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Overview

A Review of Modern Radiation Therapy Dose Escalation in Locally Advanced Head and Neck Cancer

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Abstract

The management of head and neck cancer is complex and often involves multimodality treatment. Certain groups of patients, such as those with inoperable or advanced disease, are at higher risk of treatment failure and may therefore benefit from radiation therapy dose escalation. This can be difficult to achieve without increasing toxicity. However, the combination of modern treatment techniques and increased research into the use of functional imaging modalities that assist with target delineation allows researchers to push this boundary further. This review aims to summarise modern dose escalation trials to identify the impact on disease outcomes and explore the growing role of functional imaging modalities. Studies experimenting with dose escalation above standard fractionated regimens as outlined in National Comprehensive Cancer Network guidelines using photon therapy were chosen for review. Seventeen papers were considered suitable for inclusion in the review. Eight studies investigated nasopharyngeal cancer, with the remainder treating a range of subsites. Six studies utilised functional imaging modalities for target delineation. Doses as high as 85.9 Gy in 2.6 Gy fractions (EQD2 90.2 Gy_{10}) were reportedly delivered with the aid of functional imaging modalities. Dose escalation in nasopharyngeal cancer resulted in 3-year locoregional control rates of 86.6–100% and overall survival of 82–95.2%. For other mucosal primary tumour sites, 3-year locoregional control reached 68.2–85.9% and 48.4–54% for overall survival. There were no clear trends in acute or late toxicity across studies, regardless of dose or addition of chemotherapy. However, small cohort sizes and short follow-up times may have resulted in under-reporting. This review highlights the future possibilities of radiation therapy dose escalation in head and neck cancer and the potential for improved target delineation with careful patient selection and the assistance of functional imaging modalities.

Key words: Dose escalation; functional imaging; head and neck neoplasm; radiation oncology

Introduction

Cancer of the head and neck refers to a group of tumours arising in the oral cavity, pharynx, larynx, nasal cavity, sinuses or salivary glands [1]. Despite continuing improvements in the detection of cancer and available treatments, the 5-year relative survival remains at 68.2% for all head and neck cancers (HNCs) combined [2]. In oropharyngeal cancer, there has been growing interest in treatment de-escalation for human papillomavirus (HPV)-positive cancers, given their improved prognosis [3–5]. By contrast, Ang *et al.*'s study [6] showed that patients with high-risk features, including heavy smoking history and HPV-negative disease, had a 3-year overall survival of only 46.2%. This would indicate that treatment intensification may still be an appropriate avenue to explore in this high-risk group.

Theoretically, an increase in dose delivered to the tumour should improve disease control [7–9]. However, due to the proximity of functionally important organs at risk within this area, this can be difficult to achieve without potentially increasing rates of toxicity. Modern, highly conformal treatment techniques, such as intensity-modulated radiation therapy and stereotactic radiation therapy, extend the boundaries of dose escalation while maintaining organs at risk constraints [9]. Although many studies have explored a wide range of altered fractionation schedules, as shown in the present review, the accurate

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Table 1
Summary of study characteristics. Staging according to American Joint Committee on Cancer (AJCC) guidelines. Histology as reported by the individual studies; nasopharyngeal cancer (NPC) classified by World Health Organization type. Assessment of whether patient or disease factors were considered in the analysis is reported as yes/no. This may include tumour staging, grading or volume, as well as patient factors such as p16 status and age

Reference	Study type	*n*	Median age (range)	Performance status	Sites	Staging	Histology	Patient/disease factors considered in analysis	Radiation therapy dosing		Concurrent chemotherapy (%)	Functional imaging modality
									Dose per fraction × number of fractions	Total dose		
Standard imaging – mucosal primary												
[15]	P	20	57 years (37–80)	–	OPC	II–IVB	SqCC	Yes (tumour volume)	2.27 Gy × 30 2.36 Gy × 30 2.46 Gy × 30	68.1 Gy 70.8 Gy 73.8 Gy	No	N/A
[16]	P	20	58.5 years (51–61)	KPS 70–90	OPC, LRC, HPC	III–IVA	SqCC	No	2.2 Gy × 30 2.18 Gy × 33	66 Gy 72 Gy	No	N/A
[17]	R	27	60.7 years (42–85)	–	HPC	II–IVB	SqCC	Yes (stage, tumour volume, tumour location)	2.07 Gy × 35 2.07 Gy × 37	72.6 Gy 76.8 Gy	Yes (100%)	N/A
[18]	P	65	58.6 years (38–78)	ECOG 0–1	OPC, LRC, HPC, OCC, NPC	II–IV	–	Yes (stage, grade)	2 Gy × 10 +3.6 Gy × 15	69.5 Gy	No	N/A
[19]	P	39	61 years (40–84)	KPS 60–100	OPC, HPC, OCC, LRC	IV	SqCC	No	1.4 Gy 1.45 Gy 1.5 Gy × 50	70 Gy 72.5 Gy 75 Gy	No	N/A
[20]	P	57	61 years	ECOG 0–1	OPC, LRC	II–III	SqCC	No	2.3 Gy × 30 2.4 Gy × 30 2.5 Gy × 30	69 Gy 72 Gy 75 Gy	No	N/A
[21]	P	60	DL1 58 years (35–80) DL2 62 years (43–85)	ECOG 0–1	LRC, HPC	III–IV	SqCC	No	2.25 Gy × 28 2.4 Gy × 28	63 Gy 67.2 Gy	Yes (100%)	N/A
Standard imaging – NPC												
[22]	P	50	48 years (24–74)	–	NPC	III–IVB	III = 50	Yes (stage)	2.17 Gy × 35	76 Gy	Yes (68%)	N/A
[23]	P	47	<50 years = 27 >50 years = 20	KPS 70–100	NPC	II	II = 3 III = 44	No	1.8 Gy × 30 +1.5 Gy × 12	72 Gy	No	N/A
[24]	P	193	52 years (13–72)	–	NPC	III–IVB	I = 7 II = 135 III = 51	Yes (stage, grade, age, tumour volume)	2.42 Gy × 33	74 Gy	Yes (85.5%)	N/A
[25]	R	49	50 years (18–71)	–	NPC	II–IV	I = 3 II = 6 III = 40	No	2.2 Gy × 32	70.4 Gy	Yes (100%)	N/A
[26]	R	370	50 years (9–79)	–	NPC	I–IV	I = 3 II = 76 III = 285	No	2.2 Gy × 30 2.2 Gy × 32	66 Gy 70.4 Gy	Yes (92.2%)	N/A
Functional imaging – mucosal primary												
[27]	R	123	62 years (34–87)	–	HPC, LRC	II–IV	SqCC	No	2.2 Gy × 30 2.11 Gy × 33 2 Gy × 35 2.2 Gy × 33	66 Gy 69.6 Gy 70 Gy 72.6 Gy	Yes (86%)	FDG-PET

(*continued on next page*)

Table 1 (*continued*)

Reference	Study type	*n*	Median age (range)	Performance status	Sites	Staging	Histology	Patient/disease factors considered in analysis	Radiation therapy dosing		Concurrent chemotherapy (%)	Functional imaging modality
									Dose per fraction × number of fractions	Total dose		
[28]	RCT	25	57 years (46–75)	ECOG 0–1	OPC, HPC	III–IVB	SqCC	Yes (p16 status, tumour hypoxia)	2 Gy × 35 2.2 Gy × 35	70 Gy 77 Gy	Yes (100%)	FMISO-PET
[29]	R	72	59.9 years (40–78)	KPS 70–100	OCC, OPC, HPC, LRC	III–IV	SqCC	No	2.16 Gy × 32 2.6 Gy × 32	69.1 Gy 85.9 Gy	Yes (46%)	FDG-PET
Functional imaging – NPC												
[30]	P	25	46 years	KPS 60–100	NPC	II–IV	I = 2 II = 4 III = 19	No	2.34 Gy × 30	70.2 Gy	Yes (100%)	FDG-PET
[31]	RCT	67	47.5 years (19–68)	KPS 70–100	NPC	III–IV	II = 7 III = 36	No	2 Gy × 35 2.2 Gy × 32 2.4 Gy × 32	70 Gy 70 Gy 77 Gy	Yes (100%)	FDG-PET
[10]	R	213	46 years (18–70)	KPS 70–100	NPC	III–IV	II = 30 III = 71	Yes (age, sex, stage, EBV DNA)	2.2 Gy × 33 2.35 Gy × 32 2.35 Gy × 33	72.6 Gy 75.2 Gy 77.55 Gy	Yes (98%)	FDG-PET

EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; FMISO, fluoromisonidazole; HPC, hypopharyngeal cancer; KPS, Karnofsky performance status; LRC, laryngeal cancer; OCC, oral cavity cancer; OPC, oropharyngeal cancer; P, prospective; PET, positron emission tomography; R, retrospective; RCT, randomised control trial; SqCC, squamous cell carcinoma.

delineation of the tumour volume and involved lymph nodes remains a key challenge [10].

Functional imaging modalities such as positron emission tomography (PET), dynamic contrast enhanced and diffusion weighted magnetic resonance imaging (DW-MRI) reflect biological pathways related to radiosensitivity, such as tumour hypoxia, cellular density and proliferation [11]. Within clinical practice, PET imaging is commonly used in the diagnosis and staging of many different types of cancer. However, its role in HNC dose escalation is still being investigated. Evidence suggests that the use of functional imaging modalities could help to identify the true extent of tumours [12].

The purpose of this systematic review is to summarise the dosing regimens used in HNC dose escalation trials over the past 15 years to identify their impact on disease control and toxicity rates. Additionally, dose escalation using standard anatomical imaging is compared with treatments using functional imaging modalities to identify if an increased dose can be delivered without increasing toxicity rates. This review aims to guide future research into functional imaging-guided radiation therapy dose escalation in groups of patients at high risk of disease recurrence.

Methods

Search Strategy

Following PRISMA guidelines, a review of the current literature was carried out through electronic databases and scanning of reference lists. PubMed, Embase and Cochrane databases were examined using individualised search strategies for literature related to radiation therapy dose escalation in the treatment of primary HNC. These included subject headings and free text using synonyms of 'head and neck neoplasm', 'conformal radiotherapy', 'dose escalation', 'overall survival' and 'local control' (see Supplementary material). In addition, the reference lists of full text articles were searched for additional relevant studies.

Eligibility Criteria

Studies were included in the analysis if they were published in the past 15 years and dose escalated above standard fractionated radiation therapy regimens, as per the National Comprehensive Cancer Network (NCCN) guidelines using external beam photon therapy [1]. Both randomised and non-randomised clinical trials, as well as prospective and retrospective case series, were included. The limitations applied included: full text availability, English as the primary language and studies of humans. Studies were excluded if they:

- included recurrent disease in a region previously treated with radiation therapy;
- included cancers outside of the head and neck region;
- delivered treatment using proton, carbon ion or brachytherapy techniques;

- were planning studies, literature reviews, conference abstracts or opinion pieces; or
- did not report on treatment outcomes.

Data Extraction

Information was extracted from the final papers regarding participant and tumour characteristics, treatment regimens, treatment outcomes including locoregional control (LRC), overall survival and treatment-related toxicity. Referencing manager software and predetermined Excel spreadsheets were used to manage references and assist with data extraction.

Synthesis of Results

The included studies were divided into two arms: (i) dose escalation using standard imaging and (ii) dose escalation guided by functional imaging modalities. This was further divided into nasopharyngeal cancers (NPC) and other mucosal primary cancers for assessment of disease control. Comparisons were carried out according to the study objectives, which included LRC, overall survival and toxicity. The equivalent doses in 2 Gy per fraction (EQD2) were calculated for each of the reported schedules using an α/β of 10 Gy for early responding tissues and 3 Gy for late responding tissues [13]. The repopulation term was not included in these calculations due to insufficient data [14]. The heterogeneity between studies made it difficult to perform a meta-analysis and thus necessitated a narrative synthesis report format.

Results

Literature Search

In total, 551 studies were identified through electronic databases. There were 101 duplicate studies identified and

Table 2
Disease outcomes for studies investigating primary head and neck cancer dose escalation. Rates of locoregional control and overall survival are shown for subgroups using standard imaging-guided treatment and functional imaging-guided treatment

Reference	Median follow-up	Locoregional control			Overall survival			
		2 years	3 years	5 years	1 year	2 years	3 years	5 years
Standard imaging guided								
[15]	20 months	76.3%	–	–	–	–	–	–
[16]	19 months	95%	–	–	–	95%	–	–
[17]	36 months	–	68.2%	–	–	–	51.9%	–
[18]	30.5 months	–	–	–	–	69%	–	–
[19]	10 months	–	–	–	55%	–	–	–
[20]	51.8 months	82%	–	–	–	91%	–	–
[21]	DL1 5.7 years	64.2%	–	54%	–	72.4%	–	61.9%
	DL2 6.0 years	78.4%	–	62.6%	–	74.2%	–	67.6%
Functional imaging guided								
[27]	21 months	77%	–	–	–	83%	–	–
[28]	27 months	70%	–	–	–	80%	–	–
[29]	87.7 months	–	85.9%	82.3%	–	–	48.4%	36.3%

Table 3
Disease outcomes for studies investigating nasopharyngeal cancer dose escalation. Rates of locoregional control and overall survival are shown for subgroups using standard imaging-guided treatment and functional imaging-guided treatment

Reference	Median follow-up	Locoregional control (%)				Overall survival (%)			
		1 year	2 years	3 years	5 years	1 year	2 years	3 years	5 years
Standard imaging guided									
[22]	25 months	–	95.7%	–	–	–	92.1%	–	–
[23]	30 months	–	–	87.1%	–	–	–	85.9%	–
[24]	34 months	–	–	86.6%	–	–	–	85.7%	–
[25]	48 months	98%	–	90%	90%	96%	–	82%	79%
[26]	26 months	99.7%	95.5%	–	–	–	94.1%	–	–
Functional imaging guided									
[30]	33 months	–	–	91%	–	–	–	89%	–
[31]	36 months	–	–	100%	–	–	–	95.2%	–
[10]	36 months	–	–	97.2%	–	–	–	91.8%	–

Table 4
Acute toxicity rates for the most consistently reported toxicities across the included studies. An α/β of 10 Gy was used to calculate equivalent dosing for early effects

Reference	[21] ($n = 60$) n (%)	[23] ($n = 47$) n (%)	[26] ($n = 370$) n (%)	[25] ($n = 49$) n (%)	[19] ($n = 39$) n (%)	[30] ($n = 25$) n (%)	[15] ($n = 20$) n (%)	[16] ($n = 20$) n (%)
EQD2 α/β = 10 Gy	64.31–69.44 Gy	70.35 Gy	67.1–71.57 Gy	71.57 Gy	66.5–71.88 Gy	72.19 Gy	69.63–72.92 Gy	67.1–73.08 Gy
Grade 1								
Dermatitis	17 (28)	–	–	–	–	–	–	–
Mucositis	8 (13)	–	–	–	–	–	–	1 (5)
Dysphagia	3 (5)	–	–	–	–	–	–	–
Xerostomia	14 (23)	–	–	–	–	–	–	–
Grade 2								
Dermatitis	29 (48)	23 (49)	–	–	–	–	–	18 (90)
Mucositis	24 (40)	28 (60)	–	–	–	–	–	6 (30)
Dysphagia	12 (20)	–	–	–	–	–	–	13 (65)
Xerostomia	33 (55)	–	–	–	–	–	–	18 (90)
Grade 3								
Dermatitis	14 (23)	7 (15)	–	–	0	4 (16)	5 (25)	0
Mucositis	27 (45)	11 (23)	–	–	20 (51)	9 (36)	15 (75)	13 (65)
Dysphagia	44 (73)	–	–	10 (20)	26 (67)	–	8 (40)	3 (15)
Xerostomia	11 (18)	8 (17)	–	–	–	–	–	–
Grade 4								
Dermatitis	0	0	–	–	0	1 (4)	–	–
Mucositis	0	–	–	–	0	–	–	–
Dysphagia	1 (2)	0	–	–	0	–	1 (5)	–
Xerostomia	0	0	–	–	0	–	–	–

Table 5
Late toxicity rates for the most consistently reported toxicities across the included studies. An α/β ratio of 3 Gy was used to calculate equivalent dosing for late effects

Reference	[21] ($n = 60$) n (%)	[23] ($n = 47$) n (%)	[26] ($n = 370$) n (%)	[25] ($n = 49$) n (%)	[19] ($n = 22$) n (%)	[30] ($n = 25$) n (%)	[15] ($n = 18$) n (%)	[16] ($n = 19$) n (%)
EQD2 α/β = 3 Gy	66.15–72.58 Gy	68.04 Gy	68.64–73.22 Gy	73.22 Gy	61.6–67.5 Gy	74.97 Gy	71.78–80.59 Gy	68.64–74.59 Gy
Grade 1								
Fibrosis	5 (8)	–	–	–	14 (64)	–	–	–
Dysphagia	1 (2)	–	–	–	–	–	–	11 (58)
Xerostomia	15 (25)	–	–	27 (55)	19 (86)	19 (76)	–	14 (74)
Grade 2								
Fibrosis	0	4 (9)	–	–	–	–	–	2 (11)
Dysphagia	0	–	–	–	–	–	–	0
Xerostomia	1 (2)	4 (9)	–	10 (20)	4 (18)	0	–	–
Hearing loss	–	2 (4)	–	–	–	6 (24)	–	–
Grade 3								
Fibrosis	0	1 (2)	–	0	0	–	–	–
Dysphagia	2 (3)	–	–	0	0	–	1 (5)	0
Xerostomia	0	1 (2)	–	5 (10)	0	0	4 (22)	–
Hearing loss	–	5 (10)	–	2 (4)	–	1 (4)	–	–
Grade 4								
Fibrosis	0	0	–	0	0	–	–	–
Dysphagia	1 (2)	0	–	0	0	–	4 (22)	–
Xerostomia	0	0	–		0	0	–	–
TLN	–	0	–	0	–	3 (12)	–	–

TLN, temporal lobe necrosis.

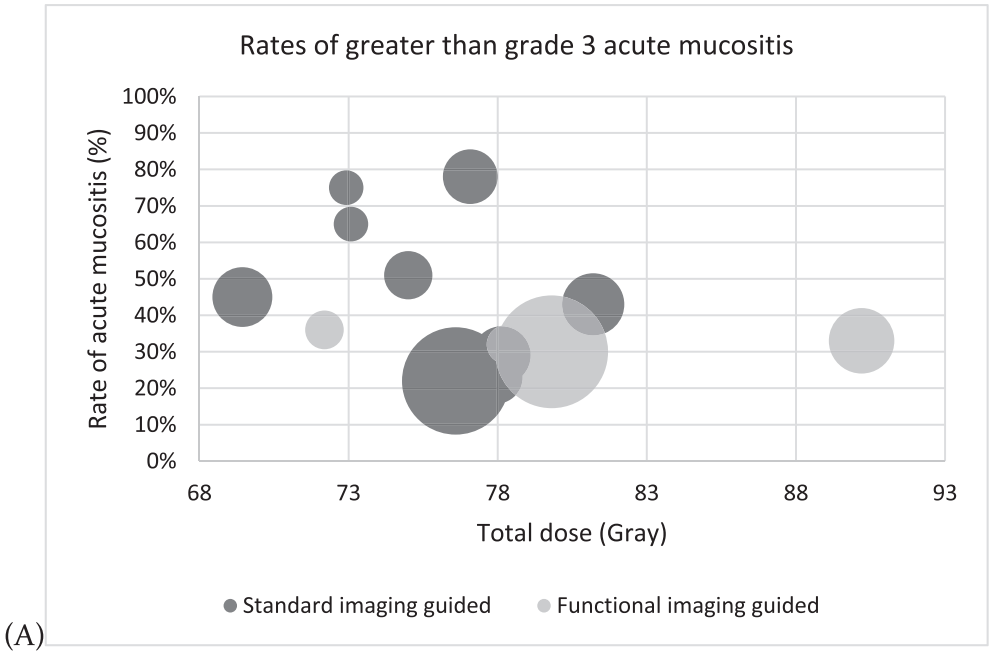
[27] ($n = 123$) n (%)	[24] ($n = 193$) n (%)	[17] ($n = 27$) n (%)	[22] ($n = 50$) n (%)	[20] ($n = 57$) n (%)	[28] ($n = 25$) n (%)	[31] ($n = 67$) n (%)	[10] ($n = 213$) n (%)	[18] ($n = 65$) n (%)	[29] ($n = 72$) n (%)
67.1–73.81 Gy	76.59 Gy	73.02–77.25 Gy	77.08 Gy	74.4–78.13 Gy	70–78.28 Gy	70–79.57 Gy	73.81–79.81 Gy	81.2 Gy	70.02–90.2 Gy
Grade 1									
–	104 (54)	–	–	17 (30)	12 (48)	44 (66)	–	–	15 (21)
–	90 (47)	–	–	11 (19)	2 (8)	10 (15)	–	–	16 (22)
–	125 (65)	–	–	15 (26)	2 (8)	–	–	–	11 (15)
–	–	–	–	–	9 (36)	–	–	–	–
Grade 2									
–	129 (67)	11 (41)	–	28 (49)	7 (28)	8 (12)	–	–	35 (49)
–	127 (66)	13 (48)	–	26 (46)	15 (90)	36 (54)	–	–	31 (43)
–	16 (8)	9 (33)	–	33 (58)	9 (36)	–	–	–	25 (35)
–	–	13 (48)	–		13 (52)	–	–	–	–
Grade 3									
–	46 (24)	–	23 (46)	11 (19)	6 (24)	4 (6)	21 (10)	7 (11)	21 (29)
–	44 (23)	–	39 (78)	17 (30)	8 (32)	21 (31)	65 (31)	28 (43)	24 (33)
–	0	17 (63)	–	7 (12)	13 (52)	–	8 (4)	–	35 (49)
–	–	–	–	–	3 (12)	–	9 (4)	–	–
Grade 4									
–	0	0	–	0	0	0	–	–	1 (1)
–	0	0	–	3 (5)	0	0	–	–	–
–	0	0	–	1 (2)	1 (4)	0	–	–	1 (1)
–	0	0	–	–	0	0	–	–	–

[27] ($n = 123$) n (%)	[24] ($n = 193$) n (%)	[17] ($n = 27$) n (%)	[22] ($n = 50$) n (%)	[20] ($n = 56$) n (%)	[28] ($n = 25$) n (%)	[31] ($n = 67$) n (%)	[10] ($n = 213$) n (%)	[18] ($n = 65$) n (%)	[29] ($n = 72$) n (%)
68.64–75.5 Gy	80.22 Gy	73.62–77.88 Gy	78.58 Gy	73.14–82.5 Gy	70–80.08 Gy	70–83.16 Gy	75.5–82.98 Gy	91.28 Gy	71.31–96.21 Gy
Grade 1									
–	–	–	–	26 (46)	10 (40)	20 (30)	–	–	50 (69)
–	–	–	–	1 (2)	10 (40)	–	–	–	26 (36)
–	74 (34)	–	–	30 (54)	12 (48)	35 (52)	–	–	31 (43)
Grade 2									
–	–	4 (15)	–	13 (23)	2 (8)	5 (7)	–	–	8 (11)
–	6 (3)	–	–	2 (4)	6 (24)	–	–	–	21 (29)
–	64 (33)	11 (41)	–	19 (34)	11 (44)	19 (28)	–	–	25 (35)
–	13 (7)	–	–	–	–	17 (25)	–	–	–
Grade 3									
–	0	1 (4)	7 (14)	0	8 (32)	0	1 (1)	4 (6)	5 (7)
–	0	–	–	1 (2)	1 (4)	–	0	–	14 (20)
–	0	1 (4)	–	1 (2)	1 (4)	0	1 (1)	3 (5)	7 (10)
–	0	–	21 (42)	–	–	0	0	–	–
Grade 4									
–	0	0	–	0	0	0	–	–	0
16 (15)	0	0	–	0	7 (28)	0	–	–	3 (4)
–	0	0	–	0	0	0	–	–	0
–	0	–	–	–	–	0	–	–	–

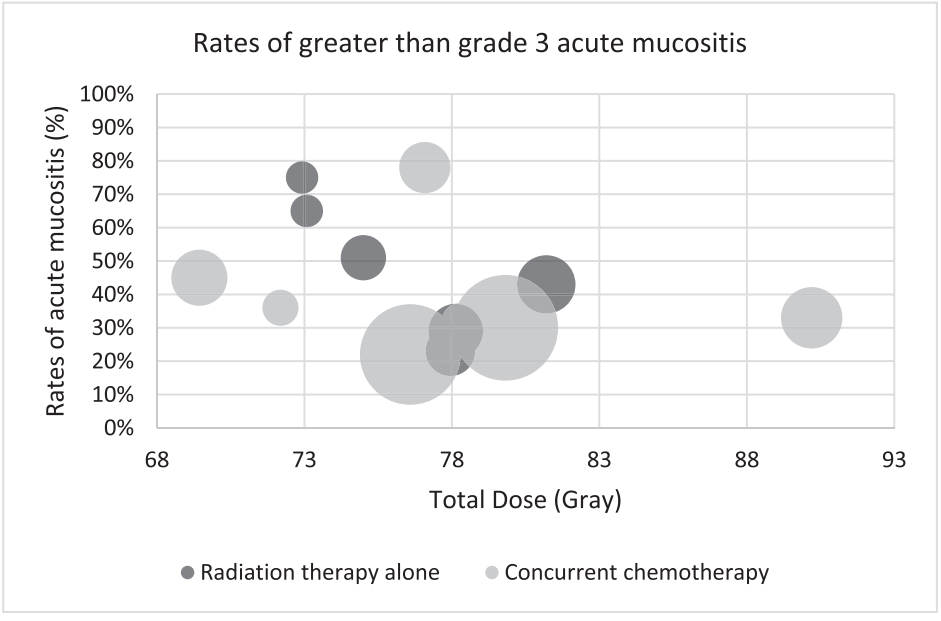
another 414 did not meet the inclusion and exclusion criteria by title and abstract screening. Eleven papers were excluded based on language and 54 were excluded based on the time period limitations. A further 22 papers were excluded after full text review. Most of these excluded studies were inappropriately designed or were not dose escalated above current standard treatments. Eighteen papers were deemed suitable for analysis (see Supplementary Figure S1).

Study Characteristics

Of the 18 studies included in the final analysis, 12 were carried out prospectively, two of which used randomised allocation to study arms. Eight of the studies included NPC alone, with the remainder treating a range of mucosal primary sites. Most focused on treatment of locally advanced disease. A summary of study characteristics is presented in Table 1.



(A)



(B)

Fig 1. Scatter plots showing the percentage rate of grade greater than 3 acute mucositis with different total doses (based on EQD2 using α/β 10 Gy for early effects). The size of the bubble represents the number of participants in each study. (A) Comparison of standard imaging-guided treatment studies versus functional imaging-guided treatment studies. (B) Comparison of studies using concurrent chemotherapy versus those using radiation therapy alone.

Risk of Bias Within Individual Studies

The Joanna Briggs Institute Critical Appraisal Checklist for Case Series was used to assess the quality of papers [32]. Of the 18 papers assessed, 14 papers were deemed to be good quality with a low risk of bias by meeting more than seven of the 10 criteria. The major flaws were clear statements regarding patient selection and sufficient details regarding the study site demographics. Disease outcomes, particularly toxicity profiles, were poorly reported across all studies (see Supplemetary Table S1).

Treatment Schedules

Individual dosing regimens are shown in Table 1. Simultaneous integrated boost was implemented by all studies to escalate dose to the tumour volume. Three studies used hyperfractionated, accelerated regimens with twice daily dosing [18,19,23]. Concurrent chemotherapy was administered in 12 studies. Cisplatin-based chemotherapy was most commonly administered together with 5-fluorouracil, although the specific agent or dose given was not always reported. Cisplatin schedules varied with weekly dosing between 20 and 40 mg/m^2 ($n = 4$) or three weekly dosing of 75–100 mg/m^2 ($n = 5$). There was large heterogeneity within and between studies in the administration of adjuvant or neoadjuvant ('induction') chemotherapy.

Using standard anatomical imaging to guide target delineation, studies delivered doses to the tumour volume of 1.5 Gy up to 2.5 Gy per fraction. Zhao *et al.* [24] delivered 74 Gy in 2.42 Gy daily fractions (EQD2 76.59 Gy_{10}) to 193 participants with NPC. Kwong *et al.* [22] delivered up to an average dose of 79.5 Gy in 2.27 Gy fractions (EQD2 77.08 Gy_{10}). Doses of 76.8 Gy in 37 fractions of 2.07 Gy (EQD2 77.25 Gy_{10}) and 75 Gy in 2.5 Gy fractions (EQD2 78.13 Gy_{10}) were also investigated [17,20]. The highest equivalent dose delivered in this group of studies was a hyperfractionated, accelerated regimen that gave 2 Gy for the first 10 fractions then 1.8 Gy twice daily for the remaining 15 fractions. The boost volume received an additional 1.8 Gy as an integrated boost to a total of 74 Gy (EQD2 81.2 Gy_{10}) [18]. Only a modest increase in total dose, above standard treatments, was achieved by the remaining studies [15,16,21,23,25].

Six studies used functional imaging modalities to guide target delineation for dose escalation purposes. The highest dose delivered was 85.9 Gy in 2.6 Gy fractions (EQD2 90.2 Gy_{10}) by Berwouts *et al.* [29]. Tumour subvolumes were defined by fluorodeoxyglucose-PET (FDG-PET)-guided dose painting using a source-to-background technique. FDG-PET was used by another two studies, which delivered total doses of 77 Gy with the simultaneous integrated boost technique. Wang *et al.* [31] used a standard uptake value of greater than 2.5 as a cut-off for auto-contouring target volumes. Liu *et al.* [10] defined 50% of the maximum standard uptake value isocontour as their boost volume to deliver 2.35 Gy per fraction (EQD2 79.81 Gy_{10}). Fluoromisonidazole is another PET tracer, which was used by one study for boosting hypoxic subvolumes of tumour. A total dose of 77 Gy in 2.2 Gy fractions (EQD2 78.28 Gy_{10}) was delivered in this study [28].

Locoregional Control and Overall Survival

The results of treatment outcomes for NPC and other mucosal primary HNCs can be found in Tables 2 and 3. Outcomes for individual studies were reportedly measured either from the date of diagnosis, the first day of treatment or the last day of treatment. Four papers reported on smoking status. Only one of the six studies that included oropharyngeal cancers reported on HPV status.

Dose escalation in NPC resulted in LRC rates at 3 years of 86.6–100% and 3-year overall survival of 82–95.2%. One study reported on outcomes at 5 years, which reached 96% LRC and 79% overall survival [15]. For all other subsites of mucosal primary HNC, 2-year LRC was 70–95% and overall survival was reported as 69–95%. At 3 years, LRC was 68.2–85.9% and 48.4–51.9% for overall survival. A poor result was seen in a study treating a large number of oral cavity tumours [19]. The 1-year overall survival was reported as 55%. Patients were only included in this study if they had advanced bulky disease and contraindications to chemotherapy.

Toxicity of Dose Escalation

Assessment of patient-reported outcomes was limited, with one study reporting patient scoring of xerostomia, which was graded according to Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment (EORTC) radiation morbidity scoring criteria [25]. Acute and late toxicity scoring within studies was assessed with either the RTOG/EORTC guidelines or various versions of the Common Terminology Criteria for Adverse Events (CTCAE). Individual data for acute and late toxicity profiles are shown in Tables 4 and 5.

The relationship between increased radiation therapy dose and toxicity was analysed using grade greater than 3 acute mucositis events, as this was reported most consistently across studies. Figure 1 shows that there were no definitive trends for developing grade 3 acute mucositis with increased radiation therapy dose. There was also no clear difference between standard and functional imaging-guided treatments. Additionally, the rates of acute mucositis did not differ appreciably when concurrent chemotherapy was used compared with those studies that administered single modality treatment. One study did reach maximum tolerated dose at 2.46 Gy per fraction due to rapid development of grade 3 mucositis. Participants were given a treatment break and were able to finish the course at a lower dose of 2.27 Gy per fraction [15]. The rate of grade greater than 3 acute dermatitis also presented little difference with increased radiation therapy dose.

Reports of late toxicity data were inconsistent across studies. Based on data available there seemed to be no clear association between increasing dose and rates of late toxicity. Reports of late grade 3 xerostomia ranged from 0 to 22% (4/18 participants) between studies. Welz *et al.*

[28] found no significant differences in late toxicity rates between dose escalated and non-dose escalated groups in their study. Studer *et al.* [27] reported an 89% laryngeal preservation rate at a median follow-up of 21 months. Liu *et al.* [17] reported late laryngeal stricture in five participants, with a functional laryngeal preservation rate of 63% at a median follow-up of 36 months. In the NPC group, Bakst *et al.* [30] reported three cases of temporal lobe necrosis, of which one required resection. Two of these participants had T4 disease with intracranial extension of the tumour.

Discussion

Despite modern advances in radiation therapy technology, there remain groups of HNC patients with high failure rates that warrant further investigation to improve treatment outcomes. Patients at high risk of treatment failure are those with a mucosal primary malignancy with the following features: locally advanced disease, negative HPV status and a heavy smoking history [6]. Multimodality treatment is often recommended for these patients. However, some individuals may be unsuitable to receive surgery or systemic therapies due to age, medical comorbidities or tumour factors such as size and location [33]. Adding additional radiation dose to standard schedules is more cost-effective than alternatives such as immunotherapy and less toxic than chemotherapy. With improved target delineation in combination with modern, highly conformal techniques, radiation therapy dose escalation may be a safe and effective solution for this select group of patients.

In patients with locally advanced disease, radiation therapy is an established treatment option that plays a major role in standard treatment guidelines. The NCCN guidelines recommend a number of fractionated schedules delivering between 60 and 70 Gy using modern conformal radiation therapy techniques [1]. The optimal total dose, fractionation schedule and addition of chemotherapy is still under debate, however. This lack of consensus was recently identified by an international survey of 14 radiation oncology centres that reported the routine use of 12 different fractionation schedules for the treatment of HNC. Only three centres were using what is considered to be the 'standard' schedule of 70 Gy in 35 fractions [34]. Given the diversity seen within this group of cancers within the head and neck, a one dose fits all approach is not possible and personalised treatments will figure prominently in the future of oncology.

The present review included studies that delivered altered fractionation schedules to cohorts of patients with newly diagnosed primary HNC, most of whom had locally advanced disease. Considering the advanced staging of many participants, dose escalation in NPC resulted in excellent LRC rates. Compared with the data from the MAC-NPC meta-analysis, the nasopharyngeal studies in this review report similar, if not improved, overall survival and progression-free survival [35]. For all other subsites of mucosal primary HNC, 3-year LRC was 68.2–85.9% and overall survival was 48.4–51.9%, consistent with previous reports using standard treatment schedules [36]. Given the known importance of HPV and smoking status for interpreting disease outcomes, it is unfortunate that these prognostic features were under-reported. Perhaps HPV status was not routinely tested at the time these studies were started. It is recommended that these features are reported in future studies to more accurately interpret disease outcomes between subgroups.

As seen in this review, variance in study design and reporting is a common problem in radiation oncology. The heterogeneity within and between studies in terms of radiation therapy dosing, chemotherapy, tumour characteristics and reporting of outcomes prevents the making of meaningful comparisons. Many of the present studies have small cohorts with short follow-up times and only two of the studies carried out random allocation to study arms. Given that many studies were retrospective, toxicity may be under-reported and is inadequate to inform on late effects of dose escalation at this stage. The use of multiple toxicity scoring guidelines further obscures these results. In an attempt to overcome this limitation, only those toxicities most consistently reported across the review studies were included in the summary table for comparison (Tables 4 and 5). Patient-reported outcomes were not assessed with a validated tool in any of the studies included in the present review, although it is possible that this end point may have been published separately.

There seemed to be no noticeable trends in acute or late toxicity profiles across studies. Despite increasing total dose or the addition of chemotherapy, reported toxicity rates seemed to remain consistent. This is in contrast to other studies showing increased toxicity with the addition of chemotherapy [36]. The reason for this may be related to the small cohort sizes and short follow-up times of the review papers, which are probably under-powered. It may also be due to under-reporting of systemic toxicities in radiation therapy focused studies. Despite the results of this review, it is known that chemotherapy can cause debilitating toxicities such as ototoxicity and peripheral neuropathy. Radiation therapy dose escalation may have a role in removing the need for concurrent chemotherapy in certain patient groups.

Overall, toxicity rates were comparable with non-dose escalated studies [37]. For example, RTOG 91-11 [36] reported a 5-year estimated laryngeal preservation rate of 83.6% (95% confidence interval 78.1–89.2%) with standard treatment that was similar to that reported by Studer *et al.* [327] using FDG-PET-guided dose escalation. These authors carried out careful patient selection for the dose escalation arm, with participants receiving standard treatment if tumour involved substantial parts of the pharynx or larynx. By contrast, Kwong *et al.* [22] dose escalated all participants despite NPC tumour volumes ranging from 32.6 to 281.5 cm^3 and reported grade 3 acute mucositis in 39/50 participants.

In the functional imaging-guided dose escalation subgroup, rates of acute grade greater than 3 mucositis were consistently reported at about 30% or less, despite doses ranging from EQD2 of 72.19 Gy_{10} to 90.2 Gy_{10}. A review of

ClinicalTrials.gov showed an increasing number of registered trials investigating the use of functional imaging modalities for guiding dose escalation studies in HNC [38]. The quantitative data provided by these imaging modalities, such as PET and DW-MRI, can reflect intratumoural heterogeneity, highlighting areas that may be more radioresistant [39]. Wang *et al.* [31] found that 85.7% of participants' tumour volumes were smaller on the FDG-PET imaging compared with computed tomography-based plans. They also found no significant difference in acute or late toxicity between the computed tomography-based non-dose escalated arm and the FDG-PET-guided dose escalated arm, indicating that the smaller volumes may allow for higher doses to be delivered.

A trial by Yang *et al.* [40] showed the benefits of creating smaller tumour volumes. They randomly assigned 212 participants with locoregionally advanced NPC to be planned based on pre-induction chemotherapy imaging or post-induction chemotherapy imaging. Using the post-induction chemotherapy imaging for contouring, lower doses were delivered to surrounding organs at risk, resulting in improved toxicity rates and quality of life scores. Overall survival and LRC remained similar in both groups. Finding methods to adapt and reduce the high dose volume is required if dose escalation is to be achieved safely.

The highest dose delivered by the studies in this review was 85.9 Gy in 2.6 Gy fractions (EQD2 90.2 Gy_{10}) given concurrently with chemotherapy using a FDG-PET-guided dose painting technique [29]. Considering the 20 Gy_{10} difference between the study arms in this trial, it is not surprising that significantly higher toxicity rates were reported in the dose escalated group ($P = 0.004$). However, this difference was reduced when adaptive planning was utilised. Significantly, they also observed an absolute benefit in local control of 8.7% at 5 years with FDG-PET-guided dose escalation ($P = 0.36$) [29]. The more recent ARTFORCE trial also aims to implement FDG-PET driven adaptive dose escalation in combination with biological markers for improved patient selection [41]. This study is designed to redistribute dose to FDG-PET avid areas, with the high-risk volume receiving up to 80 Gy in 35 fractions. The results of this study will contribute to our understanding of functional imaging-guided dose escalation.

PET was the functional imaging modality used by the studies in this review to create boost contours for dose escalation. As with anatomical imaging modalities, PET and other functional imaging sequences can still give false-positive and -negative results and should be interpreted with caution [42]. PET in particular is prone to false positives when there is inflammation of tissues [28,43]. MRI is increasingly used clinically for the diagnosis and work up of many types of cancer and there is increasing evidence for its use in HNC radiation therapy treatment planning [44,45]. DW-MRI, dynamic contrast enhanced MRI and spectroscopy are all types of MRI sequence that provide functional information. MRI has excellent soft tissue contrast, is a cost-effective alternative to PET and gives no additional radiation dose. This should be considered a future area for research in HNC target delineation with or without dose escalation.

This review had a number of exclusion criteria in an attempt to reduce the study heterogeneity. There are many planning studies in the literature that have experimented with very high doses of radiation therapy. However, given the lack of toxicity data from these studies, they were not deemed suitable for comparison. A small number of researchers have also looked at stereotactic radiation therapy with wide ranging schedules and significant methodological heterogeneity within individual studies reducing their quality. Regarding the studies that were included in the present review, the paucity of good quality reporting of outcomes reduced the strength of the findings. The use of validated, standardised tools for assessing patient-reported outcomes would be an important inclusion for future research, enabling holistic assessment of the impact of dose escalation on quality of life.

Conclusion

This review has highlighted the future possibilities of radiation therapy dose escalation in mucosal primary head and neck squamous cell carcinoma. Caution is advised when interpreting the findings due to the heterogeneity and poor reporting of included studies. Importantly, there is a scarcity of documentation regarding patient- or tumour-related variables, which could influence outcomes. However, based on the available data, dose escalation seems to be feasible to at least 10 Gy_{10} above conventionally recommended dose and fractionation. Cases of poor disease control and overall survival were evident within the included studies, highlighting the need for careful patient selection. By providing improved target delineation, the utilisation of functional imaging modalities in treatment planning may improve outcomes without increasing toxicity rates. Further prospective randomised controlled trials are needed to provide reliable data for the future treatment of HNC.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.12.004.

References

[1] Pfister DG, Spencer S, Adelstein D, Adkins D, Brizel DM, Burtness B, *et al. NCCN guidelines version 2.2018 head and neck cancers* 2018.

[2] Australian Institute of Health and Welfare. *Head and neck cancers in Australia* 2014.

[3] Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, *et al.* Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019;393:51–60. https://doi.org/10.1016/S0140-6736(18)32752-1.

[4] Seiwert TY, Foster CC, Blair EA, Karrison TG, Agrawal N, Melotek JM, *et al*. Optima: a phase II dose and volume de-escalation trial for human papillomavirus-positive oropharyngeal cancer. *Ann Oncol* 2019;30:297–302. https://doi.org/10.1093/annonc/mdy522.

[5] Ma DJ, Price KA, Moore EJ, Patel SH, Hinni ML, Garcia JJ, *et al*. Phase II evaluation of aggressive dose de-escalation for adjuvant chemoradiotherapy in human papillomavirus–associated oropharynx squamous cell carcinoma. *J Clin Oncol* 2019;37:1909–1918. https://doi.org/10.1200/jco.19.00463.

[6] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal D, Nguyen-Tan PF, *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24–35. https://doi.org/10.1111/j.1365-2214.2010.01145_7.x.

[7] Teoh M, Beveridge S, Wood K, Whitaker S, Adams E, Rickard D, *et al*. Volumetric-modulated arc therapy (RapidArc) vs. conventional fixed-field intensity-modulated radiotherapy for 18F-FDG-PET-guided dose escalation in oropharyngeal cancer: a planning study. *Med Dosim* 2013;38:18–24. https://doi.org/10.1016/j.meddos.2012.05.002.

[8] Lee DS, Kim YS, Cheon JS, Song JH, Son SH, Jang JS, *et al*. Long-term outcome and toxicity of hypofractionated stereotactic body radiotherapy as a boost treatment for head and neck cancer: the importance of boost volume assessment. *Radiat Oncol* 2012;7:85. https://doi.org/10.1186/1748-717X-7-85.

[9] Le Q-T, Tate D, Koong A, Gibbs IC, Chang SD, Adler JR, *et al*. Improved local control with stereotactic radiosurgical boost in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol* 2003;56:1046–1054. https://doi.org/10.1016/S0360-3016(03)00117-2.

[10] Liu F, Xi X-p, Wang H, Han Y-q, Xiao F, Hu Y, *et al*. PET/CT-guided dose-painting versus CT-based intensity modulated radiation therapy in locoregional advanced nasopharyngeal carcinoma. *Radiat Oncol* 2017;12:1–10. https://doi.org/10.1186/s13014-016-0739-y.

[11] Joiner M. *Basic clinical radiobiology*, 5th ed. Abingdon: Taylor & Francis Group; 2019.

[12] Dirix P, Vandecaveye V, De Keyzer F, Stroobants S, Hermans R, Nuyts S. Dose painting in radiotherapy for head and neck squamous cell carcinoma: value of repeated functional imaging with 18F-FDG PET, 18F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI. *J Nucl Med* 2009;50:1020–1027. https://doi.org/10.2967/jnumed.109.062638.

[13] van Leeuwen CM, Oei AL, Crezee J, Bel A, Franken NAP, Stalpers LJA, *et al*. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. *Radiat Oncol* 2018;13:96. https://doi.org/10.1186/s13014-018-1040-z.

[14] Fowler JF. 21 years of biologically effective dose. *Br J Radiol* 2010;83:554–568. https://doi.org/10.1259/bjr/31372149.

[15] Lauve A, Morris M, Schmidt-Ullrich R, Wu Q, Mohan R, Abayomi O, *et al*. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II — clinical results. *Int J Radiat Oncol Biol Phys* 2004;60:374–387. https://doi.org/10.1016/j.ijrobp.2004.03.010.

[16] Chakraborty S, Ghoshal S, Patil V, Oinam A, Sharma S. Preliminary results of SIB-IMRT in head and neck cancers: report from a regional cancer center in northern India. *J Cancer Res Ther* 2009;5:165. https://doi.org/10.4103/0973-1482.57121.

[17] Liu WS, Hsin CH, Chou YH, Liu JT, Wu MF, Tseng SW, *et al*. Long-term results of intensity-modulated radiotherapy concomitant with chemotherapy for hypopharyngeal carcinoma aimed at laryngeal preservation. *BMC Cancer* 2010;10:102. https://doi.org/10.1186/1471-2407-10-102.

[18] Kubes J, Cvek J, Vondracek V, Pala M, Feltl D. Accelerated radiotherapy with concomitant boost technique (69.5 Gy/5 weeks): an alternative in the treatment of locally advanced head and neck cancer. *Strahlenther Onkol* 2011;187:651–655. https://doi.org/10.1007/s00066-011-2246-2.

[19] Cvek J, Kubes J, Skacelikova E, Otahal B, Kominek P, Halamka M, *et al*. Hyperfractionated accelerated radiotherapy with concomitant integrated boost of 70-75 Gy in 5 weeks for advanced head and neck cancer. A phase I dose escalation study. *Strahlenther Onkol* 2012;188:666–670. https://doi.org/10.1007/s00066-012-0128-x.

[20] Leclerc M, Maingon P, Hamoir M, Dalban C, Calais G, Nuyts S, *et al*. A dose escalation study with intensity modulated radiation therapy (IMRT) in T2N0, T2N1, T3N0 squamous cell carcinomas (SCC) of the oropharynx, larynx and hypopharynx using a simultaneous integrated boost (SIB) approach. *Radiother Oncol* 2013;106:333–340. https://doi.org/10.1016/j.radonc.2013.03.002.

[21] Gujral DM, Miah AB, Bodla S, Richards TM, Welsh L, Schick U, *et al*. Final long-term results of a phase I/II study of dose-escalated intensity-modulated radiotherapy for locally advanced laryngo-hypopharyngeal cancers. *Oral Oncol* 2014;50:1089–1097. https://doi.org/10.1016/j.oraloncology.2014.07.018.

[22] Kwong DLW, Sham JST, Leung LHT, Cheng ACK, Ng WM, Kwong PWK, *et al*. Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;64:374–381. https://doi.org/10.1016/j.ijrobp.2005.07.968.

[23] Lu JJ, Kong L, Shakespeare TP, Loh KS, Zhang Q, Siang K, *et al*. Prospective phase II trial of concomitant boost radiotherapy for stage II nasopharyngeal carcinoma. *Oral Oncol* 2008;44:703–709. https://doi.org/10.1016/j.oraloncology.2007.09.005.

[24] Zhao LN, Zhou B, Shi M, Wang JH, Xiao F, Xu M, *et al*. Clinical outcome for nasopharyngeal carcinoma with predominantly WHO II histology treated with intensity-modulated radiation therapy in non-endemic region of China. *Oral Oncol* 2012;48:864–869. https://doi.org/10.1016/j.oraloncology.2012.03.001.

[25] Saleh-Ebrahimi L, Zwicker F, Muenter MW, Bischof M, Lindel K, Debus J, *et al*. Intensity modulated radiotherapy (IMRT) combined with concurrent but not adjuvant chemotherapy in primary nasopharyngeal cancer – a retrospective single center analysis. *Radiat Oncol* 2013;8:20. https://doi.org/10.1186/1748-717X-8-20.

[26] Kong F, Ying H, Du C, Huang S, Zhou J, Chen J, *et al*. Patterns of local-regional failure after primary intensity modulated radiotherapy for nasopharyngeal carcinoma. *Radiat Oncol* 2014;9:1–7. https://doi.org/10.1186/1748-717X-9-60.

[27] Studer G, Peponi E, Kloeck S, Dossenbach T, Huber G, Glanzmann C. Surviving hypopharynx-larynx carcinoma in the era of IMRT. *Int J Radiat Oncol Biol Phys* 2010;77:1391–1396. https://doi.org/10.1016/j.ijrobp.2009.07.005.

[28] Welz S, Mönnich D, Pfannenberg C, Nikolaou K, Reimold M, La Fougère C, *et al*. Prognostic value of dynamic hypoxia PET in head and neck cancer: results from a planned interim analysis of a randomized phase II hypoxia-image guided dose escalation trial. *Radiother Oncol* 2017;124:526–532. https://doi.org/10.1016/j.radonc.2017.04.004.

[29] Berwouts D, Madani I, Duprez F, Olteanu AML, Vercauteren T, Boterberg T, *et al*. Long-term outcome of 18F-fluorodeoxyglucose-positron emission tomography-guided dose painting for head and neck cancer: matched case-control study. *Head Neck* 2017;39:2264–2275. https://doi.org/10.1002/hed.24892.

[30] Bakst RL, Lee N, Pfister DG, Zelefsky MJ, Hunt MA, Kraus DH. Hypofractionated dose-painting intensity modulated

radiation therapy with chemotherapy for nasopharyngeal carcinoma, a prospective trial. *Int J Radiat Oncol Biol Phys* 2011;80:148–153. https://doi.org/10.1016/j.ijrobp.2010.01.026.

[31] Wang J, Zheng J, Tang T, Zhu F, Yao Y, Xu J, *et al*. A randomized pilot trial comparing position emission tomography (PET)-guided dose escalation radiotherapy to conventional radiotherapy in chemoradiotherapy treatment of locally advanced nasopharyngeal carcinoma. *PLoS One* 2015;10:e0124018. https://doi.org/10.1371/journal.pone.0124018.

[32] Joanna Briggs Institute. *JBI critical appraisal checklist for case series* 2017. Available at: http://joannabriggs.org/research/critical-appraisal-tools.html.

[33] Nottage MK, Lin C, Hughes BGM, Kenny L, Smith DD, Houston K, *et al*. Prospective study of definitive chemoradiation in locally or regionally advanced squamous cell carcinoma of the skin. *Head Neck* 2017;39:679–683. https://doi.org/10.1002/HED.

[34] Ho KF, Fowler JF, Sykes AJ, Yap BK, Lee LW, Slevin NJ. IMRT dose fractionation for head and neck cancer: variation in current approaches will make standardisation difficult. *Acta Oncol* 2009;48:431–439. https://doi.org/10.1080/02841860802372272.

[35] Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, *et al*. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol* 2015;16:645–655. https://doi.org/10.1016/S1470-2045(15)70126-9.

[36] Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, *et al*. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845–852. https://doi.org/10.1200/JCO.2012.43.6097.

[37] Nutting CM, Morden JP, Harrington KJ, Sydenham MA, Emson M, Hall E, *et al*. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127–136. https://doi.org/10.1016/S1470.

[38] Grégoire V, Thorwarth D, Lee JA. Molecular imaging-guided radiotherapy for the treatment of head-and-neck squamous cell carcinoma: does it fulfil the promises? *Semin Radiat Oncol* 2018;28:35–45. https://doi.org/10.1016/j.semradonc.2017.08.003.

[39] Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. *Radiology* 2016;278:563–577. https://doi.org/10.1148/radiol.2015151169.

[40] Yang H, Chen X, Lin S, Rong J, Yang M, Wen Q, *et al*. Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a prospective, multi-center, randomized clinical trial. *Radiother Oncol* 2018;126:37–42. https://doi.org/10.1016/j.radonc.2017.07.020.

[41] Heukelom J, Hamming O, Bartelink H, Hoebers F, Giralt J, Herlestam T, *et al*. Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE); a randomized controlled phase II trial for individualized treatment of head and neck cancer. *BMC Cancer* 2013;13:1. https://doi.org/10.1186/1471-2407-13-84.

[42] Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JPA. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst* 2008;100:712–720. https://doi.org/10.1093/jnci/djn125.

[43] Troost EGC, Bussink J, Hoffmann AL, Boerman OC, Oyen WJG, Kaanders JHAM. 18F-FLT PET/CT for early response monitoring and dose escalation in oropharyngeal tumors. *J Nucl Med* 2010;51:866–874. https://doi.org/10.2967/jnumed.109.069310.

[44] Driessen JP, Van Kempen PMW, Van Der Heijden GJ, Philippens MEP, Pameijer FA, Stegeman I, *et al*. Diffusion-weighted imaging in head and neck squamous cell carcinomas: a systematic review. *Head Neck* 2015;37:440–448. https://doi.org/10.1002/hed.23575.

[45] De Felice F, Musio D, Bulzonetti N, Maghella F, Tombolini V. Target volume delineation based on diffusion-weighted magnetic resonance imaging for locally advanced head and neck cancer. *Anticancer Res* 2016;36:4181–4186.