Reduced-dose radiation in human papillomavirus-associated oropharyngeal carcinoma can improve outcome: a systematic review and meta-analysis

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Background: Despite its effectiveness, the standard course of chemoradiation for the treatment of human papillomavirus (HPV)-related oropharyngeal carcinoma (OPC) results in considerable treatment-related adverse effects. Studies proved that HPV-positive OPC is very sensitive to radiotherapy. Using de-escalation therapy as a new strategy is critical to maintaining positive outcomes while alleviating side effects. However, some studies hold that reduced dose causes insufficient effect on tumor killing. We conducted this systematic review and meta-analysis of survival and adverse reactions in patients with HPV-related OPC by retrospective analysis and evaluated the therapeutic effect of reducing the radiation dose.

Methods: Data were double-selected and extracted by searching seven electronic databases, Original studies in all language treated HPV-associated OPC with reduced-dose and standard-dose therapies were included. Overall survival (OS), progression-free survival (PFS), and incidence rates of adverse events were obtained by pooling analyses. Statistical analyses were performed using RStudio Version 1.1.383 (RStudio, Boston, MA, USA) via the Meta-Analysis R Package (metafor). Heterogeneity was evaluated using the I^2 statistic and the Cochran Q test. We used Stata (version 15.0) for forest graph.

Results: Thirteen studies were included in this meta-analysis, involving a dose range of 66–70 Gy for the standard treatment regimen and <66 Gy for the reduced-dose group. There was no significant difference in the age of the patients in the standard and the reduced treatment groups (60.9±5.9 *vs.* 58.6±2.4 years). Nine studies were included as standard cohort and thirteen studies were enrolled as reduced-dose cohort. The 2- and 3-year overall survival rates in the reduced-dose group (95.66% and 91.51%, respectively) were superior to those in the standard-dose group (88.36% and 87.46%, respectively). There was no significant difference in PFS between the two groups. A systematic review of articles on dose reduction and the standard dose was also conducted. The most common complication in reduced-dose radiation was oral mucositis (36.4%), followed by decreased white blood cell (WBC) count (30.5%) and dry mouth (29.1%).

Conclusions: Reducing the radiation dose in patients with HPV-related OPC substantially alleviates the treatment toxicities and optimizes the quality of life of patients while at the same time maintaining favorable oncologic outcomes.

Keywords: Human papillomavirus (HPV)-related; reduced dose; oropharyngeal cancer; radiotherapy

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most common malignant tumors worldwide, with about 750,000 new cases and 360,000 cancer-related deaths in 2020 (1). About 60% of HNSCC cases are locally advanced at the time of diagnosis, and the current standard of treatment is radical concurrent chemoradiation or surgery followed by radiation therapy (2). HNSCC includes cancers of the oral cavity, larynx, hypopharynx, and oropharynx (3), while oropharyngeal carcinoma (OPC) involves carcinomas of the tonsils, base of the tongue, soft palate, and uvula. Although the incidence of head and neck cancer has steadily declined over the past few decades as smoking rates have decreased, the incidence of OPC is generally ascending, mainly due to the increase in human papillomavirus (HPV) infection (4). According to previous studies, HPV-related OPC reached 71% and 51.8% in the United States and the United Kingdom, respectively (5-8). Of these, 85–96% of cases are caused by HPV-16 infection. The latest version of the American Joint Committee on Cancer (AJCC) staging system classifies OPC into HPV-positive (HPV+) and HPV-negative (HPV–) based on their different molecular profiles, tumor characteristics, and outcomes (9). A series of preclinical and clinical studies (10,11) have shown that HPV-associated OPC has increased sensitivity to chemoradiotherapy and is associated with a more favorable prognosis (12).

Despite its effectiveness, the standard 7-week course of chemoradiotherapy for HPV-related OPC results in considerable treatment-related adverse effects (13), Radiotherapy can cause acute and late complications. Acute complications consist of dermatitis, mucositis, dysphagia, odynophagia, alopecia and so on. Besides, skin changes, xerostomia, dental caries, trismus, lymphedema, and swallowing dysfunction are common in late complications. Reports showed the interaction between the dose of radiotherapy and adverse reactions. Such as, the dose of middle and superior constrictors exceeded 55 Gy lead to long-term swallowing dysfunction, and radiotherapy combined with high-dose cisplatin can cause severe late toxicity (14). Acute and late complications give rise to discontinuation of treatment and decreased the quality of life. After radiation and high-dose cisplatin, patients with HPV-related OPC have significantly longer survival periods than those without (10), but the quality of life of these patients is significantly impaired for decades. De-escalation treatment for HPV-related OPC aims to minimize the post-treatment side effects while simultaneously prolonging survival. Research on de-escalation strategies involves the following: (I) reducing the radiotherapy dose while increasing induction chemotherapy; (II) reducing the radiotherapy dose by increasing transoral robotic surgery; (III) reducing radiotherapy dose and cisplatin; and (IV) replacing cisplatin with cetuximab (15-19).

Several clinical trials (16,18,19) have shown that the radiation dose to gross disease can be safely reduced in HPV-positive OPC patients, typically by 10–16 Gy. However, some scholars hold that reduced-dose in HPV-positive patients would only quickly reduce the tumor volume in a short period of time, but it may cause risks to patients in the long term (20). Few studies conducted systematic reviews and meta-analyses to determine whether lowering the radiation dose affects survival and adverse effects in HPV-related OPC patients. Therefore, in our study, we compared the radiation effect of reduced-dose

Highlight box

Key findings

- Reducing the radiation dose in patients with HPV-related OPC substantially mitigates treatment toxicities and optimizes the quality of life of patients while at the same time maintaining favorable oncologic outcomes.

What is known and what is new?

- It is known that patients with HPV-related OPC have significantly longer survival periods than those without.
- This analysis revealed that de-escalation treatment for HPV-related OPC minimizes the post-treatment side effects while simultaneously prolonging survival.

What are the implications, and what should change now?

- Our findings imply that lower doses of radiotherapy can achieve similar therapeutic effects and involve fewer adverse reactions.
- Numerous clinical studies are still underway, so we hope that there will be more data to support this discovery and guide future clinical treatment.

and standard-dose treatments on prognosis in HPV-related OPC and conducted a systematic review of the adverse effects following dose reduction. We present the following article in accordance with the MOOSE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5935/rc).

Methods

Search strategy

A systematic search was conducted for relevant studies published before September 15, 2021, in the PubMed, Embase, Cochrane, ProQuest, Scopus, ScienceDirect, and the Web of Science electronic databases. The subject terms "oropharynx cancer/ carcinoma" or "OPC" were combined with the following specific terms: "human papillomavirus viruses", "human papillomavirus", "HPV", "P16", and "radiotherapy".

Selection criteria

The inclusion criteria were as follows: (I) Articles involving patients diagnosed with oral cancer; (II) studies with more than 20 patients; (III) research involving patients confirmed as HPV+ or P16+ by immunohistochemistry or other evidence; and (IV) studies involving a therapeutic plan that applies dose reduction; (V) Studies of all language. (The enrolled articles were all in English after screening.); (VI) case reports, comments, editorials, and reviews were excluded.

Articles were independently screened and then selected by two reviewers. In cases of studies overlapping, only the study with the most comprehensive data was selected when the patient populations were from the same institution, based on the consensus between the two reviewers. If differences in opinion between the two reviewers needed to be resolved, a third reviewer was consulted.

Data extraction

Relevant characteristics were extracted from each study, including the first author's name, publication year, country, study design, sample size, study participant age, study participant sex (the percentage of males), stage, smoking status (the percentage of fewer than 20 packs per year), and follow-up period (*Table 1*). Two reviewers independently extracted the information from the included studies. We then extracted the radiation and chemotherapy schemes for reduced dose (RD) and standard dose (SD), respectively (*Tables 2*,*3*). According to the clinical outcomes, the 2- and 3-year overall survival (OS) and progression-free survival (PFS) rates were also obtained. Several studies reported Kaplan-Meier survival curves rather than survival outcomes directly, but the survival outcomes could also be extracted from these survival curves. During this analysis, we did not attempt to obtain missing data by contacting the studies' authors. Also, given the lack of reports on adverse reactions (AEs) in the standard dose group, only the AEs of the reduced-dose group were counted, as shown in *Table 4*.

Statistical analysis

Both random and fixed effects models were used to pool analysis of the OS and PFS for SD and RD. Given that few articles contained both the standard and reduced-dose treatments, a meta-analysis of the standard and reduced-dose treatment subsets was conducted separately. The I^2 statistic was used to measure the degree of heterogeneity caused by variability in the true effect size. Statistical analysis was performed using the SPSS (version 15.0) and R language (version 1.6.3, http://www.Rproject.org). Meta-analysis was conducted by using the R package meta (34). Forest plots were created by the metaprop function of meta package, and funnel plots were constructed by the funnel function to estimate the publication bias. Egger's test was performed to estimate the indexes of funnel asymmetry. If the funnel plot was not significantly asymmetrical, trim- and fill- analyses were performed.

Results

Literature search and study characteristics

The search process is displayed in *Figure 1*. A total of 4,634 articles published before September 15th, 2021 were identified through the initial database search. We then excluded 869 overlapping studies, and a further 3,720 articles were excluded based on their improper titles and abstracts. The full texts of the remaining 45 studies were assessed, and studies with insufficient data or inappropriate populations, treatments, and sizes were excluded. Finally, 13 studies were included in the meta-analysis, among which nine were SD studies and 13 were RD studies (*Table 1*). The selected articles were single-arm observational articles, controlled trials, or randomized studies.

Table 1 Characteristics of the included studies

Author	Year	Country	Sample size	Median/mean age of included patients (years)	Male (%)	AJCC stage	Smoking status	Follow-up period (months)
Chen (21)	2017	USA	44	60	NA	III–IV	30 (68.0%) never smoked, and 14 (32.0%) had ≤20 pack year	30
Marur (22)	2017	USA	51	58	96.0	III–IV	23 (45.0%) never smoked, and 14 (28.0%) had ≤20 pack year	35.4
Yom (23)	2021	USA	157	NA	84.7	NA	112 (71.3%) never smoked, and 45 (38.7%) had ≤20 pack year	30
Misiukiewicz (24)	2019	USA	20	56.5	95.0	NA	12 (60%) never smoked, and eight (40%) had ≤20 pack year	56
Fietkau (25)	2020	Germany	32	NA	NA	III–IVB	NA	44
Moore (26)	2021	USA	194	58	90.2	II–IV	148 (76.3%) never smoked, and 46 (23.7%) had ≤20 pack year	49
Chera (27)	2018	USA	44	61	88.6	NA	36 (81.8%) never smoked, and eight (18.2%) had ≤20 pack year	36
Echevarria (28)	2019	USA	484	NA	NA	NA	NA	36
Huang (29)	2020	Canada	315	NA	77.8	NA	101 (32.1%) never smoked, and 214 (67.9%) had ≤20 pack year	57.6
Gabani (30)	2019	USA	759	58.5	86.0	NA	NA	30.5
Tam (31)	2020	USA	2173	57	85.5	III–IV	NA	33.8
Chin (32)	2016	USA	175	56.2	92.0	III–IV	59 (33.7%) never smoked, and 116 (66.3%) had ≤20 pack year	70.8
White (33)	2020	USA	192	NA	NA	NA	NA	60

NA, not available; AJCC, American Joint Committee on Cancer.

The sample sizes of the SD studies ranged from eight to 2,049 (*Table 2*) and those of the RD studies ranged from 12 to 157 (*Table 3*). The ages of patients treated with SD were similar to those who received RD (60.9±5.9 *vs.* 58.6±2.4 years). There were no significant gender differences observed between the SD and RD groups (percentage of males, 85.8% *vs.* 84.8%). Also, the mean follow-up times of the RD and SD studies were compared. Regarding the SD treatment regimen, the total dose ranged from 66 to 70 Gy, while that of the RD regimen was <66 Gy.

OS comparison between SD and RD in HPV-related OPC patients

We conducted a meta-analysis of the SD and RD treatment groups. The results showed that the 2-year overall survival (2y-OS) and 3-year overall survival (3y-OS) were better in the RD group compared to the SD group (P<0.05, *Figure 2*). Four SD trials showed that the 2y-OS was 88.36% (86.23–90.49%), and eight SD trials indicated that the 3y-OS was 87.46% (86.91–88.01%). Meanwhile, seven RD trials showed that the 2-year OS was 95.66% (94.74–96.59%), and 11 RD trials showed that the 3-year OS was 91.51% (90.61–92.41%). There was no significant difference in PFS between RD and SD; the 2y-PFS and 3y-PFS rates were 89.29% *vs.* 90.7% and 87.07% *vs.* 89.71%, respectively (P≥0.05, *Figure 3*).

Analysis of the adverse reactions in RD patients

We performed a systematic review and analysis of the articles on RD treatment (*Table 4*). Among the four studies analyzed, Misiukiewicz *et al.* showed that the incidence rates of oral mucositis, neutropenia, and urinary retention were all 8.3%. According to Marur *et al.*, rash was the most common adverse reaction (54.9%) followed by neutrophil

Table 2 Characteristics of the included standard dose studies

Author	Sample size	Median/mean age (years)	Male (%)	T stage	N stage	RT dose	Concurrent therapy	Clinical outcomes
Misiukiewicz (24)	8	55	NA	T1-T2-4; T3-2; T4-2	N0-1; N1-N2-3; N2c-N3-4	70 Gy/35 fx to involved areas and 56 Gy/35 fx to elective neck; cSD and cPD received the latter regimen	2 of 8 patients received concurrent carboplatin	2-y OS: 83.3%; 3-y OS: 83.3%
Fietkau (25)	NA	NA	NA	NA	NA	The prescribed radiation doses included 70.6 Gy to the gross primary tumor volume, 58 Gy to involved nodal levels, and 49.6 Gy to neck regions at low-risk	Fluorouracil 600 mg/m^2; cisplatin 20 mg/m^2, days 1–5 and 29–33	2-y OS: 89.2%; 3-y OS: 83.5%
Moore (26)	115	55	90	T1-42; T2-58; T3-11; T4-4	N0-6; N1-91; N2-18	RT (60 Gy IMRT) or chemoradiotherapy (cisplatin with 60 Gy IMRT)	RT (60 Gy IMRT) or chemoradiotherapy (cisplatin with 60 Gy IMRT)	3-y OS: 93.0%
Echevarria (28)	338	NA	NA	NA	NA	≥69.3 Gy given over a median of 35 fractions in a median of 200 cGy per fraction	NA	3-y OS: 91.1%
Huang (29)	254	66.8	82	T1-T2-162; T3-T4-92	N0-N2a-93; N2b-104; N2c-47; N3-10	Moderately accelerated radiotherapy alone, 70 Gy in 35 fractions over 6 weeks	NA	3-y OS: 82.0%
Gabani (30)	655	59	86.3	T1-129; T2-199; T3-129; T4-139	N0-79; N1-90; N2a-59; N2b-216; N2c-125; N3-39; NA-47	66 Gy in 25 fractions over 5 weeks	NA	3-y OS: 79.3%
Tam (31)	2049	NA	85.5	T1-418; T2-1033; T3-549; NA-49	N0-187; N1-314; N2-139; N2a-204; N2b-911; N2c-285; NA-9	≥66 Gy in 25 fractions over 5 weeks	NA	3-y OS: 88.5%
Chin (32)	109	56.2	93.6	T1-34; T2-41; T3-15; T4a-18; T4b-0	N0-3; N1-15; N2a-17; N2b-52; N2c-22; N3-0	66 Gy to the tumor bed was 66 or 60 Gy in 33 or 30 fractions of 2 Gy each over 7 or 6 weeks	Concurrent chemotherapy comprised cisplatin (100 mg/m^2 on days 1, 22, and 43 of RT) or rarely paclitaxel (60 mg/m^2 weekly with RT) or carboplatin	2-y OS: 90.6%
White (33)	89	NA	NA	NA	NA	≥66 Gy in 25 fractions over 5 weeks	NA	2-y OS: 84.3%; 3-y OS: 82.9%

NA, not available; RT, radiotherapy; cSD, clinical stable disease; cPD, clinical progressive disease; IMRT, intensity modulated radiotherapy; OS, overall survival.

Table 3 Characteristics of the included reduced dose studies

Author	Sample size	Median/mean age of the included patients (years)	Male (%)	T stage	N stage	RT dose	Concurrent therapy	Clinical outcomes
Chen (21)	44	60	NA	T1-16; T2-18; T3-3; T4-7	N0-2; N1-3; N2a-9; N2b-19; N2c-10; N3-1	Definitive radiation given concurrently for 5–6 weeks, chemoradiotherapy was initiated at least 2 weeks following completion of induction chemotherapy	Two cycles of induction chemotherapy with 175 mg/m^2 paclitaxel infused over 3 h plus carboplatin as a 30 min infusion, given 21 days apart. This induction regimen was followed by chemoradiotherapy comprising 30 mg/m^2 paclitaxel infused over 1 h per week with definitive radiation given concurrently for 5–6 weeks	2-y OS: 98.0%
Marur (22)	51	58	96	T1-11; T2-26; T3-8; T4-6	N0-N1-7; N2a-N2b-29; N2c-15	Cases with cCR on exam/imaging received 54 Gy/27 fx to areas of initial involvement, and the uninvolved cervical nodes (caudal to bilateral clavicles) received 51.3 Gy/27 fx	Patients received IC with cisplatin 75 mg/m^2 on day 1; paclitaxel 90 mg/m^2 on days 1, 8, and 15; and cetuximab 400 mg/m^2 on day 1 of cycle 1, followed by cetuximab 250 mg/m^2 weekly; patients continued weekly cetuximab until completion of radiotherapy	2-y OS: 94.0%; 3-y OS: 94.0%
Yom (23)	157	NA	84.7	T1-115; T2-147; T3-44; N0-13; N1-62; N2a-43; N2b-188	N0-6; N1-28; N2a-24; N2b-99	60 Gy of intensity-modulated radiation therapy in 30 fractions, at five fractions per week	Concurrent with cisplatin at 40 mg/m^2 weekly	2-y OS: 96.7%; 3-y OS: 95.0%
Misiukiewicz (24)	12	57	NA	T1-T2-7; T3-5; T4-0	N0-0; N1-N2-3: N2c-N3-9	Cases with cPR/cCR on exam/imaging were randomized to 56 Gy/28 fx to involved areas & 50.4 Gy/28 fx to the elective neck	8 of 12 patients received carboplatin only as a radiosensitizer	2-y OS: 87.5%; 3-y OS: 87.5%
Fietkau (25)	NA	NA	NA	NA	NA	The prescribed radiation doses included 63.6 Gy to the gross primary tumor volume (PTV 1 = boost), 58 Gy to involved nodal levels (PTV 2), and 49.6 Gy (PTV 3) to low-risk neck regions	Paclitaxel 20 mg/m^2 on days 2, 5, 8, 11, 25, 30, 33, and 36; cisplatin 20 mg/m^2, days 1–4 and 29–32	2-y OS: 92.3%; 3-y OS: 92.3%

Table 3 *(continued)*

Table 3 *(continued)*

Author	Sample size	Median/mean age of the included patients (years)	Male (%)	T stage	N stage	RT dose	Concurrent therapy	Clinical outcomes
Moore (26)	79	61	91	T1-36; T2-27; T3-7; T4-9	N0-1; N1-66; N2-12	Received 30 Gy in 1.5-Gy fractions twice daily (separated by at least 6 hours) over 2 weeks to the primary site and dissected and elective nodal volumes	IV weekly docetaxel (15 mg/m^2) was administered on days 1 and 8 of treatment as a radiosensitizer	3-y OS: 86.3%
Chera (27)	44	61	88.6	T0-2; T1-13; T2-22; T3-7	N0-4; N1-10; N2a-2; N2b-21; N2c-7	The total delivered dose was 60 Gy at 2 Gy per fraction for 30 fractions, 5 days a week for 6 weeks to the high-risk regions. A dose of 54 Gy was delivered to anatomic regions at risk of subclinical disease (as indicated)	Cisplatin at a dose of 30 mg/m^2 was given intravenously weekly	3-y OS: 95.0%
Echevarria (28)	146	NA	NA	NA	NA	Doses of <69.3 Gy given over a median 33 fractions in a median of 200 cGy per fraction	NA	3-y OS: 86.3%
Huang (29)	61	61	59	T1-T2-47; T3-T4-14	N0-N2a-40; N2b-16; N2c-5; N3-0	60 Gy in 25 fractions over 5 weeks	NA	3-y OS: 73.0%
Gabani (30)	104	58	84.6	T1-30; T2-15; T3-12; T4-14	N0-6; N1-22; N2a-23; N2b-32; N2c-10; N3-4; NA-7	<66 Gy in 25 fractions over 5 weeks	NA	3-y OS: 82.2%
Tam (31)	124	NA	85.5	T1-29; T2-59; T3-25; NA-11	N0-8; N1-26; N2-9; N2a-11; N2b-56; N2c-13; NA-1	50 to <66 Gy in 25 fractions over 5 weeks	NA	3-y OS: 89.9%
Chin (32)	66	56.2	89.4	T1-23; T2-29; T3-8; T4a-5; T4b-1	N0-2; N1-6; N2a-11; N2b-32; N2c-12; N3-3	The total dose to the tumor bed was 66 or 60 Gy in 33 or 30 fractions of 2 Gy each over 7 or 6 weeks	Concurrent chemotherapy comprised scheduled cisplatin (100 mg/m^2 on days 1, 22, and 43 of RT) or rarely paclitaxel (60 mg/m^2 weekly with RT) or carboplatin	2-y OS: 96.8%
White (33)	103	NA	NA	NA	NA	<66 Gy in 25 fractions over 5 weeks; sdCRT: ≥66 Gy in 25 fractions over 5 weeks	NA	2-y OS: 84.3%; 3-y OS: 82.9%

NA, not available; cPR, clinical partial response; cCR, clinical complete response; IC, induction chemotherapy; RT, radiotherapy; OS, overall survival; sdCRT, standard dose chemoradiation.

Table 4 Adverse events occurred in the reduced dose group

Toxicities	Chen (21) (n=44)	Marur (22) (n=51)	Misiukiewicz (24) (n=12)	Chera (27) (n=44)
Increased ALT level		1		
Anaphylaxis		1		
Anemia	28	1		
Anorexia	11	4		
Anxiety	5			
Arthralgia	4	1		
Aspiration		1		
Increased AST level		0		
Bone pain	2			
Increased cardiac troponin I level		1		
Catheter-related infection		1		
Decreased CD4 lymphocyte count		1		
Chest pain, cardiac		1		
Constipation	17	0		
Cough	16			
Dehydration	10	6		
Dermatitis radiation	36	0		
Device-related infection		1		
Diarrhea	3	5		
Dry mouth	43	0		1
Dysphagia	23	1		17
Dyspnea		2		
Erythema multiforme		0		
Fatigue		4		
Febrile neutropenia		1	1	
Fever	3			
Gastrointestinal disorders		0		
Generalized muscle weakness		1		
Headache	4	1		
Hematologic				5
Hyperkalemia		1		
Hypokalemia	4	4		
Hypomagnesemia	5	2		
Hyponatremia	8	2		
Hypophosphatemia		1		

Table 4 *(continued)*

Table 4 *(continued)*

Toxicities	Chen (21) (n=44)	Marur (22) (n=51)	Misiukiewicz (24) (n=12)	Chera (27) (n=44)
Hypotension		2		
Hypoxia		1		
Increased creatinine	4			
Decreased lymphocyte count		6		
Oral mucositis	38	1	1	15
Myalgia		1		
Myocardial infarction		1		
Nausea	19	4		8
Neuralgia		0		
Neutropenia	9			
Decreased neutrophil count		12		
Oral pain		0		
Pain		0		
Pain in extremities		0		
Palmar-plantar erythrodysesthesia		0		
Peripheral motor neuropathy		0		
Peripheral sensory neuropathy	3	0		
Pharyngitis		0		
Pneumonia	2			
Rash, acneiform		28		
Rash, maculopapular		2		
Renal and urinary disorders, other		0		
Sepsis		1		
Skin ulceration		0		
Sore throat		0		
Thromboembolic event		4		
Tinnitus		1		
Tumor pain		0		
Urinary retention			1	
Voice alteration	6			
Vomiting		0		2
Decreased WBC count	40	6		
Wound complications		1		

ALT, alanine transaminase; AST, aspartate transaminase; CD4, cluster of differentiation 4; WBC, white blood cell.

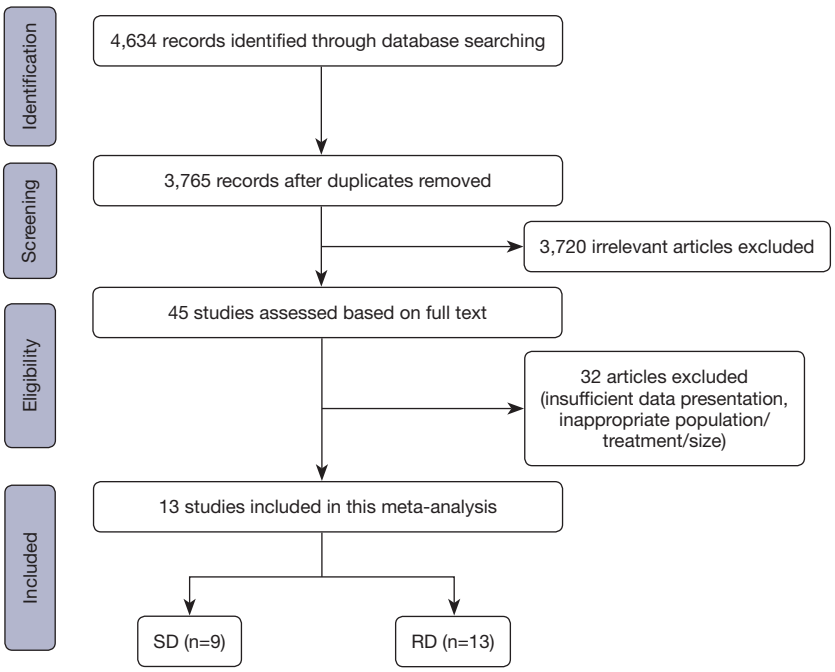

Figure 1 Flowchart of study selection. Of the 13 studies included in this meta-analysis, 9 studies included both RD and SD, and 4 studies just included in RD. SD, standard dose; RD, reduced dose.

count reduction (23.5%), dehydration, lymphocyte count reduction, and leukocyte count reduction (all 11.8%). The top three adverse reactions reported by Chera *et al.* were dry mouth (38.6%), oral mucositis (34.1%), and nausea (18.2%). Compared with the other three studies, Chen *et al.* reported the most AEs, with 43 people suffering from dry mouth, 40 people suffering from decreased white blood cell (WBC) count, and 38 people suffering from oral mucositis. In summary, the most common complication of RD was mucositis oral, affecting 36.4% of patients, followed by decreased WBC count (30.5%) and dry mouth (29.1%).

Sensitivity analysis and evaluation of publication bias

Following sensitivity analysis using the elimination method, no significant change was observed in the results, which indicated their robustness. Egger's test was performed on the indexes with more than three included studies, and the results showed no obvious publication bias.

Discussion

It is known that patients with HPV-associated OPC have an excellent prognosis. Studies have shown that these patients are more sensitive to radiation therapy (35), and can achieve the same therapeutic effect by reducing the radiation dose. Although this topic is at the forefront of oncologic research, there is currently a lack of summative assessment. Therefore, we compared the effects of reduced and standard doses in HPV-related OPC on survival and the incidence of AEs. Our results suggested that patients with HPV-related OPC could be treated with a lower dose compared to standard treatment, and there are fewer AEs after radiotherapy. This study may lead to a change in the treatment options for patients with oropharyngeal cancer.

In this study, we selected patients who were HPV-related and divided them into two groups: SD and RD treatment groups, and observed their survival conditions. As mentioned above, we observed that patients who received a RD had superior 2y-OS and 3y-OS rates than those who received SD treatment (95.66 *vs.* 91.51; 88.36 *vs.* 87.46, respectively). Moreover, the 2- and 3-year PFS rates were not significantly different between the two groups. Numerous factors influence the prognosis of OPC, such as disease stage, gender, smoking state, HPV subtype, etc. (10,23,24,36). In our research, the disease stage, gender, and smoking state were not disparate between the two groups, so we excluded their influence. HPV infection can be

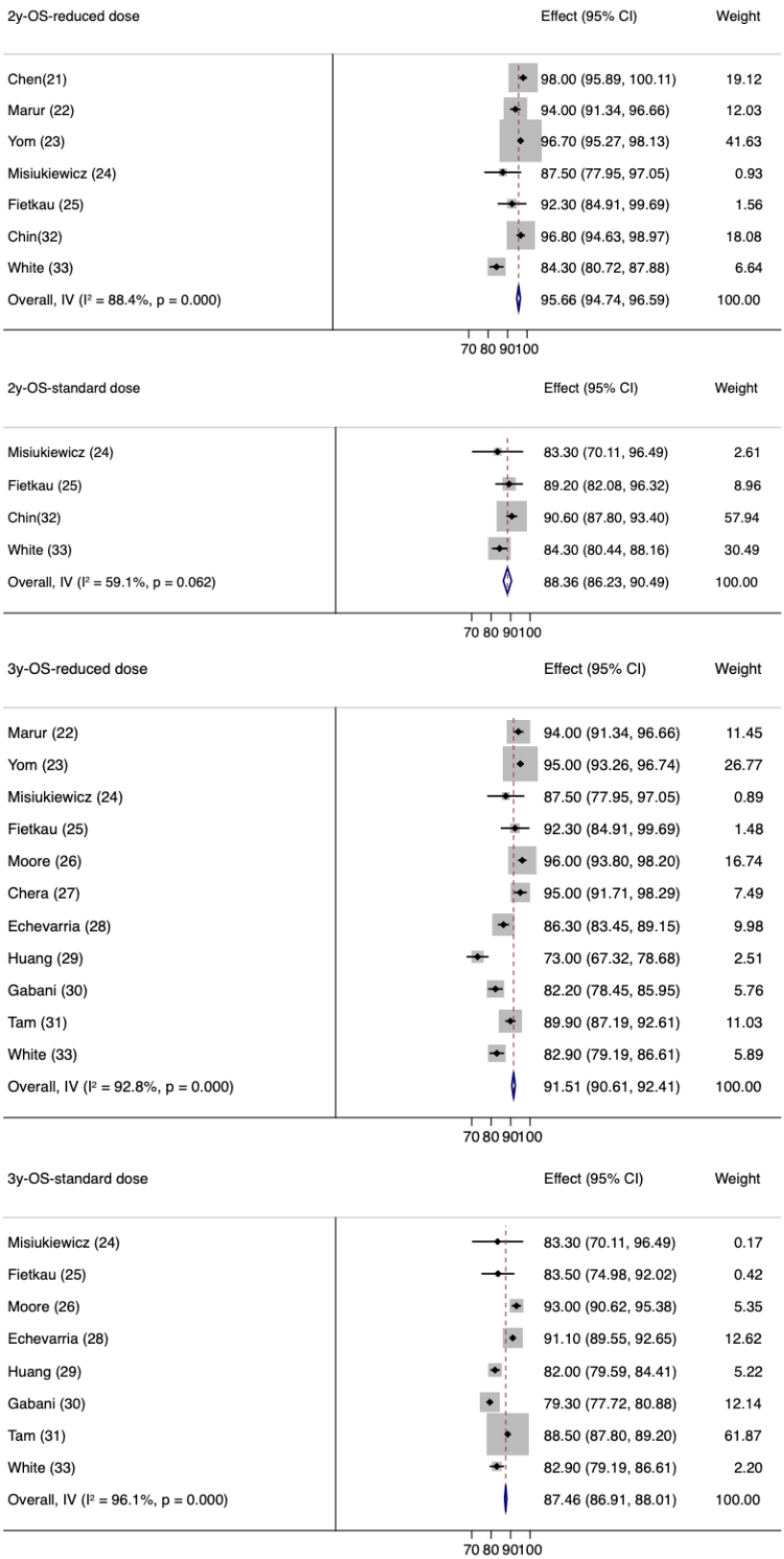

Figure 2 Meta-analysis (forest plot) of the OS reported in RD and SD studies. OS, overall survival; RD, reduced dose; SD, standard dose.

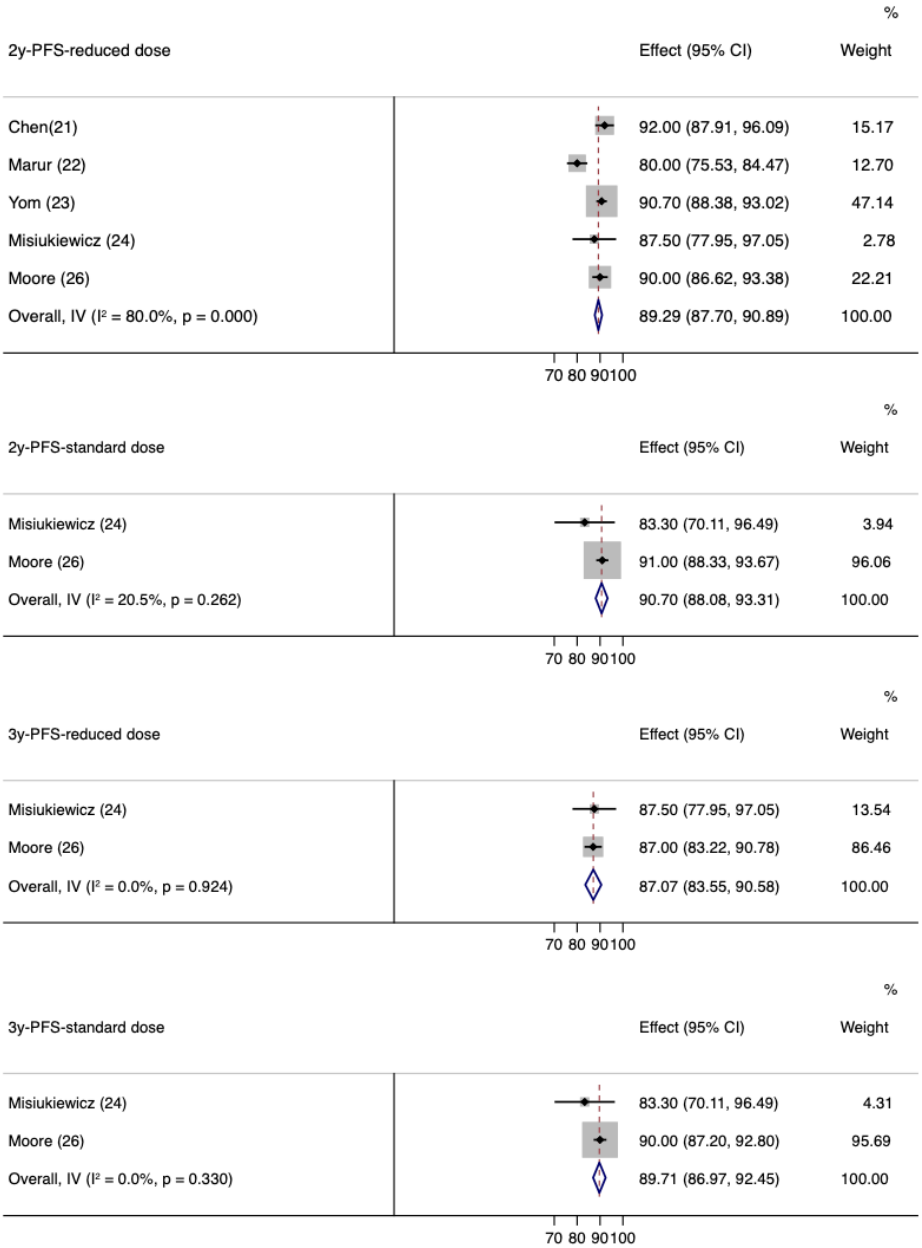

Figure 3 Meta-analysis (forest plot) of the PFS reported in RD and SD studies. PFS, progression-free survival; RD, reduced dose; SD, standard dose.

classified into P16+/HPV+, p16+/HPV−, or p16−/HPV+. Some studies have reported that the OS of p16+/HPV− and p16−/HPV+ are poor (37). However, the included studies in this meta-analysis failed to distinguish between these three specific categories, and thus, we could determine whether our results were affected by HPV status in the two groups. It is hoped that the currently ongoing clinical trials (38) consider the subtype of HPV states to ascertain whether different HPV states affect the prognosis of treatment to varying degrees and clarify which HPV has a superior effect.

In our retrospective analysis, the main AE of RD treatment was oral mucositis, occurring in 36.4% of patients. Comparing the four studies that mentioned

AEs, Fietkau *et al.* (25), Yom *et al.* (23), and Echevarria *et al.* (28) reported fewer AEs, which may be related to the use of the chemotherapy drug, carboplatin. A trial comparing cetuximab and cisplatin chemoradiotherapy (CRT) as presented by a European group at European Society for Medical Oncology (ESMO) 2018 (30), which confirmed that platinum can enhance radiosensitivity and reduce AEs. Although the reported incidence of adverse reactions seemed high in Chen *et al.* (21), they were mainly concentrated in Grades 1–2, which are relatively mild and do not significantly impact the quality of life of patients. Compared with the other three studies, Chen *et al.* employed combination treatment using paclitaxel and carboplatin instead of platinum monotherapy; thus, we speculate that the higher rates of adverse reactions in their study may be related to the multiple chemotherapy regimen combinations.

Unfortunately, detailed adverse events in the SD group were not collected in our study, so it was impossible to compare the two groups. Nevertheless, further analysis revealed that all of the relevant research results concerning radiotherapy dose reduction indicated fewer adverse reactions. Standard chemoradiotherapy regimens are associated with substantial toxic effects, including in organs involved in salivation, swallowing, and mucosal integrity, with dose-related side effects. Probability models utilized for complications in normal tissue show that with each 1 Gy increase in the mean dose to the parotid gland, the likelihood of xerostomia increases by about 5% at 1-year post-treatment (39). Likewise, the incidence of late dysphagia and gastrostomy tube dependence rises with increasing pharyngeal constrictor, larynges, and cricopharyngeal inlet doses. Thus, reducing the radiation dose in selected patients with favorable biology (HPV-related) has the potential to improve treatment tolerability while at the same time preserving long-term function.

The systematic review conducted in this study showed that lower doses could reduce post-treatment AEs, either the incidence of decreased quality of life (40) or late adverse reactions (25). Some studies (28,41-43) have shown that, after dose reduction, the symptoms of dry mouth, hypogeusia, and dysphagia continue to improve, and gastrostomy tube (PEG) placement rates and late toxicity were also lower (43-45). It has also been reported (46) that the target volume of OPC could combine dose reduction with unilateral irradiation for improving mild to moderate acute swallowing dysfunction. Taken together, these results indicate that reducing the radiation dose is conducive to improving the quality of life of patients and enhancing the functioning of affected organs.

This article had several limitations that should be noted. Firstly, the sample size of the included trials is small, and there is a lack of randomized phase III clinical trial results. Furthermore, due to the inclusion of clinical trials with potential selection bias, the compared treatment strategies and follow-up periods are largely different among various studies, which may have impacted the results. Lastly, the vast majority of included studies failed to provide long-term follow-up. HPV-related tumor recurrences continue after 3 years of therapy (10) and the cumulative incidence of late AEs consistently increases over a longer period (14), implying that toxicity reporting is likely understated, and the outcomes are likely overestimated to some extent. Nevertheless, these shortcomings do not detract from the promising short-term results of treatment de-escalation a concept that seeks to improve the therapeutic ratio for this expanding population.

Conclusions

This systematic review and pooled analysis revealed that compared to standard radiation doses, radiation dose reduction in patients with HPV-related OPC provided superior therapeutic outcomes and optimized quality of life, but had similar PFS rates. Prospective randomized trials or studies with large sample sizes are needed to validate these findings.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://atm.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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