van Bokhorst-de van der Schueren,M.A., Guaitoli PR, Jansma EP, de Vet HC. Nutrition screening tools: Does one size fit all? A systematic review of screening tools for the hospital setting. *Clin Nutr*. 2014;33(1):39-58.

7. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. 2017;36(1):49-64.

8. Jager-Wittenaar H, Dijkstra PU, Vissink A, van Oort RP, van der Laan BF, Roodenburg JL. Malnutrition in patients treated for oral or oropharyngeal cancer--prevalence and relationship with oral symptoms: An explorative study. *Support Care Cancer*. 2011;19(10):1675-1683.

9. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer--prevalence and risk factors at diagnosis: An explorative study. *Support Care Cancer*. 2007;15(9):1045-1050.

10. Nishikawa D, Hanai N, Suzuki H, Koide Y, Beppu S, Hasegawa Y. The impact of skeletal muscle depletion on head and neck squamous cell carcinoma. *ORL J Otorhinolaryngol Relat Spec*. 2018;80(1):1-9.

11. Capuano G, Gentile PC, Bianciardi F, Tosti M, Palladino A, Di Palma M. Prevalence and influence of malnutrition on quality of life and performance status in patients with locally advanced head and neck cancer before treatment. *Support Care Cancer*. 2010;18(4):433-437.

12. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*. 2015;33(1):90-99.

13. Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: A systematic review. *J Cancer Surviv*. 2018.

14. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren,M.A., et al. A rational approach to nutritional assessment. *Clin Nutr*. 2008;27(5):706-716.

15. Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: A proposal for etiology-based diagnosis in the clinical practice setting from the international consensus guideline committee. *JPEN J Parenter Enteral Nutr*. 2010;34(2):156-159.

16. Lochs H, Allison SP, Meier R, et al. Introductory to the ESPEN guidelines on enteral nutrition: Terminology, definitions and general topics. *Clin Nutr*. 2006;25(2):180-186.

17. Teitelbaum D, Guenter P, Howell WH, Kochevar ME, Roth J, Seidner DL. Definition of terms, style, and conventions used in A.S.P.E.N. guidelines and standards. *Nutr Clin Pract*. 2005;20(2):281-285.

18. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: Role of the patient-generated subjective global assessment. *Curr Opin Clin Nutr Metab Care*. 2017;20(5):322-329.

19. Acquadro C, Bayles A, Juniper E. Translating patient-reported outcome measures: A multi-step process is essential. *J Bras Pneumol*. 2014;40(3):211-212.

20. Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: Report of the ISPOR task force for translation and cultural adaptation. *Value Health*. 2005;8(2):94-104.

21. Lynn MR. Determination and quantification of content validity. *Nurs Res*. 1986;35(6):382-385.

22. Stewart AL, Napoles-Springer A. Health-related quality-of-life assessments in diverse population groups in the united states. *Med Care*. 2000;38(9 Suppl):II102-24.

23. Pettersson R. Comprehensibility. *International Symposium of the International Visual Literacy Association Verbo-Visual Literacy*. 1993;3(ED 365 299).

24. Prado CM, Lima IS, Baracos VE, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol*. 2011;67(1):93-101.

25. Sjoblom B, Gronberg BH, Benth JS, et al. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung Cancer*. 2015;90(1):85-91.

26. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res*. 2007;13(11):3264-3268.

27. Wendrich AW, Swartz JE, Bril SI, et al. Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. *Oral Oncol*. 2017;71:26-33.

28. 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*. 2013;31(12):1539-1547.

29. Chamchod S, Fuller CD, Mohamed AS, et al. Quantitative body mass characterization before and after head and neck cancer radiotherapy: A challenge of height-weight formulae using computed tomography measurement. *Oral Oncol*. 2016;61:62-69.

30. Chamchod S, Fuller CD, Mohamed AS, et al. Quantitative body mass characterization before and after head and neck cancer radiotherapy: A challenge of height-weight formulae using computed tomography measurement. *Oral Oncol*. 2016;61:62-69.

31. Maddocks M, Byrne A, Johnson CD, Wilson RH, Fearon KCH, Wilcock A. Physical activity level as an outcome measure for use in cancer cachexia trials: A feasibility study. *Supportive Care Cancer*. 2010;18(12):1539-1544.

32. Hung Y-, Bauer J, Horsley P, Waterhouse M, Bashford J, Isenring E. Changes in nutritional status, body composition, quality of life, and physical activity levels of cancer patients undergoing autologous peripheral blood stem cell transplantation. *Supportive Care Cancer*. 2013;21(6):1579-1586.

33. Fouladiun M, Korner U, Gunnebo L, Sixt-Ammilon P, Bosaeus I, Lundholm K. Daily physical-rest activities in relation to nutritional state, metabolism, and quality of life in cancer patients with progressive cachexia. *Clin Cancer Res*. 2007;13(21):6379-6385.

34. Rogers LQ, Courneya KS, Robbins KT, et al. Physical activity correlates and barriers in head and neck cancer patients. *Support Care Cancer*. 2008;16(1):19-27.

35. Veal I, Peat N, Jones GD, Tsianakas V, Armes J. Missed opportunities for physical activity management at key points throughout the chemotherapy pathway for colorectal survivors: An observational interview study. *Support Care Cancer*. 2018.

36. Cederholm T, Jensen G, Correia MIT, et al. GLIM criteria for the diagnosis of malnutrition–A consensus report from the global clinical nutrition community. *Clinical Nutrition*. 2018.

37. Boleo-Tome C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the malnutrition universal screening tool (MUST) in cancer. *Br J Nutr*. 2012;108(2):343-348.

38. Read JA, Crockett N, Volker DH, et al. Nutritional assessment in cancer: Comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). *Nutr Cancer*. 2005;53(1):51-56.

39. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997-1006.

40. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol (1985)*. 1998;85(1):115-122.

41. Prado CM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. *J Parenter Enteral Nutr*. 2014;38(8):940-953.

42. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): A new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321-336.

43. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. 1980;139(1):160-167.

44. Walsh D, Mahmoud F, Barna B. Assessment of nutritional status and prognosis in advanced cancer: Interleukin-6, C-reactive protein, and the prognostic and inflammatory nutritional index. *Support Care Cancer*. 2003;11(1):60-62.

45. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren,M.A. Development and validation of a hospital screening tool for malnutrition: The short nutritional assessment questionnaire (SNAQ). *Clin Nutr*. 2005;24(1):75-82.

46. Wild CP, Andersson C, O'Brien NM, Wilson L, Woods JA. A critical evaluation of the application of biomarkers in epidemiological studies on diet and health. *Br J Nutr*. 2001;86 Suppl 1:S37-53.

47. Acquadro C, Patrick DL, Eremenco S, et al. Emerging good practices for translatability assessment (TA) of patient-reported outcome (PRO) measures. *Journal of patient-reported outcomes*. 2017;2(1):8.

48. Eremenco S, Pease S, Mann S, Berry P. Patient-reported outcome (PRO) consortium translation process: Consensus development of updated best practices. *Journal of patient-reported outcomes*. 2017;2(1):12.

49. Polit DF, Beck CT. Generalization in quantitative and qualitative research: Myths and strategies. *Int J Nurs Stud*. 2010;47(11):1451-1458.

50. Carminati L. Generalizability in qualitative research: A tale of two traditions. *Qual Health Res*. 2018:1049732318788379.

51. Firestone WA. Alternative arguments for generalizing from data as applied to qualitative research. *Educational researcher*. 1993;22(4):16-23.

52. Buffart LM, de Bree R, Altena M, et al. Demographic, clinical, lifestyle-related, and social-cognitive correlates of physical activity in head and neck cancer survivors. *Support Care Cancer*. 2017.

53. Courneya KS, Reid RD, Friedenreich CM, et al. Understanding breast cancer patients' preference for two types of exercise training during chemotherapy in an unblinded randomized controlled trial. *Int J Behav Nutr Phys Act*. 2008;5:52-5868-5-52.

54. Marcus BH, Banspach SW, Lefebvre RC, Rossi JS, Carleton RA, Abrams DB. Using the stages of change model to increase the adoption of physical activity among community participants. *Am J Health Promot*. 1992;6(6):424-429.

55. Deci EL, Ryan RM. The general causality orientations scale: Self-determination in personality. *Journal of research in personality*. 1985;19(2):109-134.

56. Wendrich AW, Swartz JE, Bril SI, et al. Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. *Oral Oncol*. 2017;71:26-33.

57. Lonkvist CK, Vinther A, Zerahn B, et al. Progressive resistance training in head and neck cancer patients undergoing concomitant chemoradiotherapy. *Laryngoscope investigative otolaryngology*. 2017;2(5):295-306.

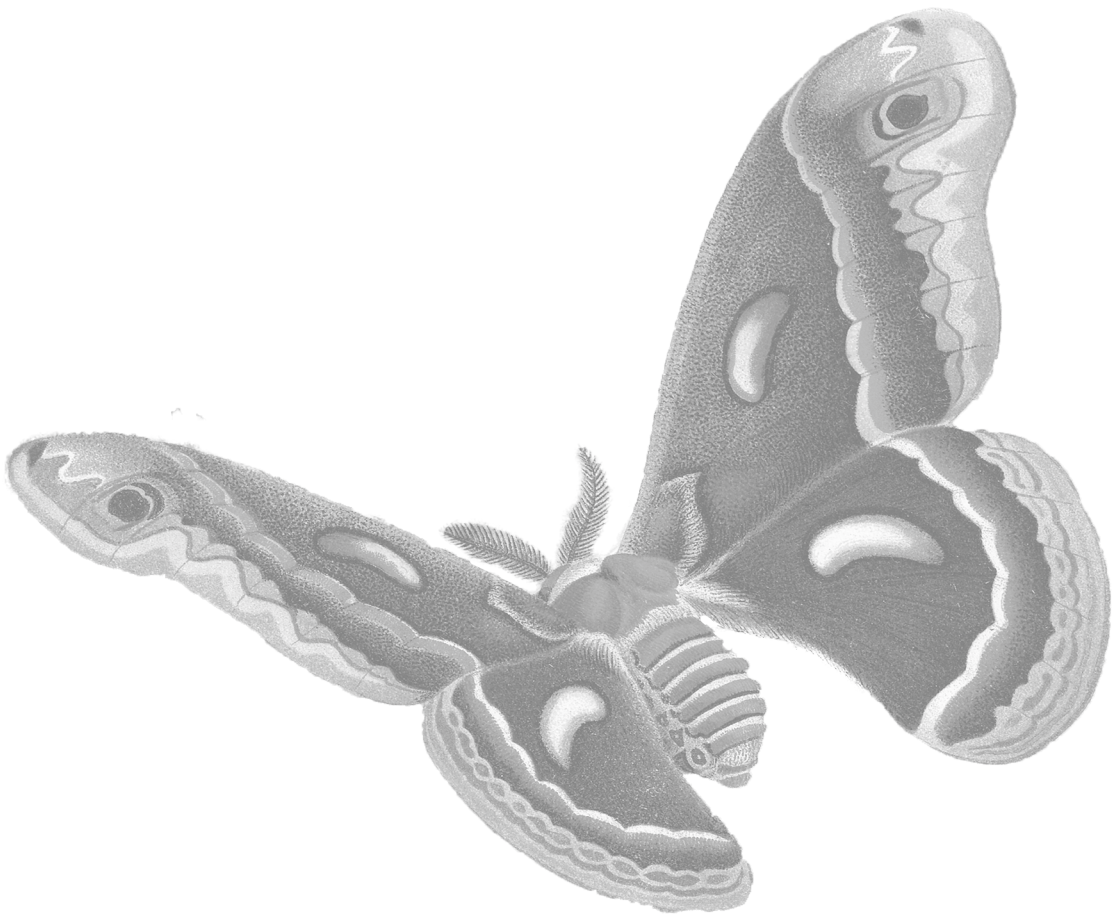
58. Sandmael JA, Bye A, Solheim TS, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: A pilot randomized trial. *Cancer*. 2017;123(22):4440-4448.

59. Grote M, Maihöfer C, Weigl M, Davies-Knorr P, Belka C. Progressive resistance training in cachectic head and neck cancer patients undergoing radiotherapy: A randomized controlled pilot feasibility trial. *Radiation Oncology*. 2018;13(1):215.

60. Capozzi LC, Lau H, Reimer RA, McNeely M, Giese-Davis J, Culos-Reed SN. Exercise and nutrition for head and neck cancer patients: A patient oriented, clinic-supported randomized controlled trial. *BMC Cancer*. 2012;12:446-2407-12-446.

61. Deci EL, Ryan RM. Self-determination theory: A macrotheory of human motivation, development, and health. *Canadian psychology/Psychologie canadienne*. 2008;49(3):182.

Samenvatting



Patiënten met hoofd-halskanker hebben een hoog risico op ondervoeding door een tekort aan voedingsstoffen en een veranderde voedingsbehoefte. Zowel de ziekte zelf, de lokalisering van de tumor en de bijwerkingen van de vaak agressieve behandeling zorgen ervoor dat niet voldoende in de verhoogde voedingsbehoefte kan worden voorzien. Ondervoeding kan het herstel van de ziekte en behandeling vertragen of verhinderen. Tijdige herkenning van ondervoeding en risicofactoren van ondervoeding is nodig om ondervoeding vroegtijdig te kunnen behandelen ofwel te voorkomen en is daarom een belangrijke stap in het voedingskundige zorgproces van patiënten met kanker. Voorbeelden van methoden die gebruikt worden voor de beoordeling van de voedingstoestand zijn de Patient-Generated Subjective Global Assessment (PG-SGA) vragenlijst en Computed Tomography (CT)-analyse van spiermassa. Naast verlies van spiermassa, kan verlies van spierfunctie, zoals spierkracht, worden beschouwd als een kenmerk van ondervoeding. Mogelijk kan voldoende beweging verlies van spiermassa en -functie voorkomen tijdens en na de behandeling van patiënten met hoofd-halskanker.

De doelstelling van dit proefschrift was drieledig. Het eerste doel was de diagnostische waarde van methoden voor het beoordelen van ondervoeding te bestuderen, inclusief het beoordelen van lichaamssamenstelling met CT-analyse. Het tweede doel was het vertalen en geschikt maken van de PG-SGA voor de Nederlandse setting. Het derde doel was om denkpatronen te verkennen die lichamelijke activiteit kunnen beïnvloeden bij patiënten met hoofd-halskanker.

In **Hoofdstuk 2** is met een literatuurstudie onderzocht welke beoordelingsmethoden worden gebruikt voor het vaststellen van ondervoeding bij patiënten met kanker. Verder is onderzocht in welke mate deze methoden inhoudelijk overeenkomen met internationaal geaccepteerde definities van ondervoeding. Op basis van deze definities kan ondervoeding

worden gedefinieerd als een multidimensionaal construct, waarbinnen vier domeinen kunnen worden onderscheiden: 1. Voedingsstoffenbalans, 2. Lichaamsvorm, lichaamsomvang en lichaamssamenstelling, 3. Lichaamsfunctie en 4. Inflammatoire factoren. Binnen deze gemeenschappelijke domeinen werden sleutelonderwerpen geformuleerd en gebruikt om de inhoudelijke overeenstemming - inhoudsvaliditeit – met de definities van beoordelingsmethoden voor het vaststellen van ondervoeding in getallen uit te drukken. Een methoden-inhoudsvaliditeitsindex ($M\text{-}CVI_{A\text{-}C}$) van 0.80 of meer werd als acceptabel beschouwd. Uit de studie bleek dat 37 methoden werden gebruikt om ondervoeding vast te stellen in studies bij patiënten met kanker. Inhoudsvaliditeit was daarbij beperkt en wisselend. De Mini Nutritional Assessment ($CVI_{A\text{-}C}$=0.72), PG-SGA ($M\text{-}CVI_{A\text{-}C}$=0.61) en Subjective Global Assessment ($M\text{-}CVI_{A\text{-}C}$ =0.53) scoorden het hoogst qua inhoudsvaliditeit.

Van alle methoden voor het vaststellen van ondervoeding scoorde de PG-SGA op inhoudsvaliditeit een plaats in de top drie, echter er was nog geen Nederlandse vertaling van het instrument beschikbaar. In **Hoofdstuk 3** wordt beschreven hoe de originele Engelstalige versie van de PG-SGA is vertaald en aangepast voor de Nederlandse setting met behulp van een gestructureerde werkwijze volgens de ISPOR aanbevelingen. Daarbij werden inhoudsvaliditeit, begrijpelijkheid en moeilijkheid van de PG-SGA verkend, zoals ervaren door hulpverleners en kankerpatiënten. Indexen op schaalniveau van 0.80-0.90 werden als acceptabel beschouwd en schaalindexen van ≥0.90 werden als excellent beschouwd. Door gebruik van heen- en terugvertalingen en een pilottest kwam een Nederlandse versie van de PG-SGA tot stand waarbij doel, betekenis en indeling van de oorspronkelijk Amerikaanse PG-SGA behouden bleven. Patiënten waren tevreden over begrijpelijkheid (S-CI=0.99) en gemakkelijkheid (S-DI=0.96) van de PG-SGA. Professionals ervaarden de PG-SGA als relevant (S-CVI=0.89) en begrijpelijk (S-CI=0.81), maar moeilijk (S-DI=0.55). Omdat

ervaren moeilijkheid kan wijzen op een behoefte aan training is in **Hoofdstuk 4** onderzocht *of* en *hoe* een enkele training in het gebruik van de PG-SGA de ervaren begrijpelijkheid en moeilijkheid verandert onder diëtisten. Nederlandse diëtisten die niet bekend waren met gebruik van de PG-SGA beantwoordden een vragenlijst voor en na een eendaagse training in het gebruik ervan. Op schaalniveau verbeterden de indexen voor begrijpelijkheid en moeilijkheid significant ($p<0.001$) van niet acceptabel (S-CI=0.69; S-DI=0.57) voor de training, naar excellent voor begrijpelijkheid (S-CI=0.95) en acceptabel voor moeilijkheid (S-DI=0.86) na de training.

In **Hoofdstuk 5** werd in een retrospectieve studie de relatie onderzocht tussen een lage spiermassa index (SMI), gemeten met CT op thoracaal (T4) of lumbaal (L3) niveau, en aan toxiciteit gerelateerd vroegtijdig stoppen met chemotherapie bij patiënten met hoofd-halskanker. Tussen SMI en vroegtijdig stoppen met chemotherapie werd een duidelijke relatie gevonden in zowel de enkelvoudige analyse ($p=0.007$, OR=0.96 [0.94-0.99]) als de multivariate analyse waarin gecorrigeerd werd voor andere variabelen ($p=0.021$, OR 0.96 [0.92-0.99]). De multivariate analyse liet bovendien potentiële interactie zien met type chemotherapie, aanwezigheid van co-morbiditeit, een combinatie van roken en alcoholinname en geslacht.

Om denkpatronen te verkennen die lichamelijke activiteit kunnen beïnvloeden bij patiënten met hoofd-halskanker is in **hoofdstuk 6** het beeld dat hoofd-halskanker survivors hebben van fysieke activiteit in kaart gebracht en vergeleken met hun objectief gemeten lichamelijke activiteit. Hiertoe werden kwalitatieve en kwantitatieve gegevens van patiënten die voor hoofd-halskanker waren behandeld geanalyseerd en geïntegreerd. Lichamelijke beperkingen leverden belangrijke barrières voor lichamelijk activiteit. Lichamelijke activiteit werd gezien als een gewoonte en geassocieerd met positieve gevoelens of beloningen. Een gebrek aan intentie om lichamelijke activiteit te verhogen kan gerelateerd zijn aan het beeld van

hoofd-halskanker survivors dat hun huidige activiteitenniveau voldoende is, terwijl het gemeten niveau van lichamelijke activiteit laag was. Terwijl sommige deelnemers het gevoel hadden dat zij geen hulp nodig hebben met lichamelijke activiteit, waren anderen onzeker over mogelijke schade als gevolg van lichamelijke activiteit.

Uit dit proefschrift blijkt dat het nog steeds een uitdaging is om de meest passende en effectieve werkwijze te vinden voor preventie en behandeling van ondervoeding bij patiënten met hoofd-halskanker. Echter, de PG-SGA is nu beschikbaar en lijkt een passend instrument voor de screening en vaststelling van (risico op) ondervoeding en levert informatie voor interventies op maat. Doordat ondervoeding een zeer complex probleem is, is een multidimensionele aanpak noodzakelijk. Bij een dergelijke aanpak is het nodig aandacht te besteden aan voedingsstoffenbalans, lichaamssamenstelling (voldoende spiermassa) en lichaamsfunctie, mogelijke invloed van inflammatoire factoren en voldoende lichamelijke activiteit.

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About the author

Martine Sealy was born in 1972 in Sneek, in Friesland, The Netherlands. She completed her secondary pre-university education at RSG Magister Alvinus in Sneek. From 1990-1996, she studied Nutrition and Dietetics at the Hanze University of Applied Sciences in Groningen. After finishing her study, she started working as dietitian in the Isala Hospital in Zwolle and as a research assistant at the department of Research and Development at Friesland Dairy Foods in Leeuwarden. Since 2000, Martine is working at the Hanze University of Applied Sciences, where she is still teaching in the Program of Nutrition and Dietetics in the School of Health Care Studies. In 2014, she completed the master program Evidence Based Practice at the University of Amsterdam. She started her PhD research in 2013 at the Research Group Healthy Ageing, Allied Health Care and Nursing at the Hanze University of Applied Sciences and Department of Maxillofacial Surgery at the University Medical Center Groningen. In 2016 she was trained in the assessment of body composition with Computed Tomography at the Cross Cancer Institute in Edmonton, Alberta, Canada. Currently, Martine continues her activities at the Research Group Healthy Ageing, Allied Health Care and Nursing as coordinator of the Hanze Health and Ageing Study and project leader in the Living Lab Malnutrition.

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