REVIEW

Prevalence and Impact of Computed Tomography–Defined Sarcopenia on Survival in Patients with Human Papillomavirus–Positive Oropharyngeal Cancer: A Systematic Review

Anna Edwards,[1,2,3] Brett GM Hughes,[4,5] Teresa Brown,[1,3] and Judith Bauer[1,6]

[1]School of Human Movement and Nutrition Sciences, The University of Queensland, Brisbane, Queensland, Australia; [2]Nutrition and Dietetics, Toowoomba Hospital, Darling Downs Health, Toowoomba, Queensland, Australia; [3]Dietetics and Food Services, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [4]Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [5]School of Medicine, The University of Queensland, Brisbane, Queensland, Australia; and [6]Department of Nutrition, Dietetics, and Food, Monash University, Melbourne, Victoria, Australia

ABSTRACT

Sarcopenia is a known independent prognostic factor for decreased survival in patients with head and neck cancer; yet, its importance for the growing number of younger patients diagnosed with human papillomavirus (HPV)–positive oropharyngeal carcinoma (OPC+) has not been established. This systematic literature review aimed to determine the prevalence and impact of computed tomography (CT)–defined sarcopenia on survival outcomes for adult OPC+ patients (>18 y) undergoing any treatment modality. Prospective studies were searched using PubMed, Embase, CENTRAL, CINAHL, and Web of Science up until and including February 2022. Bias was assessed using the Quality In Prognosis Studies (QUIPS) tool, and certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. In total, 9 studies (total pooled OPC+ patients, $n = 744$) were identified and included in this review; 2 at low, 6 at moderate, and 1 at high risk of bias. All studies varied in sarcopenia assessment methods and skeletal muscle index threshold cutoff values. These studies demonstrated the cumulative prevalence of sarcopenia for OPC+ patients to be 42.9% (95% CI: 37.8%, 47.9%). While overall survival (3 studies, $n = 253$) and progression-free survival (1 study, $n = 117$) was lower in sarcopenic OPC+ patients, this was not statistically significant. GRADE certainty of evidence for impact of pretreatment sarcopenia on overall survival was low and progression-free survival was very low. Although these studies showed there to be a high prevalence of pretreatment sarcopenia in patients with OPC+, which may decrease survival, the impact on progression-free survival is very uncertain. Further, high-quality research utilizing consistent sarcopenia definitions and assessment methods that are conducted specifically in OPC+ is required to strengthen evidence certainty and determine if sarcopenia is an independent prognostic factor for this population. *Adv Nutr* 2022;13:2433–2444.

Statement of Significance: This systematic literature review demonstrates computed tomography–defined sarcopenia prevalence at diagnosis for patients with human papillomavirus–positive oropharyngeal cancer (OPC+) to be 42% and may be associated with decreased survival. Recognizing the impact sarcopenia has on outcomes for patients with OPC+ has important implications for informing appropriate nutrition interventions, to help optimize outcomes into survivorship.

Keywords: sarcopenia, human papillomavirus, head and neck cancer, nutrition, survival

Introduction

Human papillomavirus (HPV) is now the most common etiology of oropharyngeal squamous cell carcinoma (OPC) worldwide (1). The incidence of HPV-positive OPC (OPC+) is rising, particularly in patients under the age of 45 y (2, 3). These patients are known to have a markedly improved prognosis compared with those with HPV-negative (OPC–) disease (i.e., carcinogen-related) (4), and at diagnosis are more likely to be younger, asymptomatic, overweight and/or obese, well-nourished, and nonsmokers (2, 5, 6). The eighth edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system (2018) recommends separate staging models for OPC– and OPC+ disease, given the different histopathological,

biological, and clinical characteristics (7). Regardless, patients appear to be as susceptible to the well-established negative sequelae of malnutrition as seen for other head and neck cancer (HNC) populations (8).

Malnutrition and critical weight loss (defined as weight loss ≥5% in 1 mo) (9) can adversely affect cost, clinical, and patient-centered outcomes, including reduced quality of life and survival (9–11). Current treatment regimens for OPC+ often include intensive radiotherapy and cisplatin-based chemotherapy, which may result in acute and long-term treatment toxicity. This may further compound malnutrition morbidity into the survivorship phase (12). However, despite emerging research investigating the impact of HPV status on nutritional status (13), limitations of these studies often include comparing patients with OPC+ with heterogenous HNC populations (2, 14), and inconsistencies with evaluation of nutritional status and malnutrition risk (15). Furthermore, patients with an identical BMI can have high variability in body composition (15).

International diagnostic criteria define malnutrition as loss of skeletal muscle mass (SMM), in addition to involuntary weight loss, low BMI, and etiological factors (16). Methods to assess and monitor muscle mass change have become a key focus for oncological research. Sarcopenia is defined as a loss of SMM in addition to reduced function and strength (17), although currently, most oncological research reports loss of SMM only (15, 16), with international consensus regarding a uniform definition and assessment yet to be established in oncology (17). Body-composition analysis and muscle evaluation using computed tomography (CT) analysis at the third lumbar vertebrae (L3) is the gold-standard method at the tissue-organ level to diagnose sarcopenia (18). Sarcopenia is a known independent poor prognostic factor for various oncological populations, including HNC, and has been associated with excess chemotherapy dose-limiting toxicity, increased postoperative complications, and reduced survival (15, 19–21). A 2021 meta-analysis of 7 studies (pooled $n = 1059$) reported the cumulative prevalence of sarcopenia in a heterogenous HNC population to be 42% (22). Relatedly, sarcopenic obesity (resulting in a combination of depleted SMM and increased fat mass) is an emerging, yet overlooked critical issue in oncological research, given that patients may be burdened with the adverse effects of both conditions (15, 23).

Irrespective of an improved prognosis, intensive treatment for patients with OPC+ remains similar to those with OPC– disease and the risk of malnutrition for this population is high. Gaining a greater understanding of nutrition outcomes relative to HPV status could help deliver more targeted nutritional interventions for patients with OPC+, thus enabling improved nutritional and treatment outcomes, and improving quality of life into the survivorship phase. This study aimed to perform a systematic review of studies reporting sarcopenia prevalence and/or incidence in patients with OPC+, to determine the prognostic significance of sarcopenia on survival outcomes.

Methods

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (24). This review was registered prospectively on the PROSPERO International Register of Systematic Reviews database on 26 of April 2021 (Registration number CRD42021245495).

Eligibility criteria

Eligibility criteria were formed based on a Population Intervention, Comparison, and Outcomes (PICO) statement (**Supplemental Table 1**). The inclusion criteria for this literature search were empirical studies published in the English language, adult patients (>18 y of age) undergoing any treatment modality for OPC (i.e., cancers of the base of tongue, tonsils, soft palate, and pharynx) with known OPC+ status, and reported prevalence and/or incidence of CT-defined sarcopenia. Additional outcomes of interest were not specified to ensure that all studies that also reported on survival were included. No limitations were placed on study type, publication date, population sex, sample size, location, sarcopenia definition, or diagnostic anatomical site. Conference abstracts and review articles were excluded, with only peer-reviewed, full-text articles eligible for inclusion. Studies not reporting HPV status in relation to OPC were excluded.

Search strategy

A systematic literature search was undertaken by the primary author AE with the search strategy developed in consultation with a medical librarian of the online databases PubMed, Embase, CENTRAL, CINAHL, and Web of Science. An example of the search strategy for CINAHL can be seen in **Supplemental Table 2**. Keywords and medical subject heading (MeSH) search terms relating to sarcopenia, OPC, and HPV were used. The search was conducted up to February 2022. Once duplicates were removed, the title and abstract of all identified articles were first screened by the primary author AE, and subsequently by co-author JB to ensure interrater reliability. Full-text versions of potentially eligible articles were then reviewed independently by all authors, with the reference lists of all articles and prior systematic reviews hand-searched to ensure that all relevant publications of interest were

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Address correspondence to AE (e-mail: anna.edwards@uq.net.au).
Abbreviations used: AJCC, American Joint Committee on Cancer; CRT, chemoradiation; CT, computed tomography; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HNC, head and neck cancer; HPV, human papillomavirus; OPC, oropharyngeal carcinoma; OPC+, human papillomavirus–positive oropharyngeal carcinoma; OPC–, human papillomavirus–negative oropharyngeal carcinoma; OS, overall survival; PFS, progression-free survival; QUIPS, Quality In Prognosis Studies; RT, radiotherapy; SMI, skeletal muscle index; SMM, skeletal muscle mass; TNM, tumor-node-metastasis.

included. Any conflicting opinions were resolved through discussion to reach a consensus to determine final article selection.

Data extraction

Data extraction was performed by primary author AE of all eligible articles with an assessment of the data-extraction table independently conducted by all authors to ensure extraction correctness. Data extracted included study design, year of study, study population characteristics and number, diagnosis, treatment modality, HPV definition and prevalence, sarcopenia definition and prevalence, muscle mass evaluation and threshold values, overall survival (OS) and progression-free survival (PFS), and any confounders identified by the authors. If required, authors of the respective article were contacted to obtain missing details.

Quality assessment

Quality assessment of each article was undertaken by authors AE and BGMH using the Quality In Prognosis Studies (QUIPS) tool (25). The QUIPS tool was specifically chosen as it provides a comprehensive assessment of 6 bias domains commonly seen in studies of prognostic factors (25–27). These 6 bias domains each consist of 3 to 9 subdomains and included the following: study participation, attrition, prognostic factor and outcome measurement, confounding, statistical analysis, and reporting. An overall rating of "low," "moderate," or "high" risk of bias was determined by each author, with any discrepancies resolved through consultation with a third author JB. The online software system *Robvis* (Risk-of-bias VISualization) was used to create risk-of-bias plots (28). Evidence was synthesized for each identified outcome to evaluate the overall certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system and associated website GRADEPro (29). Data were critically appraised and summarized into tables of evidence in relation to 4 domains—risk of bias, imprecision, inconsistency, and indirectness—with a rating ("very low," "low," "moderate," or "high") applied to indicate the overall certainty of evidence.

Data synthesis and analysis

Due to the heterogeneity present among the identified studies, a meta-analysis could not be performed. Studies were categorized by their study design, population characteristics, treatment modalities, definition of sarcopenia assessment and diagnosis, impact on survival, impact of concurrent sarcopenic obesity, and adjustment factors. The level of evidence was assessed for each outcome, and results presented in a narrative summary. The cumulative prevalence of pretreatment sarcopenia in patients with OPC+ overall was assessed using the Cochrane Review Manager 5.4 software (REVMAN 5.4) (30). For this review, the terms of "sarcopenic" and "non-sarcopenic" were applied throughout to ensure consistency with interpretation.

Results

Results of the literature search are shown in **Figure 1**, with key characteristics summarized in **Tables 1** and **2**. In total, 179 studies were identified during the literature search and an additional 2 studies identified from hand searching. Of these, 9 reported outcomes relating to sarcopenia specific to OPC+ status (31–39) (total pooled patients with OPC, $n = 1293$; $n = 744$ patients with OPC+) and included in the analysis (Table 1). Eight studies (32–39) were observational retrospective cohort studies, using medical record review and imaging data audit, and 1 study was a post hoc analysis of a prospective cohort study (31). All were published between 2016 and 2022. Study locations included The Netherlands ($n = 5$) (32–34, 36, 39), the United States ($n = 2$) (35, 37), Australia (31), and Japan ($n = 1$) (38). Study populations included patients with diagnoses defined as head and neck squamous cell carcinoma (31, 36, 39), locally advanced HNC (32, 34), stage III to IV HNC (7th edition) (35), OPC (33, 37), and squamous cell carcinoma of the oropharynx, inclusive of primary and recurrent disease (38). Three studies (33, 37, 38) were conducted solely in OPC populations and 6 (31, 32, 34–36, 39) in a heterogenous HNC population with subanalysis conducted to stratify for OPC. Study sample sizes for OPC ranged from 53 to 269, with OPC+ sample sizes ranging from 21 to 197 (see Table 1). All studies reported sarcopenia prevalence at diagnosis in relation to HPV status, and all compared patients with a low skeletal muscle index (SMI; i.e., sarcopenic) with patients without a low SMI, respectively (i.e., non-sarcopenic). None of the studies investigated the impact of sarcopenia presence at diagnosis on survival outcomes for patients with OPC+ compared solely with patients with OPC–; therefore, prevalence rates at diagnosis and impact on survival and PFS (if available) specific to OPC+ only were reported. In addition, no study reported on sarcopenic obesity prevalence and/or incidence specific to patients with OPC+ at any time point.

Risk of bias

The QUIPS tool assessment of overall risk of bias was "low" for 2 studies (31, 39), "moderate" for 6 studies (32–37), and "high" for 1 study (38). Regarding each domain, there was a "moderate" risk for the study participation domain in 6 studies (32–36, 38) attributable predominantly to the retrospective observational study designs and mixed populations reported, often only stratifying in analysis for OPC and/or HPV status (**Figures 2** and **3**). A "high" risk of bias was seen for the attrition domain in 4 studies (32–34, 36) with concerns regarding a 20% attrition rate (33), almost 50% of the original sample excluded from analysis (32), minimal data presented regarding drop-out rates (34), and the inclusion of a high proportion of patients with an unknown HPV status (36). A "high" risk of bias was seen for outcome measurement in 2 studies (33, 34) due to follow-up duration not being reported and variability in post-treatment time-point assessments (33, 34), and "medium" due to the use of the third cervical vertebrae (C3) for sarcopenia assessment (32–35, 37, 39) and use of a

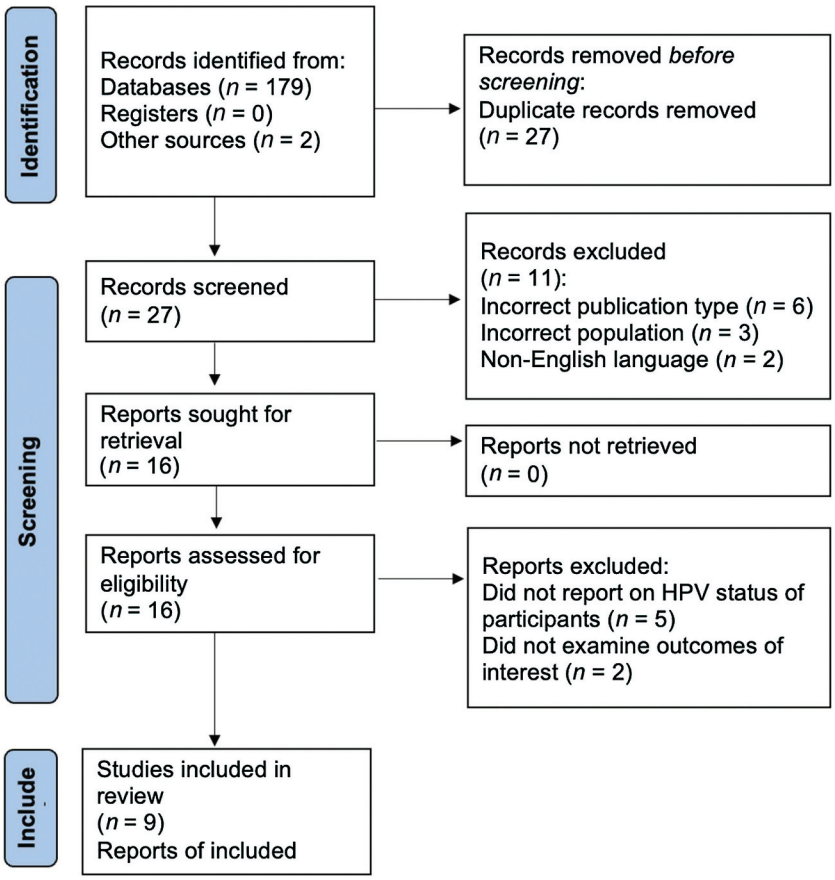

FIGURE 1 PRISMA flow diagram of search strategy, study selection, and identification process of eligible studies for this systematic review investigating the prevalence and impact of CT-defined sarcopenia on survival for patients with human papillomavirus-positive oropharyngeal cancer (OPC+). CT, computed tomography; HPV, human papillomavirus; OPC, oropharyngeal cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

cohort-specific optimal stratification method to determine cutoff values to diagnose sarcopenia (32–34). A "moderate" risk of bias due to the prognostic factor measurement domain (reporting p16 status only or the inclusion of patients with missing HPV status data in analysis) was seen for 7 studies (32, 34–39) and additional exclusion of patients with OPC+ from all survival analyses in 2 studies (32, 36). Last, a "high" risk of bias was seen for the confounding domain in 4 studies (32, 35, 36, 38) (Figures 2 and 3), as they reported limited details regarding treatment regimens, tolerance, and/or completion; nutritional status of patients at baseline; and the use of the obsolete (7th edition) AJCC staging systems for diagnoses.

Sarcopenia definition and assessment

A comparison of sarcopenia assessment methodology used in each study is summarized in Table 2. All of the identified studies used positron emission tomography–CT (PET-CT) imaging, with 5 at the level of C3 (32–35, 39) and 4 at the level of L3 (31, 36–38). Of the studies utilizing C3 for analysis, all used the Swartz et al. (40) algorithm to estimate L3 SMI values. A variety of commercially available software packages were used to analyze body composition by each study; however, all used skeletal muscle threshold reference values of −29 to +150 Hounsfield units (HU) during analysis. Six distinct sarcopenia definitions were identified with SMI cutoff threshold values (cm^2/m^2) applied using Western population–derived values in all studies. Two studies (33, 34) did not stratify for sex when determining SMI cutoff threshold values; and only 3 studies (31, 35, 38) used separate SMI cutoff threshold values for patients with a BMI (kg/m^2) ≤25.0. None of the identified studies reported skeletal muscle radiodensity or CT slice thickness used in analysis; and although 7 (31–36, 39) described the use of a single researcher to undertake the analysis, only 2 studies (31, 36) reported whether this researcher was trained in analysis. Intra-rater reliability was not described for any of the studies identified.

Sarcopenia prevalence and/or incidence

All studies reported sarcopenia prevalence at diagnosis in patients with OPC+, although only 1 (36) reported sarcopenia incidence specific to this population post–treatment completion. Sarcopenia prevalence ranged from 19% (n = 16) (32) to 61.5% (n = 48) (31) (Table 2). The cumulative

TABLE 1 Study characteristics, including country, study design, population characteristics, sample size, assessment methods, and treatment modalities for the 9 studies eligible in this systematic review investigating the prevalence and impact of CT-defined sarcopenia on survival for patients with human papillomavirus-positive oropharyngeal cancer (OPC+)[1]

Study (ref), year, location	Study design	Diagnosis, recruitment, AJCC edition	HPV analysis, HPV/p16 reported	Total OPC sample (*n*) (OPC+/p16+ sample, *n*)	Mean BMI (in kg/m^2) ± SD/BMI specific to HPV/p16 status	Imaging	Treatment modality
Ahern et al. (31), 2022, Australia	Observational, post hoc analysis of a prospective study	Mixed HNC, 2012–2018, 8th edition	p16 staining, p16	$n = 98$ ($n = 78$)	Not reported	PET-CT/CT at baseline (pretreatment; not further defined)	Definitive or adjuvant RT ± chemotherapy ± surgery of curative intent
Bril et al. (32), 2022, The Netherlands	Observational, retrospective	Mixed HNC, 2008–2015, 7th edition	p16 staining, PCR on HPV status, HPV	$n = 92$ ($n = 41$)	OPC+ 25.7 vs. OPC– 23.0, $P < 0.01$	CT or MRI at the head and neck region ≤3 mo pretreatment	Concurrent CRT (high-dose cisplatin regimen) of curative intent
Chargi et al. (33), 2020, The Netherlands	Observational, retrospective	OPC, 2009–2016, 7th edition	P16 staining, PCR on HPV status, HPV	$n = 216$ ($n = 69$)	Not reported	CT or MRI at the head and neck region ≤1 mo pretreatment	Definitive or adjuvant RT ± chemotherapy ± surgery of curative intent
Chargi et al. (34), 2021, The Netherlands	Observational, retrospective	Mixed HNC, 2012–2018, not reported	Not described, HPV	$n = 73$ ($n = 21$)	Not reported	CT or MRI at the head and neck region ≤1 mo pretreatment	Concurrent CRT ± surgery (high-dose cisplatin regimen) of curative intent
Ganju et al. (35), 2019, USA	Observational, retrospective	Mixed HNC, 2012–2016, 7th edition	Not described, p16	$n = 154$ ($n = 117$)	Obese (>30) p16+ $n = 44$ (38.6%) vs. p16– $n = 34$ (26.4%)	CT at RT planning	Concurrent CRT
Grossberg et al. (36), 2016, The Netherlands	Observational, retrospective	Mixed HNC, 2003–2013, 7th edition	PCR on HPV status, HPV	$n = 53$ ($n = 37$)	Not reported	PET-CT/CT of the abdomen pre-RT (<60 d pretreatment)	Definitive or adjuvant RT ± chemotherapy of curative intent
Olson et al. (37), 2020, USA	Observational, retrospective	OPC, 2005–2017, 8th Edition	PCR on HPV status, HPV	$n = 225$ ($n = 197$)	Not reported	PET-CT or CT of the abdomen (<60 d pretreatment)	Primary surgical resection or definitive RT ± chemotherapy
Tamaki et al. (38), 2018, Japan	Observational, retrospective	OPC, 2006–2015, not reported	Not described, HPV	$n = 113$ ($n = 85$)	OPC+ 28.2 vs. OPC– 24.2, $P = 0.010$	PET-CT at diagnosis	Definitive or adjuvant RT ± chemotherapy ± surgery of curative intent
Van Rijn-Dekker et al. (39), 2020, The Netherlands	Observational, retrospective	Mixed HNC, 2007–2016, 7th edition	Not described, p16	$n = 269$ ($n = 99$)	Not reported	CT at diagnosis	Definitive or adjuvant RT ± chemotherapy of curative intent

[1] Sarcopenia defined by Chargi et al. (33) as per the European Working Group on Sarcopenia in Older People criterion as the presence of low skeletal muscle mass. AJCC, American Joint Committee on Cancer; CRT, chemoradiation; CT, computed tomography; HNC, head and neck cancer; HPV, human papillomavirus; OPC, oropharyngeal cancer; OPC+, human papillomavirus–positive oropharyngeal cancer; OPC–, human papillomavirus–negative oropharyngeal cancer; p16, tumor suppressor protein that inhibits cyclin-dependent kinase 4A often used as a surrogate marker to determine human papillomavirus status; p16+, p16 positive; PET-CT, positron emission tomography–computed tomography; ref, reference; RT, radiotherapy.

TABLE 2 Definitions, assessments, cross-section locations, prevalence, and adjustment factors used for the 9 studies in this systematic review investigating the prevalence and impact of CT-defined sarcopenia on survival in patients with human papillomavirus-positive oropharyngeal cancer (OPC+)[1]

Study (ref), year, country	Sarcopenia assessments, software	Site	SMI cutoff (cm^2/m^2), method	Outcome: sarcopenia prevalence at diagnosis		Other outcomes reported specific to OPC+ status
				OPC+	OPC−	
Ahern et al. (31), 2022, Australia	Muscle mass, Slice-o-Matic (TomoVision)	CT-L3	♀ ≤41 and ♂ ≤43 (for BMI ≤25.0), ♂ ≤53 (for BMI ≥25.0), Martin et al. (51)	*n* = 48 (61.5%)	*n* = 16 (80.0%)	—
Bril et al. (32), 2022, The Netherlands	Muscle mass, Volumetool 1.6.5 (University Medical Center Utrecht)	CT-C3	♀: ≤10.7 cm^2; ♂: ≤13.1 cm^2; optimal stratification (defined using an ROC curve in relation to chemotherapy dose-limiting toxicity)	*n* = 16 (19%)	*n* = 31 (36.9%)	—
Chargi et al. (33), 2020, The Netherlands	Muscle mass, Slice-o-Matic (TomoVision)	CT-C3	♀ and ♂: ≤43.0 for OS and ≤43.2 for DFS; optimal stratification (defined using an ROC curve in relation to OS and DFS)	*n* = 33 (23.6%)	*n* = 77 (55%)	—
Chargi et al. (34), 2021, The Netherlands	Muscle mass, Slice-o-Matic (TomoVision)	CT-C3	♀ and ♂: ≤46.6; optimal stratification (defined using a ROC curve in relation to OS and DFS)	*n* = 14 (24.6%)	*n* = 36 (63.2%)	—
Ganju et al. (35), 2019, USA	Muscle mass, ImageJ (National Institute of Health)	CT-C3	♀ ≤41 and ♂ ≤43 (for BMI ≤25.0), ♂ ≤53 (for BMI ≥25.0), Martin et al. (51)	*n* = 65 (55.6%)	*n* = 78 (60.5%)	OS, PFS
Grossberg et al. (36), 2016, The Netherlands	Muscle mass, Pinnacle 9.6 (Phillips Medical Systems)	CT-L3	♀ ≤38.5 and ♂ ≤52.4, a priori algorithm based on Prado et al. (52) and Parsons et al. (53)	*n* = 12 (32.4%)	Not defined	OS
Olson et al. (37), 2020, USA	Muscle mass, Slice-o-Matic (TomoVision)	CT-L3	♀ ≤38.5 and ♂ ≤52.4, a priori algorithm based on Prado et al. (52) and Parsons et al. (53)	*n* = 107 (54.3%)	Not defined	—
Tamaki et al. (38), 2018, Japan	Muscle mass, ImageJ (National Institute of Health)	CT-L3	♀ ≤41 and ♂ ≤43 (for BMI ≤25.0), ♂ ≤53 (for BMI ≥25.0), Martin et al. (51)	*n* = 23 (27.1%)	*n* = 9 (33.3%)	—
Van Rijn-Dekker et al. (39), 2020, The Netherlands	Muscle mass, Somatom Sensation Open (Siemens)	CT-C3	♀ ≤30.6 and ♂ ≤42.4 SMI as per the cohort's lowest gender-specific quartile	*n* = 16 (20%)	*n* = 57 (71.3%)	OS

[1] Sarcopenia defined by Chargi et al. (33) as per the European Working Group on Sarcopenia in Older People criteria as the presence of low skeletal muscle mass. C3, third cervical vertebrae; CDLT, chemotherapy dose-limiting toxicity as described by Bril et al. (32); CT, computed tomography; DFS, disease-free survival; HPV, human papillomavirus; L3, third lumber vertebrae; OPC, oropharyngeal cancer; OPC+, human papillomavirus–positive oropharyngeal cancer; SMI, skeletal muscle index; OPC−, human papillomavirus–negative oropharyngeal cancer; OS, overall survival; PFS, progression-free survival; ref, reference; ROC, receiver operating characteristic curve; ♀, female; ♂, male.

FIGURE 2 QUIPS diagram (traffic light plot) completed for this systematic review investigating the prevalence and impact of CT-defined sarcopenia on survival for patients with human papillomavirus-positive oropharyngeal cancer (OPC+). CT, computed tomography; HPV, human papillomavirus; OPC, oropharyngeal cancer; QUIPS, Quality In Prognosis Studies.

prevalence of sarcopenia at diagnosis for patients with OPC+ was 42.9% (95% CI: 37.8%, 47.9%) (**Figure 4**). Analysis based on the anatomical site demonstrated a cumulative prevalence of sarcopenia at L3 to be 46.1% (95% CI: 31.1%, 61.2%) (**Figure 5**A) and C3 to be 29.5% (95% CI: 12.9%, 46.1%) (Figure 5B). Six studies (31–35, 39) reported lower prevalence rates of sarcopenia at diagnosis for patients with OPC+ compared with patients with OPC– disease; and 2 (36, 37) did not report sarcopenia prevalence at diagnosis for patients with OPC– disease (Table 2). Only 1 study (38) compared sarcopenia prevalence at diagnosis for patients with OPC+ with those with OPC–, which demonstrated no

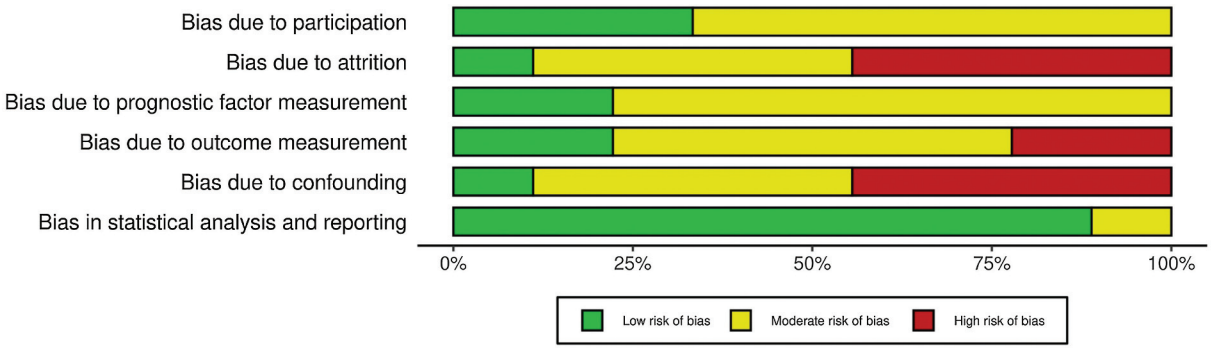

FIGURE 3 QUIPS diagram (weighted summary plot) completed for this systematic review investigating the prevalence and impact of CT-defined sarcopenia on survival for patients with human papillomavirus-positive oropharyngeal cancer (OPC+). CT, computed tomography; HPV, human papillomavirus; OPC, oropharyngeal cancer; QUIPS, Quality In Prognosis Studies.

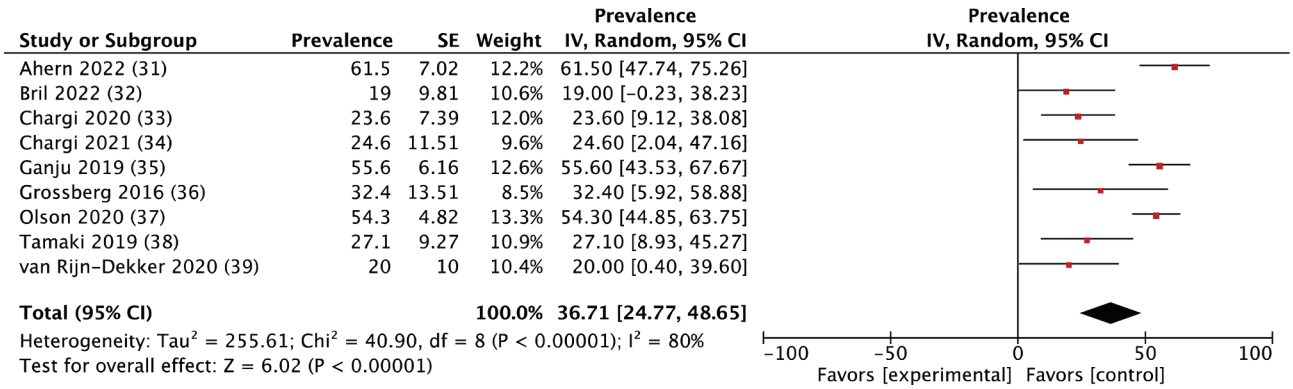

FIGURE 4 REVMAN 5.4 forest plot completed for this systematic review investigating the prevalence and impact of CT-defined sarcopenia on survival for patients with human papillomavirus-positive oropharyngeal cancer (OPC+). CT, computed tomography; HPV, human papillomavirus; IV, inverse variance; OPC, oropharyngeal cancer.

significant difference [$n = 23$ (27.1%) vs. $n = 9$ (33.3%), $P = 0.701$] between populations.

Survival outcomes

Three studies (35, 36, 39) reported survival outcomes in patients with OPC+ with concurrent sarcopenia at diagnosis. No study compared survival outcomes for patients with sarcopenia based on HPV status (i.e., sarcopenic OPC+ vs. sarcopenic OPC–), and no study investigated survival outcomes for patients with OPC+ with or without sarcopenia as a primary study outcome. OS was defined as the time from diagnosis to date of death or date of last known follow-up (35), time from diagnosis to the date of death due to any cause (36), and from the first day of radiotherapy to date of death or date of known last follow-up (39). The median follow-up time reported ranged from 24 (39) to 68.2 (36) mo.

OS (35, 36, 39) and PFS (33) were lower for patients with OPC+ with concurrent sarcopenia when compared with those without sarcopenia; however, this was not statistically significant. Ganju et al. (35) demonstrated no significant difference for either OS (p=0.82) or PFS (p=0.38) between sarcopenic and non-sarcopenic patients with OPC+ (median follow-up: 35.1 mo). Grossberg et al. (36) reported that, although baseline sarcopenia presence (defined as

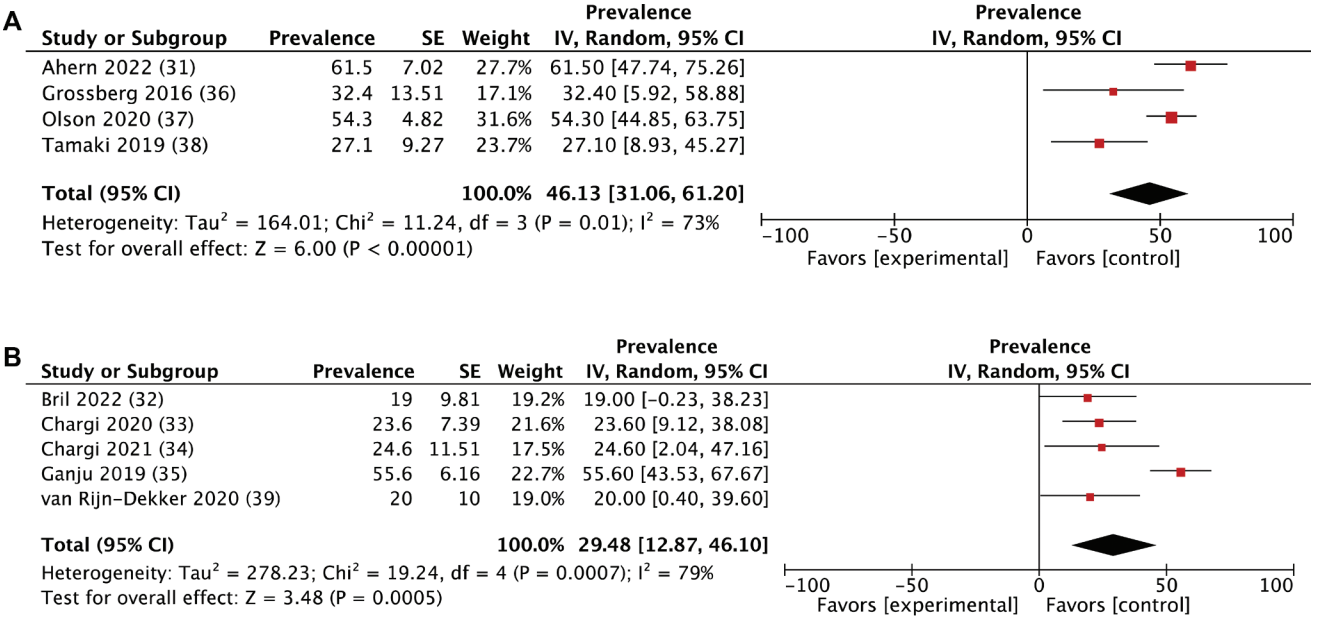

FIGURE 5 REVMAN 5.4 forest plot completed for this systematic review investigating the prevalence and impact of CT-defined sarcopenia at the level of the third lumbar vertebrae (L3) (A) and third cervical vertebrae (C3) (B) on survival for patients with human papillomavirus-positive oropharyngeal cancer (OPC+). CT, computed tomography; HPV, human papillomavirus; IV, inverse variance; OPC, oropharyngeal cancer.

TABLE 3 GRADE certainty of evidence of patient survival outcomes in this systematic literature review investigating the prevalence and impact of CT-defined sarcopenia versus non-sarcopenia on survival for patients with human papillomavirus-positive oropharyngeal disease (OPC+)[1]

Outcome (ref), no. of studies	Certainty assessment					Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	
Overall survival (35, 36, 39), $n = 3$	Observational	Serious[2]	Not serious	Not serious	Serious[3]	⊕⊕◯◯ Low
Progression-free survival (35), $n = 1$	Observational	Serious[4]	Not serious	Not serious	Very serious[5]	⊕◯◯◯ Very low

[1]CT, computed tomography; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HPV, human papillomavirus; OPC+, human papillomavirus–positive oropharyngeal cancer; ref, reference; ⊕⊕◯◯, denotes low certainty of evidence according to GRADE; ⊕◯◯◯, denotes very low certainty of evidence according to GRADE.
[2]Risk of bias "serious" as per assessment using the Quality In Prognosis Studies (QUIPS) tool.
[3]Imprecision deemed "serious" due to pooled small OPC+ patient study numbers (<400).
[4]Risk of bias "serious" as per assessment using the QUIPS tool.
[5]Imprecision deemed "very serious" due to pooled small OPC+ patient study numbers (<100).

skeletal muscle depletion) demonstrated a trend towards decreased OS for sarcopenia patients with OPC+ versus non-sarcopenic patients (HR: 2.75; 95% CI: 0.83, 13.62), this was not statistically significant ($P = 0.09$) nor was post-radiotherapy skeletal muscle depletion (data not reported; median follow-up: 68.2 mo). Van Rijn-Dekker et al. (39) concurred with these findings, reporting no difference in OS for patients with OPC+ based on sarcopenia presence ($P = 0.150$; median follow-up: 24 mo). GRADE certainty of evidence for OS was low, downgraded due to serious bias and imprecision, and was very low for PFS, downgraded due to serious bias and very serious imprecision (**Table 3**).

Sarcopenic obesity

No study reported the prevalence, incidence, and/or impact of sarcopenic obesity on survival in patients with OPC+. However, 2 studies (33, 38) reported the prognostic significance of the presence of sarcopenic obesity at diagnosis on OS with adjustment for HPV status. Sarcopenic obesity was defined in both studies as the presence of low SMM concurrent with a BMI ≥27 (33, 38). Chargi et al. (33) demonstrated that patients with sarcopenic obesity had a significantly lower median OS compared with patients without sarcopenic obesity [22.0 mo (IQR: 4.9–32.8) vs. 38.7 mo (IQR: 16.0–57.9); $P = 0.03$; 3-y OS rate of 39% vs. 60%, respectively] but not PFS [23.7 mo (IQR: 5.5–33.4) vs. 35 mo (IQR: 10.6–57.1); $P = 0.17$; 3-y PFS rate of 51% vs. 70%, respectively]. Sarcopenic obesity was the only significant negative prognostic factor for OS (HR: 4.4; 95% CI: 1.5, 12.9; $P < 0.01$) and PFS (HR: 3.9; 95% CI: 1.0, 14.8; $P = 0.04$) in patients with OPC on multivariable analysis, independent of HPV status (33). Tamaki et al. (38) also demonstrated sarcopenic obesity to be a negative prognostic factor for OS (HR: 4.4; 95% CI: 1.5, 12.9; $P < 0.01$) and PFS (HR: 3.9; 95% CI: 1.0, 14.8; $P = 0.04$) in patients with advanced OPC, independent of HPV status.

Discussion

This is the first systematic literature review to our knowledge examining the prevalence and impact of CT-defined sarcopenia on survival for patients with OPC+. The cumulative prevalence of sarcopenia of 42.9% ($n = 744$) was similar to the prevalence reported in a heterogenous patient population with HNC (42%; 27 studies, $n = 7704$) (22). Although not significant, a trend was seen towards reduced OS for patients with OPC+ and pre-existing sarcopenia at diagnosis, suggesting potential prognostic value in the 3 studies reporting this outcome. The evidence for PFS is very uncertain, due to serious bias and very serious imprecision.

The use of CT scans to assess SMI and diagnose sarcopenia is an evolving and important tool for the nutritional assessment and management of patients with HNC, given it is now well established that weight loss alone may not be reflective of the degree of SMM lost (18). This is particularly important for patients with OPC+, as many present as well nourished with minimal symptom burden (including absence of weight loss) at diagnosis, yet are equally predisposed to developing nutritional issues and malnutrition as other HNC populations, due in part to the intensive multimodal treatment used to achieve remission (12, 13, 41, 42). The use of the level of L3 is considered the gold standard at the tissue-organ level for body-composition analysis (18, 43–45). However, CT imaging protocols for patients with HNC, inclusive of OPC, do not always extend to L3 and subsequently the secondary use of CT imaging for research was delayed when compared to other oncological populations (43, 46). In this review, only 4 studies (31, 36–38) used L3 for body-composition analysis, while the remaining 5 studies (32–35, 39) used C3, an anatomical site yet to be fully validated for skeletal muscle evaluation in the HNC population (47, 48). The C3 studies used the algorithm by Swartz et al. (40) based on 52 Dutch patients with HNC to estimate the skeletal muscle cross-sectional area at L3 from C3. A recent Australian study (49) demonstrated this method to be unsuitable at both the individual and group level, with weak agreement seen for sarcopenia identification in an overweight population. The use of differing threshold measurement values therefore may increase the risk that some patients with sarcopenia may not be appropriately identified (49, 50). In this review, studies utilizing L3 demonstrated a higher cumulative prevalence of sarcopenia at diagnosis (46.1%) than those using C3 (29.5%),

further supporting this view. To allow for the prognostic significance of sarcopenia in the OPC+ population to be fully elucidated, the clinical reproducibility of methods to accurately assess for and diagnose sarcopenia to allow timely nutrition interventions requires further research.

The lack of methodological consensus of sarcopenia definitions and thresholds for classifying sarcopenia in patients with OPC makes comparison between studies challenging, consistent with findings of other studies in the broader HNC literature (43, 51–53). Chargi et al. (33) used an optimal stratification method (in relation to OS and disease-free survival) to determine cohort-specific cutoff values for their OPC population (inclusive of OPC+); however, both utilized scans at the level of C3 for analysis. Ahern et al. (31), Ganju et al. (35), and Tamaki et al. (38) used the body-composition cutoff values determined by Martin et al. (51); however, these were established using 1473 patients with gastrointestinal and lung carcinomas. Grossberg et al. (36) and Olson et al. (37) both used an a priori algorithm based on the studies by Prado et al. (52) ($n = 250$ obese patients; BMI $\geq$30) with solid tumors of the gastrointestinal or respiratory tract) and Parsons et al. (53) ($n = 104$ patients with advanced cancer). Bril et al. (32) also used an optimal stratification method (in relation to chemotherapy dose-limiting toxicity presence) to determine cutoff values in a heterogenous, locally advanced HNC population with high numbers of active smokers; and similarly, van Rijn-Dekker et al.'s (39) use of a cohort-specific sarcopenia cutoff value (set according to the lowest sex-specific quartile) in a heterogenous HNC population also reporting high numbers of active smokers and rates of alcohol use and treatment delivery with radiotherapy only was not reflective of the OPC+ population, nor first-line treatment modalities. OPC+ typically occurs in a younger, nonsmoking population, absent of any traditional carcinogenic-related risk factors (54). Research identifying distinct cutoff values for sarcopenia assessment specific to OPC+ is therefore warranted to minimize the premature dismissal of this potentially clinically relevant and modifiable risk factor.

Patients with OPC+ are more likely to present as well nourished at diagnosis and in the overweight and/or obese BMI categories, consistent with the general population (5, 38, 41). Sarcopenia can often be overlooked in patients with concurrent obesity (20); however, patients with sarcopenic obesity may have higher rates of mortality, dose-limiting treatment toxicities, and treatment complications than those with sarcopenia alone (15, 55). Given that current body surface area calculations used to scale chemotherapy dosing do not discern for differences in body composition (56), greater proportions of fat mass may amplify the therapeutic dose prescribed (15, 20, 57). This may be particularly pertinent for patients with sarcopenic obesity receiving hydrophilic chemotherapeutic agents, as the metabolism and distribution of these drugs primarily occurs in lean tissues, which are reduced in volume in this population (15, 20, 23, 58, 59). Recent evidence also suggests that patients with sarcopenic obesity display lower rates of febrile neutropenia, implying potential "under-dosing" of patients (60, 61). Although a positive association between sarcopenia and dose-limiting toxicities has been consistently reported (11, 32, 39, 58, 59, 62), the relation between sarcopenic obesity and treatment toxicity remains poorly understood and requires further investigation. Only 2 studies (33, 38) in this review assessed sarcopenic obesity, and none in relation specifically to OPC+. The higher BMI at diagnosis often seen for patients with OPC+ may not only mask underlying sarcopenia but may also reduce patient and clinician concern regarding weight loss during treatment, impeding adherence to nutritional guidelines and risking nutritional decline (5, 41, 63). To fully understand the prognostic significance that sarcopenic obesity has for patients with OPC+, research identifying distinct cutoff values that also assess for sarcopenic obesity is warranted.

High-dose escalation radiotherapy regimens that aim to target tumor volumes while sparing dose volumes to surrounding organs at risk and healthy tissue have the potential to reduce chronic treatment-related toxicities and improve quality of life into survivorship for patients with OPC+ (63, 64). However, higher precision treatment means less margin for error, including treatment-induced anatomical changes resulting from weight loss. Any deviations from the planned treatment geometry may risk the potential under- and/or overdosing of target volumes to tissues at risk, worsening treatment toxicity (5, 65), or equally risk reducing an already de-escalated treatment (2, 66). Weight maintenance, and in particular preservation of the specific body compositional ratios that are present at treatment planning (i.e., sarcopenia prevention), will only become more critical in the OPC+ population to ensure optimal treatment tolerance and successful administration of de-escalated precision radiotherapy.

Major strengths of this review include the rigorous approach to literature identification, bias assessment, and synthesis, using both QUIPS and GRADE, as well as the focus being solely on studies that analyzed results for the OPC+ population separately from the general HNC population. However, limitations of the current review are acknowledged and include the following: the small pooled number of patients from the available studies; a lack of consensus regarding sarcopenia assessment, anatomical landmarks used, and definition; variations in the number of confounders accounted for in analysis; and use of varying AJCC TNM staging systems when describing diagnoses for the OPC+ patient population. Additionally, none of the studies identified investigated either the impact of sarcopenia presence at diagnosis on outcomes for patients with OPC+ compared with patients with OPC–, nor rates of sarcopenia incidence for OPC+ during treatment and/or post-treatment phase. Instead, HPV status was either a secondary outcome or a confounder, then adjusted for in analysis.

There is a high prevalence of pretreatment CT-defined sarcopenia in the growing epidemic of younger patients diagnosed with OPC+. Sarcopenia may reduce OS, but the evidence for PFS is very uncertain. Further high-quality

research conducted specifically in patients with OPC+ using AJCC 8th edition staging is warranted to determine if CT-defined sarcopenia is an independent prognostic factor on survival outcomes for this population, to promote optimal health into survivorship.

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