



# The effect of skeletal muscle mass on dose-limiting toxicities during (chemo)radiotherapy in patients with head and neck cancer: A systematic review and *meta-analysis*

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## ABSTRACT

Radiotherapy (RT) is a standard treatment for head and neck cancer (HNC) and chemoradiotherapy (CRT) is indicated for patients with locally advanced disease. Toxicities during treatment are common and can lead to early cessation of chemotherapy and radiotherapy (RT) interruptions, which can affect oncologic outcomes. Skeletal muscle mass (SMM) is a new biomarker to predict toxicities and overall survival. The aim of this systematic review is to provide an overview of studies towards the associations between SMM and dose limiting toxicity (DLT) and/or RT interruptions in HNC patients.

A systematic literature search was conducted and yielded 270 studies. Inclusion criteria were articles published in English that investigated the effect of low SMM measured in humans with HNC on toxicities during CRT or RT. Studies that did not investigate oral cavity, oropharynx, larynx, hypopharynx, nasopharynx cancers or carcinoma of unknown primary were excluded. This led to the inclusion of 22 original studies.

The prevalence of low SMM ranged from 19.7 % to 74.7 %. SMM was often assessed by measuring the cross-sectional muscle area at the level of the third cervical vertebra on computed tomography scans. Cut-off values used to categorize patients in SMM groups varied. In the *meta-analyses* heterogeneity was moderate ( $I^2 = 68\%$  and  $50\%$  respectively). Patients with low SMM had higher, but only borderline significant, odds of DLT during CRT (OR 1.60; 95 % CI 1.00–2.58;  $p = 0.0512$ ) and RT interruptions (OR 1.89; 95 % CI 1.00–3.57;  $p = 0.0510$ ) compared to patients without low SMM.

To conclude, in HNC patients low SMM, defined with different methods and cut-off values, is associated with DLT and RT interruptions during (C)RT, although the difference is only borderline statistically significant.

## Introduction

Each year, worldwide around 600.000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed [1]. Radiotherapy (RT) is a standard treatment for HNSCC. Chemoradiotherapy (CRT) with cisplatin is applied in advanced stage HNSCC [2–8]. Cisplatin-based CRT

is limited to patients who are considered fit enough; yet despite this exclusion criterion more than 30 % of patients receiving cisplatin tri-weekly, experience cisplatin dose limiting toxicity (DLT). Nephrotoxicity, ototoxicity, neurotoxicity, hematologic toxicities, mucositis and dermatitis are typical causes of DLT [9–12]. A cumulative cisplatin dose of 200 mg/m<sup>2</sup> or more is advised to optimize locoregional control, and

**Abbreviations:** HNSCC, head and neck squamous cell carcinoma; RT, radiotherapy; CRT, chemoradiotherapy; DLT, dose limiting toxicity; SMM, skeletal muscle mass; CT, computed tomography; MRI, magnetic resonance imaging; HNC, head and neck cancer; CSMA, cross-sectional muscle area; LSMI, lumbar skeletal muscle index; BMI, body mass index; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; CTCAE, Common Terminology Criteria for Adverse Events; OR, odds ratio.

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therefore DLT is unwanted [13,14]. DLT can also occur during RT (with or without chemotherapy), typically as RT interruption or early termination of treatment. To identify characteristics that are associated with DLT is therefore relevant.

Low skeletal muscle mass (SMM) is found to be associated with, and a predictor of DLT [15–17]. SMM can easily be measured on pre-treatment computed tomography (CT) or magnetic resonance imaging (MRI) scans, mostly performed during routine diagnostic work-up for head and neck cancer (HNC). SMM in patients with HNC can be assessed by outlining the cross-sectional muscle area (CSMA) through semi-automatic segmentation of the skeletal muscles at the third cervical vertebra. The CSMA at the third cervical vertebra can be translated into the CSMA at the third lumbar vertebra by using a formula that takes age, weight, length and sex as additional variables. The lumbar skeletal muscle index (LSMI), which is commonly used to measure SMM, can then be determined by adjusting for length [18–22]. However, some other methods to assess SMM are used in common practice [23,24]. Cut-off values to determine low SMM are under debate; some studies emphasize the importance of sex and body mass index (BMI) as separate categories for cut-off values whilst others do not use these [15,25–29]. It is essential to mention that cut-off values are calculated for different types of HNC subsites and patient populations (e.g. by region or country), and hence might only be applicable for distinct patient groups with HNC.

SMM can be influenced by nutritional status, therefore it is plausible that not only SMM affects the rate of DLT but DLT can also affect SMM on its turn. Mucositis, dysphagia and xerostomia can impede adequate nutritional intake during treatment, so possibly patients with low SMM prior to treatment are more prone to enter this negative feedback loop [30].

A systematic review has demonstrated the harmful effects of low SMM on overall and progression free survival in patients with HNC [31]. Studies on the associations between low SMM on DLT are also conducted, however to our knowledge a systematic review has not yet been published. The aim of this systematic review is to provide a thorough overview of studies in patients with HNC, regarding the effect of low SMM on DLT during CRT or on impediments during RT. We assess the risk of DLT including RT interruptions for patients with low SMM via a meta-analysis, and additionally report the incidence of specific toxicities in patients with HNC and low SMM compared to patients without low SMM.

## Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards were applied for this review. We performed a systematic search in the following databases: MEDLINE, Embase, Cochrane and Scopus, from earliest date available until the 7th of February 2023. The search strings are reported in Supplement A. The search terms included and variants of them were: ‘skeletal muscle mass’, ‘sarcopenia’, ‘head and neck cancer’, ‘antineoplastic agents’ and ‘toxicity’. These are described in detail in Supplement 2. The search strings were checked by the librarian (Mrs. P.H. Wiersma) of the University of Utrecht.

The studies retrieved from the search were systematically assessed first by title and abstract and later by full-text, by three researchers independently (AS, HS and BM). In case of disagreement between two researchers, a resolution was found after discussion and consulting the senior author (RB). Inclusion criteria were articles regarding DLT and SMM in HNC patients treated with CRT or RT. The articles had to be in English and full-text had to be available. Articles considering surgical treatment only, HNC tumors that were not located in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx or of unknown primary, conference abstracts and animal studies were excluded.

After inclusion, the researchers independently extracted data from the studies into predefined systematic tables for outcomes. Extracted

data consisted of authors, year of publication and country where the study was conducted. Patient characteristics collected were number of patients, age, tumor locations and tumor stages. Moreover, type of treatment (CRT or RT), method to assess SMM, cut-off values of low SMM, prevalence of low SMM and definitions of toxicity and DLT were collected. Results extracted from the studies for patients with low SMM and patients without low SMM were number of DLTs, (if reported) the odds ratio (OR) obtained from univariate and multivariate analysis for DLT and prevalence of mucositis, dysphagia, xerostomia and renal failure. Extracted data were compared between researchers (AS, HS and BM) and in case of inconsistencies a consensus was reached between researchers.

To assess the methodologic quality of the included studies, the Newcastle-Ottawa scale was used: the researchers (AS, HS and BM) applied the scale independently and compared results [32]. In case of disagreement, the issue was discussed between researchers and the senior author until consensus was achieved. Agreement percentages were calculated and Cohen’s kappa was used to assess inter-rater reliability.

A meta-analysis was executed on the risk of DLT between patients with low and without low SMM. All studies from the systematic review were included at first and scanned. Studies were then excluded from the meta-analysis for the following reasons: 1) SMM was not (and could not be) dichotomized, i.e. low versus without low SMM; 2) DLT definition was not clear; 3) overall toxicities instead of dose limiting toxicities were assessed; 4) no OR could be calculated due to limited availability of data ( $n < 10$  per group, or not reported); 5) an intervention was done to influence DLT; 6) not SMM but another factor (e.g.) age was the main covariate to analyze its association with DLT; 7) the same patient cohort was used in another more recent study, which was included. A second meta-analysis was performed among patients undergoing RT only, on the risk of RT interruptions. Studies were in- and excluded for the same reasons as above, but numbers 2) and 3) were substituted by the following: radiotherapy interruptions were not reported per SMM category.

Heterogeneity was quantified using  $\tau^2$  and  $I^2$  statistic tests, and the  $I^2$  percentages were interpreted as follows:  $<50\%$  low heterogeneity,  $50\text{--}75\%$  moderate heterogeneity, and  $>75\%$  considerable heterogeneity. A random effects model was performed and a  $p$ -value  $< 0.05$  was considered as statistically significant. The results were visualized in forest plots. All statistical analyses were performed using R 4.3.1. GUI (The R Foundation for Statistical Computing), package meta and metafor.

## Results

The search yielded 326 studies of which 278 remained after exclusion of duplicates, which were screened by title and abstracts. In total 25 articles were judged to be eligible and fully read and this led to inclusion of 22 articles for qualitative synthesis. Supplement 2 includes the PRISMA flowchart.

### Study characteristics

In Table 1 and Table 2 an overview of the study and patient characteristics is presented. Study population sizes ranged between 51 and 977 patients, all diagnosed with HNC. Most studied HNC tumors were advanced-stage (stage III or higher) and located in the oropharynx, followed by the hypopharynx, larynx and nasopharynx. Not all studies differentiated between locations, and some made one group of larynx and hypopharynx tumors [33–35]. Most studies included patients receiving either RT or CRT. CRT regimens differed between studies: some included patients receiving induction chemotherapy or CRT in the adjuvant setting and in almost all studies multiple regimens were included such as cisplatin and carboplatin. The criteria for toxicity widely ranged, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and version 5.0. were most often used [10,36].

**Table 1**  
Study and patient characteristics part 1.

Author and date	Country of study	Study design	Type of cancer	Number of patients (% male vs female)	Age in years low versus no low SMM; Mean $\pm$ SD or median [range], or otherwise specified	Treatment	Number of patients with adjuvant CRT (%) in cohort	Definition of toxicity	Definition of DLT
Bentahila et al. 2022 [37]	France	Retrospective cohort	HNSCC	212 (83 vs 17)	62.28 $\pm$ 8.83 vs 59.71 $\pm$ 9.53	CRT multiple modalities, ICT and adjuvant included	42 (19.81)	CTCAE v4.03	Treatment-induced acute and late toxicity and unscheduled interruption
Bril et al. 2021 [16]	Netherlands	Retrospective cohort	HNSCC	153 (73 vs 27)	59.9 $\pm$ 6.3 vs 59.8 $\pm$ 7.3	Cis100 CRT, ICT and adjuvant excluded	Only primary CRT included	Not mentioned	Cumulative cisplatin dose < 200 mg/m <sup>2</sup>
Chargi et al. 2022 [42]	Netherlands	Retrospective cohort	LA-HNC	343 (69 vs 31)	59.4 vs 55.5	Cis100 CRT, ICT excluded	69 (20.1)	Not mentioned	$\geq$ 50 % cisplatin dose reduction, $\geq$ 4 days treatment delay and termination of cisplatin-base chemotherapy after 1th or 2th cycle.
Cho et al. 2018 [47]	South Korea	Retrospective cohort	LA-HNC	221 (81 vs 19)	64 [18–94] vs 56 [18–86]	CRT, modality unknown, ICT; RTo	Not mentioned	RTOG toxicity criteria	Interruption of RT ( $\geq$ 5 days), no RT completion
Ganju et al. 2019 [41]	United States	Retrospective cohort	HNSCC	246 (81 vs 19)	<65y: n = 19 (24 %), >65y: n = 60 (76 %) vs < 65y: n = 84 (50.3 %), >65y: n = 83 (47.7 %)	CRT, mostly cisplatin, ICT and adjuvant included	54 (22)	Not mentioned	Chemotherapy > 1 week delay or not completing all cycles, RT number of days missed
Haehl et al. 2022 [33]	Germany	Retrospective cohort	HNSCC	280 (unknown)	Not specified, only persons > 65 years	CRT, mostly cisplatin, adjuvant included; RTo	Not mentioned	CTCAE v5	Cumulative dose < 200 mg/m <sup>2</sup> for cisplatin and < 450 mg/m <sup>2</sup> for carboplatin
Hua et al. 2020 [40]	China	Retrospective cohort	Nasopharyngeal cancer	862 (74 vs 26)	45.84 $\pm$ 10.78 vs 45.70 $\pm$ 10.23	Cis80-100 or Cis30-35 CRT	Not mentioned	CTCAE v4.0	Not mentioned
Huang et al. 2019 [38]	Taiwan	Randomized controlled trial	HNC	64 (94 vs 6)	Placebo group: 52.6 $\pm$ 10.3 Glutamine group 52.2 $\pm$ 9.5	CRT, weekly or triweekly cisplatin or carboplatin +- 5FU, or paclitaxel; RTo	41 (64)	CTCAE v4.03	Not mentioned, people who did not complete RT excluded
Huang et al. 2021 [52]	Taiwan	Prospective cohort	Nasopharyngeal cancer	82 (67 vs 33)	45.7 $\pm$ 10.7	CRT, Cis100 or lobaplatin (30 mg/m <sup>2</sup> ), supplementary anti-eGFR treatment: 15.9 %	Not mentioned	RTOG toxicity criteria; CTCAE v5.0	Reduction of drug dose, delay or definite termination
Huang et al. 2021-B [53]	Taiwan	Retrospective cohort	OSCC	175 (86, 14)	54 $\pm$ 9.5 vs 54 $\pm$ 10.4	adjuvant CRT, platinum-based +- 5FU +- oTU	175 (100)	CTCAE v5.0	Not mentioned
Jin et al. 2022 [34]	United States	Retrospective cohort	HNC	51 (82 vs 18)	59 vs 58	CRT, mostly weekly cisplatin, adjuvant included; RTo	20 (39)	CTCAE v5.0	Missing > 1 treatment days
Karavolia et al. 2022 [48]	Netherlands	Retrospective cohort	HNC	977 (69 vs 31)	67 $\pm$ 10 vs 63 $\pm$ 10	CRT, multiple modalities; RTo; ICT and adjuvant excluded	Primary surgery patients excluded	CTCAE 4.0, mucositis graded by RTOG guidelines.	Not mentioned
Lere-Chevaleyre et al. 2022 [45]	France	Retrospective cohort	advanced HNC	92 (78 vs 22)	57.2 $\pm$ 7.5	ICT with TPF	Not mentioned	CTCAE v4.0	Not mentioned
Morse et al. 2022 [35]	United States	Retrospective cohort	HNSCC	272 (82 vs 18)	Not specified, 221 persons < 70 yrs, 51 $\geq$ 70 years	Cisplatin CRT, ICT included.	57 (21)	CTCAE v4.0, CRT only, induction CRT excluded	RT: any missed treatments, CT: delays > 1 week, not all planned cycles completed
Nagpal et al. 2021 [17]	India	Retrospective cohort	LA-HNSCC	300 (88 vs 12)	Mean: 60.4	Cisplatin CRT, some carboplatin, ICT and adjuvant excluded	Primary surgery patients excluded	CTCAE 5.0	Not applicable: Patients who did not complete all cycles were excluded
Sealy et al. 2020 [43]	Canada	Retrospective cohort	HNC	213 (77 vs 23)	57.9 $\pm$ 10.3	Cis100, Cis40, carboplatin CRT, adjuvant included	108 (51)	Not mentioned	Incompletion of 1 cycle or more, but dose reduction or switch to carboplatin was not

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Table 1 (continued)

Author and date	Country of study	Study design	Type of cancer	Number of patients (% male vs female)	Age in years low versus no low SMM; Mean $\pm$ SD or median [range], or otherwise specified	Treatment	Number of patients with adjuvant CRT (%) in cohort	Definition of toxicity	Definition of DLT
Thureau et al. 2021 [51]	France	Prospective cohort	HNSCC	243 (77 vs 23)	61 $\pm$ 9.04	Cis100, cetuximab CRT; RTo, adjuvant included	152 (63)	CTCAE 4.0	Incomplete RT dose delivery, interruption > 3 days, CRT dose reduction
van Rijn-Dekker et al. 2020 [49]	Netherlands	Retrospective cohort	HNSCC	744 (75 vs 25)	66 $\pm$ 10 vs 62 $\pm$ 10	CRT, multiple modalities; RTo; adjuvant included	Not mentioned	Xerostomia and dysphagia, patient-rated and CTCAE v4.03	Not mentioned
Wendrich et al. 2017 [15]	Netherlands	Retrospective cohort	HNSCC	112 (64 vs 36)	54.5 $\pm$ 9.4	Cis100, some carboplatin CRT, ICT and adjuvant excluded	Adjuvant surgery patients excluded	Any toxicity	Dose-reduction of 50 %, postponement of treatment of 4 days or termination of chemotherapy after the first or second cycle. Switch to carboplatin was not CDLT if no significant dose reduction occurred
Willemsen et al. 2020 [39]	Netherlands	Retrospective cohort	LA-HNSCC	137 (68 vs 32)	(low FFMI) 59.6 $\pm$ 8.2 vs 59.2 $\pm$ 7.3	Cis100, cetuximab CRT; adjuvant included	32 (23)	CTCAE 4.0	Not mentioned, however mention treatment changes in muscle-wasted patients
Xing et al. 2021 [44]	China	Retrospective cohort	LA-HNSCC	96 (75 vs 25)	46.5 [23–70]	Neoadjuvant chemotherapy with docetaxel and cisplatin; some with gemcitabine and cisplatin	Only neoadjuvant chemotherapy patients included	CTCAE v4.03	Mention cumulative dose given and number of cycles, no specific definition
Zwart et al. 2022 [50]	Netherlands	Combined cohort*	HNSCC	196 (65 vs 35)	64.2 $\pm$ 11.2	CRT, multiple modalities; RTo; adjuvant included but after surgery only surgical complications are mentioned instead of toxicities	61 (45)	CTCAE v4.0	Not specified

\*Prospective biobank but muscle mass retrospectively assessed.

HNC=head and neck cancer, HNSCC=head and neck squamous cell carcinoma, LA-HNC=locally advanced head and neck cancer, LA-HNSCC=locally advanced head and neck squamous cell carcinoma, OSCC=oral squamous cell carcinoma.

CRT = chemoradiotherapy, ICT=induction chemotherapy, CT=chemotherapy RTo = radiotherapy only, RTOG=Radiation Therapy Oncology Group, CTCAE=Common Terminology Criteria Adverse Events.

Cis100 = cisplatin chemoradiotherapy dosed triweekly in 100 mg/m<sup>2</sup>, Cis40 = cisplatin chemoradiotherapy dosed weekly in 40 mg/m<sup>2</sup>, Cis80-100 = cisplatin chemoradiotherapy dosed triweekly in 80–100 mg/m<sup>2</sup>, Cis30-35 = cisplatin chemoradiotherapy dosed weekly in 30–35 mg/m<sup>2</sup>, 5FU=5-fluorouracil, oTU = oral tegafur-uracil, TPF=docetaxel, cisplatin and 5-fluorouracil.

**Table 2**  
Study and patient characteristics, part 2.

Author and date	Age in years low versus no low SMM; Mean $\pm$ SD or median [range], or otherwise specified	Tumor location (if reported with number of patients with low SMM versus normal SMM (percentages))	Tumor stage (if reported with number of patients with low SMM versus normal SMM (percentages))
Bentahila et al. 2022 [37]	62.28 $\pm$ 8.83 vs 59.71 $\pm$ 9.53	Oropharynx 23 (43) vs 77 (49) Hypopharynx: 6 (11) vs 11 (7) Larynx: 17 (31) vs 46 (29) Oral cavity: 2 (4) vs 3 (2) Nasopharynx: 6 (11) vs 21 (13)	II: 4 (7) vs 7 (4) III: 11 (21) vs 40 (26) IV: 38 (72) vs 109 (70)
Bril et al. 2021 [16]	59.9 $\pm$ 6.3 vs 59.8 $\pm$ 7.3	Oropharynx HPV+: 16 (20) vs 25 (36) Oropharynx HPV-: 31 (40) vs 20 (29) Hypopharynx: 30 (40) vs 20 (29) Larynx 7 (10) vs 4 (6) Oropharynx: 78 (40) vs 51 (36) Hypopharynx: 26 (10) vs 22 (15) Larynx: 10 (10) vs 8 (6) Oral cavity: 58 (30) vs 29 (20) Nasopharynx: 18 (10) vs 27 (20) Paranasal sinus: 6 (3) vs 5 (3)	II: 2 (2) vs 2 (3) III: 30 (36) vs 36 (52) IV: 52 (62) vs 31 (45)
Chargi et al. 2022 [42]	59.4 vs 55.5	Oropharynx: 78 (40) vs 51 (36) Hypopharynx: 26 (10) vs 22 (15) Larynx: 10 (10) vs 8 (6) Oral cavity: 58 (30) vs 29 (20) Nasopharynx: 18 (10) vs 27 (20) Paranasal sinus: 6 (3) vs 5 (3)	III: 33 vs 26 IV: 166 vs 118
Cho et al. 2018 [47]	64 [18–94] vs 56 [18–86]	Oropharynx: 25 (20) vs 33 (29) Hypopharynx: 28 (30) vs 22 (19) Larynx: 15 (10) vs 17 (15) Oral cavity: 5 (5) vs 2 (1) Nasopharynx: 33 (30) vs 41 (36)	III: 37 (35) vs 33 (29) IVa/b: 69 (65) vs 82 (71)
Ganju et al. 2019 [41]	<65y: n = 19 (24 %), >65y: n = 60 (76 %) vs <65y: n = 84 (50.3 %), >65y: n = 83 (47.7 %)	Oropharynx: 63 (61) vs 91 (64) Larynx: 29 (28) vs 30 (21) Other: 11 (11) vs 22 (15)	III: 30 (29) vs 27 (19) IV: 73 (71) vs 116 (81)
Haehl et al. 2022 [33]	Not specified, only persons > 65 years	Not reported	Not reported
Hua et al. 2020 [40]	45.84 $\pm$ 10.78 vs 45.70 $\pm$ 10.23	Nasopharynx: 170 vs 692 In propensity score matching cohort 154 vs 154	II: 21 (12) vs 100 (14) III: 102 (60) vs 471 (68) IV: 47(28) vs 121 (18)
Huang et al. 2019 [38]	Placebo group: 52.6 $\pm$ 10.3 Glutamine group 52.2 $\pm$ 9.5	Nasopharynx: 16 (25) Oropharynx: 7 (11) Hypopharynx: 3 (5) Larynx: 1 (2) Oral cavity: 42 (66)	I: 6 (9) II: 8 (13) III: 14 (22) IV: 36 (56)
Huang et al. 2021 [52]	45.7 $\pm$ 10.7	Nasopharynx: 37 vs 45	II: 25 (30) III: 45 (55) IVa: 12 (15)
Huang et al. 2021-B [53]	54 $\pm$ 9.5 vs 54 $\pm$ 10.4	Buccal: 37 (33) vs 21 (33) Lower gum: 17 (15) vs 10 (16)	I: 9 (8) vs 7 (11) II: 23 (21) vs 15 (24)

**Table 2 (continued)**

Author and date	Age in years low versus no low SMM; Mean $\pm$ SD or median [range], or otherwise specified	Tumor location (if reported with number of patients with low SMM versus normal SMM (percentages))	Tumor stage (if reported with number of patients with low SMM versus normal SMM (percentages))
Jin et al. 2022 [34]	59 vs 58	Tongue: 33 (29) vs 26 (41) Other sites: 25 (23) vs 6 (10) Oropharynx: 4 (19) vs 18 (58) Hypopharynx/larynx: 8 (38) vs 11 (36) Oral cavity: 8 (38)/ 2 (6) Salivary gland: 1 (5) vs 0 (0)	III: 5 (5) vs 5 (8) IV: 75 (67) vs 36 (57) I: 1 (5) vs 4 (13) II: 2 (10) vs 8 (26) III: 6 (29) vs 9 (29) IV: 12 (57) vs 10 (32)
Karavolia et al. 2022 [48]	67 $\pm$ 10 vs 63 $\pm$ 10	Larynx: 73 (30) vs 363 (50) Other locations: 171 (70) vs 370 (50) Oropharynx: 26 (29) Hypopharynx: 27 (29) Larynx: 31 (34) Oral cavity: 7 (8) Unknown primary: 1 (1)	I-II: 56 (23) vs 242 (33) III-IV: 188 (77) vs 491 (67) II: 2 (2) III: 27 (29) IVa: 44 (48) IVb: 19 (21)
Lere-Chevaleyre et al. 2022 [45]	57.2 $\pm$ 7.5	Oral cavity: 7 (8) Unknown primary: 1 (1) Oropharynx: 176 (65) Larynx/hypopharynx: 61 (22) Other: 35 (13)	III: 61 (22) IVa: 195 (72) IVb: 16 (6) III: 60 (20)
Morse et al. 2022 [35]	Not specified, 221 persons < 70 yrs, 51 =>>70 years	Oropharynx: 198 (66) Hypopharynx: 50 (17) Supraglottic larynx: 52 (17) Pharynx: 144 (68) Larynx: 22 (10) Oral cavity: 31 (15) Other: 16 (8) Oropharynx: 79 (33) Hypopharynx: 39 (16) Larynx: 39 (16) Oral cavity: 69 (28) Unknown primary: 17 (7)	IV: 240 (80) I: 2 (1) II: 6 (3) III: 27 (13) IV: 171 (80) X: 7 (3) I: 19 (8) II: 50 (21) III: 57 (24) IV: 117 (48)
Nagpal et al. 2021 [17]	Mean: 60.4	Oropharynx: 198 (66) Hypopharynx: 50 (17) Supraglottic larynx: 52 (17) Pharynx: 144 (68) Larynx: 22 (10) Oral cavity: 31 (15) Other: 16 (8) Oropharynx: 79 (33) Hypopharynx: 39 (16) Larynx: 39 (16) Oral cavity: 69 (28) Unknown primary: 17 (7)	IV: 240 (80) I: 2 (1) II: 6 (3) III: 27 (13) IV: 171 (80) X: 7 (3) I: 19 (8) II: 50 (21) III: 57 (24) IV: 117 (48)
Sealy et al. 2020 [43]	57.9 $\pm$ 10.3	Oropharynx: 80 (40) vs 189 (34) Hypopharynx: 33 (20) vs 38 (7) Larynx: 58 (30) vs 273 (49) Oral cavity: 16 (8) vs 27 (5) Nasopharynx: 2 (1) vs 28 (5) Oropharynx: 56 (50) Hypopharynx: 14 (13) Larynx: 8 (7) Nasopharynx: 27 (24) Other: 7 (6) Oropharynx: 14 (30) vs 39 (41) Hypopharynx: 7(19) vs 12 (13) Larynx: 11 (30) vs 20 (21)	I: 13 (7) vs 71 (13) II: 32 (17) vs 114 (21) III: 22 (12) vs 110 (20) IV: 122 (65) vs 260 (47) III: 8 (13) vs 9 (18) IV: 53 (87) vs 42 (82)
Thureau et al. 2021 [51]	61 $\pm$ 9.04	Oropharynx: 14 (30) vs 39 (41) Hypopharynx: 7(19) vs 12 (13) Larynx: 11 (30) vs 20 (21)	II-III: 7 (19) vs 17 (17) IV: 32 (81) vs 80 (83)
van Rijn-Dekker et al. 2020 [49]	66 $\pm$ 10 vs 62 $\pm$ 10	Oropharynx: 56 (50) Hypopharynx: 14 (13) Larynx: 8 (7) Nasopharynx: 27 (24) Other: 7 (6) Oropharynx: 14 (30) vs 39 (41) Hypopharynx: 7(19) vs 12 (13) Larynx: 11 (30) vs 20 (21)	I: 13 (7) vs 71 (13) II: 32 (17) vs 114 (21) III: 22 (12) vs 110 (20) IV: 122 (65) vs 260 (47) III: 8 (13) vs 9 (18) IV: 53 (87) vs 42 (82)
Wendrich et al. 2017 [15]	54.5 $\pm$ 9.4	Oropharynx: 14 (30) vs 39 (41) Hypopharynx: 7(19) vs 12 (13) Larynx: 11 (30) vs 20 (21)	II-III: 7 (19) vs 17 (17) IV: 32 (81) vs 80 (83)
Willemsen et al. 2020 [39]	(low FFMI) 59.6 $\pm$ 8.2 vs 59.2 $\pm$ 7.3	Oropharynx: 14 (30) vs 39 (41) Hypopharynx: 7(19) vs 12 (13) Larynx: 11 (30) vs 20 (21)	II-III: 7 (19) vs 17 (17) IV: 32 (81) vs 80 (83)

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Table 2 (continued)

Author and date	Age in years low versus no low SMM; Mean $\pm$ SD or median [range], or otherwise specified	Tumor location (if reported with number of patients with low SMM versus normal SMM (percentages))	Tumor stage (if reported with number of patients with low SMM versus normal SMM (percentages))
		Oral cavity: 5 (14) vs 17 (16) Nasopharynx: 2 (5) vs 5 (5) Unknown primary: 1 (3) vs 2 (2) Other: 0 (0) vs 2 (2)	
Xing et al. 2021 [44]	46.5 [23–70]	Nasopharynx	II: 1 (1) III: 40 (42) IV: 55 (57)
Zwart et al. 2022 [50]	64.2 $\pm$ 11.2	Oropharynx: 69 (35) Hypopharynx: 10 (5) Larynx 56 (28) Oral cavity: 60 (31) Nasopharynx: 1 (1)	I: 23 (12) II: 24 (12) III: 37 (18) IV: 112 (57)

FFMI=fat free mass index, SMM=skeletal muscle mass.

Most studies used CTCAE to grade toxicity and created another definition to explain DLT, which varied from very specific cut-off values such as a cumulative dose of less than 200 mg/m<sup>2</sup> to toxicity leading to dose reduction, long delay or treatment discontinuation, to more generalized definitions such any treatment delay [16,33,37].

Assessment of skeletal muscle mass

The methods to assess SMM are presented in Table 3. Most studies measured the CSMA at the level of the third cervical vertebra using CT or sometimes MRI scans. One study used the mid-upper-arm muscle circumference and one calculated the fat free mass index using bioelectrical impedance analysis [38,39]. Others delineated CSMA using CT or MRI scans, at thoracic or lumbar levels.

Cut-off values for low SMM in studies using CT or MRI scans to delineate a cross-sectional skeletal muscle area varied. Most chose to report cut-off values with LSMI as base quantity with cm<sup>2</sup>/m<sup>2</sup> as unit and used formulas to translate a cervical skeletal muscle index to LSMI, only three studies reported cervical skeletal muscle index cut-off values [16,34,40]. Several studies created cut-off values per sex and BMI: LSMI cut-off values for males with BMI<25 kg/m<sup>2</sup> was 43 cm<sup>2</sup>/m<sup>2</sup> and for males with a BMI>25 kg/m<sup>2</sup> was 53 cm<sup>2</sup>/m<sup>2</sup>. For females, cut-off values in these studies was 41 cm<sup>2</sup>/m<sup>2</sup> regardless of their BMI [35,41] LSMI cut-off values for males in other studies ranged between 40.8 cm<sup>2</sup>/m<sup>2</sup> and 52.4 cm<sup>2</sup>/m<sup>2</sup>. For females LSMI cut-off values ranged between 29 cm<sup>2</sup>/m<sup>2</sup> and 38.5 cm<sup>2</sup>/m<sup>2</sup>. Studies that did not distinguish between sex or BMI for cut-off values, reported a LSMI cut-off of 43.2 cm<sup>2</sup>/m<sup>2</sup> for low SMM [15,42]. Some studies reported cut-off values, but also used continuous data for LSMI in regression analyses on DLT [15,43–45]. The prevalence of low SMM ranged from 25.5 % until 75.9 %.

Assessment of study quality

The methodologic quality of the studies according to the Newcastle-Ottawa scale is reported in Supplement 3 and the median score was seven, with a range between five and nine points. Many studies did not report follow-up data and drop-outs, did not report multivariate regression analyses to account for influencing variables on DLT other than low SMM and few did not demonstrate that the population did not have toxicities beforehand, which led to a lower grade in the Newcastle-Ottawa scale. We considered the quality of all studies sufficient for our review. For the Newcastle-Ottawa scale, the agreement between researchers was 98.9 %, with a Cohens kappa of 0.97 which indicates

Table 3

Assessment of skeletal muscle mass.

Author and date	Skeletal muscle mass assessment	Cut-off low SMM (standard as LSMI in cm <sup>2</sup> /m <sup>2</sup> )	Prevalence of low SMM (in %)
Bentahila et al. 2022 [37]	L3 PET/CT	M:43.3, F:33.09	25.5
Bril et al. 2021 [16]	C3 CT	CSMI M:13.1 cm <sup>2</sup> and W:10.7 cm <sup>2</sup>	54.9
Chargi et al. 2022 [42]	C3 CT or MRI	$\leq$ 43.2	58.01
Cho et al. 2018 [47]	L3 CT	M: 49, F: 31	48
Ganju et al. 2019 [41]	C3 CT	BMI<25 M:43, BMI>25 M:53, F:41	58.1
Haehl et al. 2022 [33]	C3 CT	M:45.5, F:34.3, LSMA: M:144.3, F:92.2	51.4
Hua et al. 2020 [40]	C3 CT	CSMI 18.82 cm <sup>2</sup> /m <sup>2</sup>	19.7
Huang et al. 2019 [38]	MAMC	Not specified	Not specified
Huang et al. 2021 [52]	L3 CT	M: 40.8, F 34.9	45.1
Huang et al. 2021-B [53]	C3 CT	M<46.7, F<30.3	64
Jin et al. 2022 [34]	C3	Muscle index: 9.3 mm <sup>2</sup> /m <sup>2</sup>	39.2
Karavolia et al. 2022 [48]	C3 CT	M:42.0, F:31.2	25
Lere-Chevaleyre et al. 2022 [45]	L1 CT	M: 46, F: 29	75.9
Morse et al. 2022 [35]	C3 CT	M+BMI<25: 43, M+BMI=>25:53; F<41	58
Nagpal et al. 2021 [17]	C3 CT	M:40.8, F:34.9, 32 for analysis predict outcomes	91
Sealy et al. 2020 [43]	T4 or L3 (PET)-CT	None, outcome based on standard deviation	Not applicable
Thureau et al. 2021 [51]	L3 CT	M:52.4, F:38.5	36.7
van Rijn-Dekker et al. 2020 [49]	C3 CT	M:42.4, F:30.6	25.4
Wendrich et al. 2017 [15]	C3 CT	$\leq$ 43.2	54.5
Willemsen et al. 2020 [39]	FFMI	<P10 (below 10th percentile)	29
Xing et al. 2021 [44]	L3 CT	M:52.4, F:38.5	34.4
Zwart et al. 2022 [50]	C3 CT or MRI	Specifically for toxicities: M:46.49, F:37.90	34.7 (for all-cause toxicity)

LSMI=lumbar skeletal muscle index, LSMA=lumbar skeletal muscle area, CSMI=cervical skeletal muscle index, MAMC=mid-upper-arm muscle circumference, FFMI=fat free mass index, BMI=body mass index C3 = third cervical vertebra, L1 = first lumbar vertebra, L3 = third lumbar vertebra, T4 = fourth thoracic vertebra, CT=computed tomography scan, PET=positron emission tomography, MRI=magnetic resonance imaging scan, M=male, F=female.

almost perfect agreement [46].

The effect of low SMM on toxicities and DLT

In Table 4 and Table 5 the results of the studies are presented. The cumulative incidence of toxicities during therapy, according to the definition operated by the specific study, ranged from 29 % to 88 % for patients with low SMM and from 19 % to 88 % for patients without low SMM. One study reported grade 4 toxicities only, defined by the CTCAE, and showed an incidence of 10 % for patients with low SMM versus an incidence of 3 % for patients without low SMM (p = 0.011) [16]. Bentahila et al. provided several toxicity rates (grade 3 or higher) for patients with low and without low SMM and compared these results. No

**Table 4**

The effect of low skeletal muscle mass on toxicities.

Author and date	Description	Toxicity prevalence*	Mucositis*	Dermatitis*	Dysphagia*	Xerostomia*	Renal failure*
Bentahila et al. 2022 [37]	Reported toxicities from grade 3 or higher	—	7 (12.96) vs 34 (21.52) p = 0.169	12 (22.22) vs 34 (21.52) p = 0.914	Dysgeusia: 7 (12.96) vs 21 (13.29) p = 0.951	0.0 (0) vs 4 (2.53) p = 0.574	2 (3.7) vs 1 (0.63) p = 0.16
Bril et al. 2021 [16]	—	—	—	—	—	—	—
Chargi et al. 2022 [42]	Reported toxicities leading to DLT	154 (44.9)	—	—	—	—	12 (6.0) vs 29 (20.1); p = 0.09
Cho et al. 2018 [47]	Reported toxicities from grade 3 or higher	31 (29.2) vs 40 (34.8); p = 0.378	16 (15.1) vs 31 (27.0); p = 0.031	7 (6.6) vs 6 (5.2); p = 0.778	2 (1.9) vs 1 (0.9); p = 0.863	—	—
Ganju et al. 2019 [41]	—	91 (37)	most common for prolonged treatment break	—	—	—	—
Haehl et al. 2022 [33]	Different results for muscle area, in this table only LSMI	Grade 3: 100(69.4) vs 90 (66.2), Grade 4: 14(9.7) vs 4(3.0); p = 0.011	—	—	—	—	—
Hua et al. 2020 [40]	All patients completed treatment so no DLT. Scores are given for the propensity score matching cohort, toxicities from grade 3–4	52 (33.8) vs 41 (26.6); p = 0.038	50 (33.1) vs 33 (21.3); p = 0.038	6 (3.9) vs 2 (1.3); p = 0.017	—	3 (1.9) vs 0 (0.0); p = 0.166	0 (0) vs 0 (0); p = 0.934
Huang et al. 2019 [38]	Compared patients receiving glutamine vs placebo. Only OR for mucositis given.	—	1.01 (0.82–1.24); p = 0.961	—	—	—	—
Huang et al. 2021 [52]	Reported toxicities from grade 3 or higher. Analysis on sarcopenia as dichotomous variable	21 (56.8) vs 19 (40); OR 1.42, 95 % CI=0.90–2.24; p = 0.183	OR 0.77 (0.25–2.42); p = 0.66	—	—	—	—
Huang et al. 2021-B [53]	Only reported anemia, neutropenia and infection as toxicities	—	—	—	—	—	—
Jin et al. 2022 [34]	Reported toxicities from grade 3 or higher.	10 (47.6) vs 6 (19.4), Hazard ratio 5.71, p = 0.008	—	—	—	—	—
Karavolia et al. 2022 [48]	Also reports patient-rated scores, but not presented in this table.	—	—	—	Grade 3 (12) vs (6); p = 0.003	46 (19) vs 117 (16); p = 0.32	—
Lere-Chevalere et al. 2022 [45]	Reported toxicities from grade 3 or higher.	57 (62), 76.5 % vs 46.7 %; p = 0.008	LSMI was significantly lower: 30.7 +- 6.9 vs 37.2 +- 7.7 cm2/m2; p = 0.002	—	—	—	0 (0)
Morse et al. 2022 [35]	Mainly looked at differences between age groups instead of SMM	—	Most common reason for breaks (36.3 %)	—	—	—	—
Nagpal et al. 2021 [17]	Did not include 28 patients who did not complete CT.	Sarcopenic patients were more likely to have toxicity	Grade 3: 57 % vs 36 % and grade 4: 9 % vs 5 %	—	Grade 3: 40 % vs 27 %	Grade 2 (late): more in patients with low SMM	—
Sealy et al. 2020 [43]	SMM as continuous variable in univariate and multivariate analysis	—	—	—	—	—	—
Thureau et al. 2021 [51]	Specific toxicities in this table consist of grade 3 or higher	Two or one toxicities in patients, RT: 42 (87.5) vs 59 (88.1); p = 0.93. CRT: 35 (87.5) vs 70 (83.3); p = 0.55	RT: 9 (18.8) vs 11 (16.4); p = 0.89. CRT: 10 (25.0) vs 17 (20.2); p = 0.78	RT: 4 (8.3) vs 6 (9.1); p = 0.69. CRT: 4 (10.0) vs 8 (9.5); p = 0.66	RT: 31 (47.7) vs 11 (16.9); p = 0.3. CRT: 15 (37.5) vs 30 (35.7); p = 0.84	—	—
van Rijn-Dekker et al. 2020 [49]	—	—	Only physician rated toxicities are reported here. Late symptoms 6 mpmths after treatment are not reported in this table.	—	Grade 2 or more: 33.9 % vs 20 %; p = 0.001	Grade 1: 30 (15.9) vs 71 (12.8); p 0.437	—
Wendrich et al. 2017 [15]	SMM as continuous variable in univariate and multivariate analysis	—	—	—	—	—	—
Willemsen et al. 2020 [39]	Reported toxicities from grade 2 or higher. FFMI used for body measurements, <10th percentile versus normal	19 (48) vs 18 (19); p = 0.001	—	—	—	—	22 % vs 4 %; p = 0.015

(continued on next page)

Table 4 (continued)

Author and date	Description	Toxicity prevalence*	Mucositis*	Dermatitis*	Dysphagia*	Xerostomia*	Renal failure*
Xing et al. 2021 [44]	Reported toxicities from grade 3 or higher.	57.6 % vs 52.4 %; $p = 0.628$ but with different cut-off lower SMM showed more toxicities: 64.4 % vs 37.8 %; $p = 0.019$ .	—	—	—	—	—
Zwart et al. 2022 [50]	Reported toxicities from grade 3 or higher.	33 (24.4)	2.3 %		Total: 29 (21.5). Univariate log regression: 2.70 (1.12–6.47), 0.026. Multivariate log regression: 2.50 (1.02–6.14), 0.046	3.0 %	

\*Outcomes are reported as number of patients with low SMM versus normal SMM (percentages) if available, and if tested with a p-value or as total amount.

CRT = chemoradiotherapy, RT=radiotherapy, LSMI=lumbar skeletal muscle index; SMM=skeletal muscle mass; FFMI=fat-free mass index, DLT=dose limiting toxicity, CDLT=chemotherapy dose limiting toxicity, OR=odds ratio; 95 % CI=95 % confidence interval.

significant difference in specific toxicity rates was found, e.g., mucositis, dysphagia, dermatitis, xerostomia and renal failure. However, toxicity related interruptions differed significantly between SMM groups, with a lower incidence in patients with low SMM (62 % vs 74 %,  $p = 0.019$ ) [37]. Other studies showed significant increased incidence of mucositis in patients with low SMM [40,45,47]. Hua et al. showed that dermatitis was seen more often in low SMM patients [40]. The incidence of dysphagia toxicity was significantly higher in patients with low SMM in the studies of Karavolia et al. and van Rijn-Dekker et al., and SMM was found to be predictive for dysphagia by Zwart et al. [48–50]. No difference in acute xerostomia incidence was reported. Renal failure seemed more apparent in patients with low SMM in one study, however in another study this was vice-versa [39,42].

DLT, specifically for RT, ranged between 19 % vs 61 % versus 14 % to 74 % for patients with and without low SMM. DLT, attributed to chemotherapy ranged between 36 % vs 100 % versus 10 % to 96 % for patients with and without low SMM. Thureau et al. reported an incidence for RT DLT of 3 % and for CRT of 46 %. The amount of patients who completed treatment was reported for both CRT and RT only groups and within these groups differences in completion of treatment between patients with low SMM versus without low SMM were compared. In the CRT group with low SMM 57.5 % completed treatment in comparison to 52.9 % in the CRT group without low SMM ( $p = 0.63$ ). In the RT group with low SMM 97.9 % completed treatment compared to 97.0 % in the RT only group without low SMM ( $p = 1$ ) [51].

The association between low SMM and CRT specific DLT was reported in nine studies [15,16,35,41–45,52]. In univariate analyses these studies reported an odds ratio of 1.86 to 3.75 for patients with low SMM compared to patients without low SMM, when used as binary variables. Some studies used continuous variables for SMM (e.g. higher values mean more muscle mass) to assess associations with DLT, consequently these odds ratios are different and ranged from 0.92 to 0.96, indicating less DLT for higher SMM [15,43,45]. Not all studies reported multivariate analyses, but if reported, low SMM remained significantly associated with DLT [15,16,35,41–43,45,52].

#### Meta-analysis

Of the 22 studies in this review, seventeen were excluded from the meta-analysis on DLT during CRT. Of these, eight were excluded because these did not report the amount of DLT per SMM category but reported on toxicities in general [34,40,44,45,48–50,53], one study was excluded because it only reported RT interruptions [47], one study was excluded because it reported on the effect of age (and not SMM) on DLT [35], one study was excluded because it excluded patients who did not finish CRT independent of DLT [17], one study was excluded because data amongst number of patients having DLT per category was not subtractable from

the article [43], one study was excluded because it measured SMM as fat-free mass index [39], one study was excluded because the patient cohort was similar to a more recent study (which was included) [15], and one study was excluded because it looked at the effect of glutamine on DLT [38].

In Figure 1A the forest plot for the odds ratio (OR) of seven studies, consisting of 1441 patients, examining the odds of DLT in patients with low SMM compared to the odds in patients without low SMM, is presented. Heterogeneity across these studies was moderate ( $I^2 = 68$  %). Patients with low SMM had higher OR of developing DLT than patients with no low SMM, but this was only borderline statistically significant (OR 1.60; 95 % CI 1.00–2.58;  $p = 0.0512$ ).

In the meta-analysis on RT interruptions, 17 studies were excluded because these did not report on radiotherapy interruptions specifically [15–17,34,35,40,42–45,48–50,52,54], one study looked at the effect of glutamine [38] and one measured SMM as fat-free mass index [39].

In Figure 1B the forest plot for the OR of five studies, consisting of 1074 patients, examining the odds of RT interruptions in patients with low SMM compared to the odds in patients without low SMM, is presented. Heterogeneity across these studies was moderate ( $I^2 = 50$  %). RT interruptions differed borderline statistically significantly (OR 1.89; 95 % CI 1.00–3.57;  $p = 0.0510$ ) between patients with low SMM compared to patients without low SMM.

#### Discussion

In this review, 22 studies were analyzed. Almost all studies found at least one significant association between low SMM and CRT or RT toxicities. Meta-analyses of the OR of DLT and RT interruptions indicated higher risk of CRT and RT toxicities for patients with low SMM than for patients without low SMM, but the differences were borderline statistically significant.

To our knowledge this is the first review to assess the effect of low SMM on CRT and RT toxicities in patients with HNC. A recent systematic review has demonstrated the negative effect of low SMM on survival in HNC patients, but it did not describe its effects on toxicities [55].

Across all included studies, low SMM appeared to be significantly related to DLT. Unfortunately, it is not possible to attribute these toxicities directly to the chemotherapy or RT, since most studies do not distinguish between toxicity caused by chemotherapy or RT. This can also be justified, as it is commonly unclear whether the toxicity is triggered by chemotherapy, the radio-sensitizing effect of chemotherapy or RT itself. Moreover, the regimens applied in the studies are heterogeneous, varying from RT only to concomitant CRT and even induction chemotherapy regimens. Cisplatin is a routinely used radiosensitizer in the treatment of advanced HNSCC and improves locoregional control and overall survival when administered as a triweekly high dose

**Table 5**

The effect of low skeletal muscle mass on dose limiting toxicity.

Author and date	DLT prevalence*, **	OR CDLT Univariate analysis (95 % CI); p-value	OR CDLT Multivariate analysis (95 % CI); p-value
Bentahila et al. 2022 [37]	CRT: 25 (100) vs 65 (95.59) p = 0.561, RT: 8 (61.4) vs 26 (74.29) p = 0.019	—	—
Bril et al. 2021 [16]	CRT: 30 (35.7) vs 7 (10.1); p < 0.01	3.75 (1.58–8.90); p < 0.01	3.99 (1.56–10.23); p = 0.01
Chargi et al. 2022 [42]	CRT: 102 (51.3) vs 52 (36.1); p < 0.01	1.86 (1.20–2.89); p = 0.006	1.75 (1.06–2.90); p = 0.03
Cho et al. 2018 [47]	RT interruption => 5 days: 20 (18.9) vs 9 (7.8); p = 0.015, no completion of RT: 4 (3.8) vs 6 (5.2); p = 0.75	—	—
Ganju et al. 2019 [41]	64 (45) vs 27 (26); p = 0.01	reported only for toxicity but not CDLT	—
Haehl et al. 2022 [33]	RT completed: 116 (80.6) vs 121 (89); p = 0.093 CRT completed: 83 (57.6) vs 85 (62.5); p = 0.464	—	—
Hua et al. 2020 [40]	—	—	—
Huang et al. 2019 [38]	—	—	—
Huang et al. 2021 [52]	—	2.36 (0.92–6.03); p = 0.07	Males only: 4.0 (1.20–13.36); p = 0.024
Huang et al. 2021-B [53]	—	—	—
Jin et al. 2022 [34]	Prolonged treatment delays were not associated with sarcopenic patients, p = 0.625	—	—
Karavolia et al. 2022 [48]	—	—	—
Lere-Chevaleyre et al. 2022 [45]	7 due to toxicity, 6 following treatment related death, 4 due to tumor progression	—	LSMI as continuous variable: 0.92 (0.85–0.99); p = 0.043
Morse et al. 2022 [35]	Total 99 (36.5)	—	CRT: 2.14 (1.25–3.66); p < 0.01. RT prolonged break: 2.70 (1.03–7.11); p = 0.044
Nagpal et al. 2021 [17]	20 % had a treatment break > 1 week. Treatment gaps were 2.5 (median), and did not differ between low and now low SMM.	—	—
Sealy et al. 2020 [43]	61 (28.6) patients had early termination	0.96 (0.94–0.99); p = 0.007	0.95 (0.92–0.98); p = 0.001
Thureau et al. 2021 [51]	RT: 3 (3), CRT: 58 (46)	—	—
van Rijn-Dekker et al. 2020 [49]	—	—	—

**Table 5 (continued)**

Author and date	DLT prevalence*, **	OR CDLT Univariate analysis (95 % CI); p-value	OR CDLT Multivariate analysis (95 % CI); p-value
Wendrich et al. 2017 [15]	27 (44.3) vs 7 (13.7); p < 0.001	0.93 (0.88–0.98); p = 0.005	0.93 (0.88–0.98); p = 0.005
Willemsen et al. 2020 [39]	Scheme changes: 45 % vs 25 %; p = 0.019, CDLT: 57 % vs 25 %; p = 0.004	—	—
Xing et al. 2021 [44]	—	0.947 (0.903–0.993); p = 0.025	—
Zwart et al. 2022 [50]	Multivariate regression: OR 3.33, 95 % CI 1.41–7.82; p = 0.006	—	—

\*Outcomes are reported as number of patients with low SMM versus normal SMM (percentages), and if tested with a p-value.

\*\*If provided by the study, radiotherapy and chemo(radio)therapy related dose limiting toxicities will be reported separately.

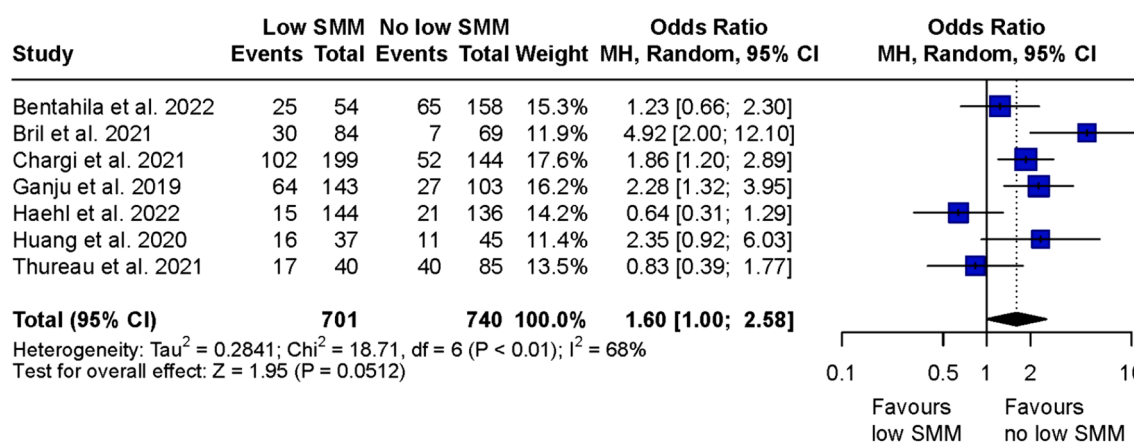
CRT = chemoradiotherapy, RT=radiotherapy, LSMI=lumbar skeletal muscle index; SMM=skeletal muscle mass; FFMI=fat-free mass index, DLT=dose limiting toxicity, CDLT=chemotherapy dose limiting toxicity, OR=odds ratio; 95 % CI=95 % confidence interval.

[56–58]. Though efficient, high rates of acute and late toxicities are common, often leading to DLT [59]. Since a cumulative dose of 200 mg/m<sup>2</sup> or more is superior compared to a dose of less than 200 mg/m<sup>2</sup> in terms of oncologic outcome, strategies to prevent DLT are warranted [13,60]. Based on the results from the studies in this review, it seems plausible that cisplatin is more toxic in patients with low SMM, but it is difficult to fully interpret because multiple studies also included patients receiving other types of chemotherapy.

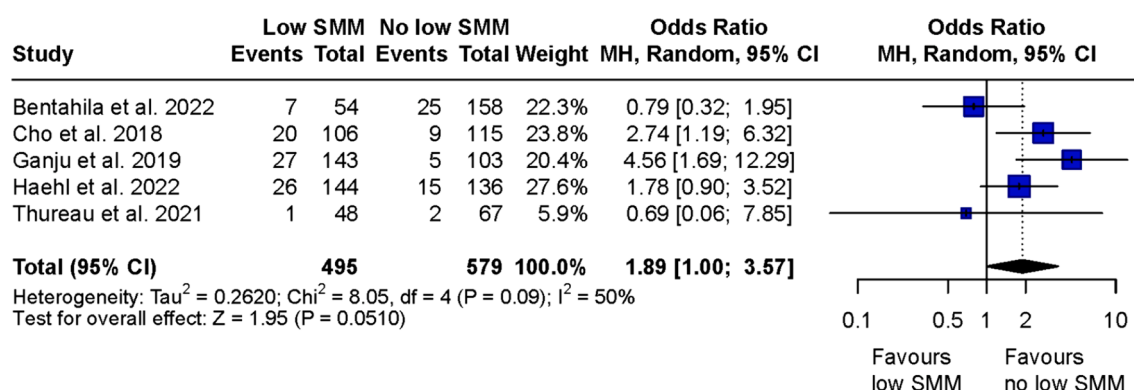
Thureau et al. reported toxicities specifically for RT (n = 116) and CRT (n = 127), and interestingly found no significant differences between toxicity rates for patients with low SMM (n = 88) versus patients without low SMM (n = 152) in either treatment category [51]. On the other hand, Morse et al., reported associations between low SMM and CDLT for both CT and RT interruptions [35]. The incidence of dysphagia was significantly higher in patients with low SMM, which is in line with previous research that showed that sarcopenia is a contributor to the risk of extended dependency on feeding tubes feeding tube dependency after CRT [61].

This study provides a broad overview, a meta-analysis and a quality assessment of studies on DLT in HNC patients with and without low SMM, which to our knowledge is not yet done. A limitation of our study is heterogeneity: cut-off values widely ranged, as did methods to assess SMM and the definitions of DLT and toxicities. Ganju et al. and Morse et al. used sex and BMI to classify cut-off values whilst Wendrich et al., Willemsen et al., Sealy et al., Huang 2019 et al., Hua et al., Chargi et al., did not make categories [15,35,38–43]. Recently Chargi et al., proposed other cut-off values with categories [26]. The formula to calculate LSMI already includes sex, weight and height [18]. Hence, it might be possible that creating additional categories for cut-off values taking these variables into account might increase the effect of SMM on DLT.

Moreover the methods used to assess SMM were diverse, from SMM assessment at cervical, thoracic and lumbar vertebrae to methods using the mid-arm muscle circumference [38]. Since the formula of Swartz is validated, it can be assumed that it does not matter at which level the measurement was done and if CT or MRI was used [18,20,22,62]. Some studies used LSMI as measurement unit to define low SMM, others used cervical skeletal muscle index, percentiles of fat-free mass index or did not specify cut-offs values at all. Definitions of outcomes also ranged between the studies. The definitions low SMM and sarcopenia are used intertwiningly, while the European Working Group on Sarcopenia in



**Figure 1A.** Forest plot for odds ratios between low skeletal muscle mass (SMM) and dose limiting toxicity in head and neck cancer patients treated with chemoradiotherapy.



**Figure 1B.** Forest plot for odds ratios between low skeletal muscle mass (SMM) and radiotherapy interruptions in head and neck cancer patients.

Older People (EWGSOP) defines sarcopenia as having low SMM, low muscle quality and decreased muscle function [25]. DLT definitions were mostly based on the incompleteness of CRT but one study excluded patients who did not finish chemotherapy [17]. By excluding studies based on non-English language we might have caused bias. However, in total five studies with a different language were found in the initial search but all were also excluded based on other exclusion criteria than language.

The utility of SMM measurement can be promising and guide the physician and patient in their shared decision-making regarding treatment options in each individual patient. Currently, patients older than 70 years are excluded from cisplatin-based CRT, as are patients with absolute contra-indications such as renal failure [7]. SMM might serve as an additional patient characteristic to either advise cisplatin-based CRT or withdraw from the use of cisplatin. Moreover, newer cisplatin regimens such as a weekly schedule, with cisplatin dosed as 40 mg/m<sup>2</sup> per BSA might be equally effective in treating patients with HNC while causing less toxicities, especially in those with low SMM [63]. Hopefully, a currently running trial (CISLOW study, NL76533.041.21) will be able to draw a more definite conclusion towards the utility of SMM measurements as parameter for the preferred cisplatin schedule. Several studies have been performed showing excellent results when using automated deep learning systems to assess SMM [64–66]. When these systems are incorporated into clinical decision making, treating physicians can give their patients better insight into the expected treatment outcomes, prognosis and adapt treatment, such as a different cisplatin regimen, according to the patients characteristics.

## Conclusions

SMM seems to be associated with toxicities, DLT and RT interruptions in HNC patients undergoing CRT or RT. However, studies towards DLT and low SMM vary widely in methods. It is necessary to create a golden standard for assessing SMM and recommendations regarding cut-off values in specific patient groups, so SMM can be used as a precise biomarker for adverse events and counselling tool in shared decision making and define strategies to decrease DLT in the overall HNC population. The results of an ongoing randomized clinical trial comparing different cisplatin schemes in head and neck cancer patients with low SMM have to be awaited before eventual implementation of low SMM as decision tool in clinical practice.

## CRediT authorship contribution statement

**A.W.M.A. Schaeffers:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing. **H.A. Scholten:** Writing – review & editing, Investigation, Formal analysis, Data curation. **M.A. van Beers:** Writing – review & editing, Visualization, Investigation. **B.W. Meussen:** Writing – review & editing, Investigation, Conceptualization. **E.J. Smid:** Writing – review & editing, Supervision. **C.H. van Gils:** . **L.A. Devriese:** Writing – review & editing, Visualization, Supervision, Conceptualization. **R. de Bree:** Conceptualization, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Review & Editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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