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# Quality assessment of cancer cachexia clinical practice guidelines

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ABSTRACT

*Objectives:* The aim of this study was to investigate the quality of clinical practice guidelines of cancer cachexia and identifying gaps limiting knowledge.

*Methods:* A systematic search of relevant guideline websites and literature databases (including PubMed, NCCN, NGC, SIGN, NICE, and google) was undertaken from inception to March 2017 to identify and select clinical guidelines related to cancer cachexia. Four independent reviewers assessed the eligible guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument. Agreement among reviewers of the guidelines was measured by using intra-class correlation coefficient (ICC). The number of recommendations, strength of recommendation, and levels of evidence were determined.

*Results:* Nine cancer cachexia guidelines published from 2006 to 2017 were identified. An overall high degree of agreement among reviewers to each domain was observed (ICC ranged from 0.75 to 0.91). The median scores and range for each AGREE II domain were as follows: (i) scope and purpose (median = 61.1%, range: 13.9% to 80.7%); (ii) stakeholder involvement (median = 26.4%, range: 8.3% to 81.9%); (iii) rigour of development (median = 35.9%, range: 3.6% to 84.4%); (iv) clarity and presentation (median = 56.9%, range: 30.6% to 76.4%); (v) applicability (median = 19.8%, range: 0% to 77.1%) and (vi) editorial independence (median = 27.1%, range: 0% to 85.4%). Two cancer cachexia guidelines (ESPEN, 2017 and University of Queensland, 2013) scored higher on all domains and were classified as recommended for clinical practice, among which, one was developed by European Society for Parenteral and Enteral Nutrition and European Partnership for Action Against Cancer, and the other was developed by University of Queensland. In addition, more than a half recommendations were based on nonrandomized studies (Level C, 50.0%) and expert opinion (Level D, 8.2%).

*Conclusions:* The quality of cancer cachexia guidelines was highly heterogeneous among different domains even within the same guideline. There is significant room for improvement to develop high quality cancer cachexia guidelines, which urgently warrants first-class research to minimize the vital gaps in the evidence for formulation of cancer cachexia guidelines.

## Introduction

Cancer-related cachexia is a disorder characterized by loss of body weight with specific losses of skeletal muscle and adipose tissue. Cachexia is driven by a variable combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism and inflammation [1]. The development of cancer cachexia is common in people with solid tumors such as pancreatic, lung, gastric and colorectal cancer. Weight loss and malnutrition are observed frequently in patients with cancer cachexia, especially for cancer patients after surgery (malabsorption), radiotherapy (nausea, pain, diarrhoea, mucositis), and chemotherapy (nausea, vomiting, diarrhoea, mucositis). The majority of cancer patients experience weight loss as their disease progresses and in general, weight loss is a major prognostic indicator of poor survival and impaired response to cancer treatment [2]. The incidence of malnutrition amongst patients with cancer

*Abbreviations:* AGREE II, Appraisal of Guidelines for Research and Evaluation II; ICC, intraclass correlation coefficient; ASPEN, American Society for Parenteral and Enteral Nutrition; ESPEN, European Society for Parenteral and Enteral Nutrition; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NCCN, National Comprehensive Cancer Network; FNCLCC, Federation of the French Cancer Centers; NHMRC, National Health and Medical Research Council

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cachexia has been estimated at between 40 and 80% [3,4]. The prevalence of malnutrition depends on the tumor type, location, stage and treatment [5]. The consequences of malnutrition may include an increased risk of complications, decreased response and tolerance to treatment, a lower quality of life, reduced survival and higher healthcare costs [6–8].

Cancer cachexia has been implicated in the deaths of 30–50% of all cancer patients, as many die from the wasting associated with the condition [9]. Unfortunately, assessment and management of cancer cachexia remains the major challenge for clinicians and vary significantly in clinical practice. Several clinical guidelines have been developed by local, national and international organizations, which recommended numerous interventions including pharmacotherapies and non-pharmacotherapies have been trailed in patients with cancer cachexia to stimulate appetite or attenuate metabolic changes [10–12]. Ideally, evidence-based guidelines are expected to combine current evidence that will aid clinical decision making and identify major gaps between knowledge and treatment [13]. The usefulness of guidelines primarily depends on the quality, rigorous methodology and transparency of development [14]. It is important to determine whether the recommendations are indeed based on high quality evidence [15,16]. However, systematic evaluation of existing guidelines related to cancer cachexia is still lacking worldwide, and the distribution of the level of evidence underlying the recommendations in cancer cachexia guidelines has not been delineated.

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) is a reliable and useful tool for assessment of guidelines [17–20]. We hypothesized that the quality of existing cancer cachexia guidelines could be systematically appraised using the AGREE II instrument.

Therefore, we thoroughly reviewed guidelines on the assessment and management of cancer cachexia in electronic databases and guideline organizations' website. We sought to assess their methodological quality by using AGREE instrument, identify gaps limiting evidence based practice and highlight potential opportunities for improvement.

## Methods

### *Study design*

This study conducted a comprehensive review of clinical guidelines using the AGREE II instrument.

### *Review protocol*

This study was performed in accordance with the guidelines from preferred reporting items for systematic reviews and meta- analyses (PRISMA) [21].

### *Identification of guidelines*

Systematic searches were performed in PubMed database combining the term 'cachexia' and a filter to identify guideline documents (Practice Guideline [pt] OR Guideline [pt] OR guideline* [ti] OR statement [ti], recommendations [ti] OR consensus [ti]). We also searched the websites of guideline development organizations including NCCN (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp), NICE (https://www.nice.org.uk/guidance) and SIGN (http://www.sign.ac.uk/), and guideline databases such as GIN (http://www.g-i-n.net/) and NGC (https://www.guideline.gov/). Besides, we searched Google website as well as the references of all the obtained guidelines to include more potential guidelines.

Two reviewers (S.W.Q. and Y.L.) independently evaluated search results to determine inclusion or exclusion of references and extracted the general characteristics of each guideline. Disagreements were resolved by consensus or by consulting the third expert adjudicator (H.Y.).

### *Selection of guidelines*

The inclusion criteria were as follows: (i) complete guideline text is available in English; and (ii) guideline contains recommendations regarding cancer cachexia interventions. If the guideline had updates, only the most recent version was assessed. For every guideline ultimately included, we thoroughly searched for accompanying technical and supporting documents to better inform our assessments. The following literatures will be excluded: duplicate guidelines, guidelines for patients, editorials, translations of guidelines, secondary or multiple publications and short summaries. The translations of guidelines had the possibility of missing information from original version, which might influence the accuracy of our evaluation, so we exclude them.

### *Quality appraisal of guidelines*

We employed the latest version of the AGREE II instrument to evaluate each cancer cachexia guideline meeting our inclusion criteria. According to AGREE II handbook, each guideline was scored on 23 items within six domains. Domain 1 (scope and purpose) is divided into three items: guideline objectives, health questions, and population application. Domain 2 (stakeholder involvement) is based on three items: guideline development group, preferences of target population, and target users. Domain 3 (rigour of development) includes eight items: systematic methods used to search evidence, criteria for selection, strengths and limitations of the evidence, methods for formulating the evidence, health benefits and side effects of recommendations, explicit links between recommendation and supporting evidence, expert reviewers, and updating guideline for future use. Domain 4 (clarity and presentation) includes three items: recommendations are specific and unambiguous, different options for management, and key recommendations. Domain 5 (applicability) includes four items: facilitators and barriers, advice/tools to implement recommendations into practice, resources for implications and auditing criteria. Domain 6 (editorial independence) is based on two items: editorial independence from the funding body and conflicts of interest of the guideline development members.

In this study each cancer cachexia guideline was scored by four independent reviewers (S.W.Q., Y.L, W.X.Q and B.Z.X) according to AGREE II user manual. Among the four reviewers, S.W.Q majors in nursing for advance cancer, Y.L is a methodologist in guideline development and B.Z.X is a medical doctor. Besides, Y.L and W.X.Q had rich experiences in the application of AGREE II and published a study about using AGREE II to assess clinical guidelines [22,23], S.W.Q and B.Z.X were trained to use the AGREE II instrument through the online tutorials on the AGREE website.

The user manual defines each item and assists the user in determining a guideline's score for that item. Items were scored based on a scale ranging from 1 (absence of item) to 7 (item is reported with exceptional quality). Domain scores were calculated by summing item scores within each domain from each reviewer, then standardizing them as a percentage of the maximum possible score.

Overall assessment included whether the guideline would be recommended for use in practice [19]. Generally, the AGREE group divided the overall assessment into three categories: recommended, recommended with modifications, and not recommended. The consensus was reached according to the performance of 23 items assessment and the global judgment by reviewers. Each guideline was classified as: "recommended" for overall scores > 60%, "recommended with modifications" for scores between 30% and 60%, and "not recommended" for scores < 30% [18].

### *Strength of recommendation and level of evidence*

We extracted the information of strength of recommendation and level of evidence to identify major gaps between evidence and