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RESEARCH PAPER

Impact of elective nodal irradiation ≥ 60 Gy on severe weight loss during intensity-modulated radiation therapy in patients with head and neck squamous cell carcinoma

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ABSTRACT

Background: This study aimed to investigate the association between radiotherapy-related factors and the incidence of severe weight loss (WL) during radiotherapy in patients with head and neck squamous cell carcinoma (HNSCC) in the intensity-modulated radiation therapy (IMRT) era.

Materials and methods: Seventy-nine patients with HNSCC who received IMRT between January 2011 and December 2020 were reviewed. The 10% WL was defined as severe WL. The median prescribed doses of IMRT were 70 Gy for the high-risk planning target volume (HRPTV); 60 Gy for the intermediate-risk planning target volume (IRPTV); 54 Gy for the low-risk PTV.

Results: Larger volumes of ≥ 60 Gy (PTV60Gy) had a significant impact on WL, whereas volumes of ≥ 70 Gy and ≥ 54 Gy did not. PTV60Gy to the ipsilateral level II or III necks had a significant impact on WL, whereas PTV60Gy to the ipsilateral levels I, IV, V, or VII did not. The primary site of the nasopharynx/oropharynx had a significant impact on WL, whereas the hypopharynx/larynx did not. In the stepwise regression and multivariate analyses, primary site and PTV60Gy volume were important factors for severe WL.

Conclusions: Reducing the PTV60Gy volume can be useful in reducing severe WL. Because the clinical significance of IRPTV is unclear, the omission of IRPTV should be considered while balancing risks and benefits.

Key words: weight loss; planning target volume; intensity-modulated radiation therapy; head and neck; squamous cell carcinoma

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Introduction

Weight loss (WL) is often observed during radiotherapy for head and neck squamous cell carcinoma (HNSCC). WL is mainly induced by radiation mucositis of the oral cavity and pharynx. Although the effects of WL before radiotherapy have consistently been reported to be associated with decreased overall survival, the effects of WL during radiotherapy are controversial [1–3].

WL during radiotherapy occurs even in modern precise radiotherapy, such as intensity-modulat-

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ed radiation therapy (IMRT), including volumetric modulated arc therapy (VMAT), and leads to anatomical changes affecting dose distribution [4]. Although some studies suggest that routine replanning is not necessary during IMRT, it has a significant benefit in appropriately selected patients [5, 6].

Some studies have demonstrated the association between planning target volume (PTV) and WL during radiotherapy [7, 8]. However, there has been no detailed assessment of the relationship between prescribed doses, the volume of PTV, and PTV sites in the neck. Some institutions (including ours) use the lymph node regions adjacent to the primary tumor and/or metastatic lymph nodes as intermediate-risk PTV (IRPTV) and irradiate this area at higher doses than other prophylactic neck regions [low-risk PTV (LRPTV)] [9], despite the absence of gross tumors; however, the necessity of IRPTV remains unclear [10]. Therefore, this study aimed to evaluate the relationship between doses/volume/sites of the PTV and WL during IMRT treatment for HNSCC.

Materials and methods

Participants

In total, 79 patients with HNSCC who were treated with IMRT between January 2011 and December 2020 at our institution were reviewed. This retrospective study was approved by the institutional review board of our institution.

IMRT was delivered using a 6-MV X-ray from a linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA, USA). The gross tumor volumes plus 5–10 mm margins were defined as high-risk clinical target volume (HRCTV). Lymph node regions adjacent to the primary tumor and/or metastatic lymph nodes were defined as intermediate-risk clinical target volumes (IRCTV). Whereas the prophylactic regions of the neck were defined as low-risk clinical target volume (LRCTV). The planning target volumes were made by adding 5 mm margins to the HRCTV, IRCTV, and LRCTV (HRPTV, IRPTV, and LRPTV, respectively). The most common treatment plan was as follows: 70 Gy delivered in 35 fractions to the HRPTV, 60 Gy delivered in 35 fractions to the IRPTV, and 54 Gy delivered in 35 fractions to the LRPTV.

Concurrent chemo/biotherapy was administered to 65 patients (platinum, n = 59; cetuximab, n = 6). Platinum chemotherapy consisted of cisplatin 80 mg/m^2 every three weeks. The cisplatin dosage was reduced or switched to carboplatin, considering the general condition of the patients. Cetuximab was initiated one week before radiotherapy at a loading dose of 400 mg/m^2, followed by a weekly infusion of 250 mg/m^2 or the duration of radiotherapy.

The patients were divided into two groups using a cut-off of 10% WL (= severe WL). Body weight was measured at the beginning and every week during IMRT treatment. Image guidance for the set-up was performed before all fractions of the IMRT treatment. In addition, WL was compared between the start of IMRT and the time of the most minimal weight. When oral intake became difficult during IMRT treatment, percutaneous endoscopic gastrostomy feeding, nasogastric tube feeding gastrostomy, or intravenous hyperalimentation was performed.

Statistical analyses

Statistical analyses were performed using the JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA). Descriptive statistics were generated for percentage WL, as well as patient-, disease-, and treatment-related factors. Because there were no established optimal cutoff values for each PTV volume for predicting WL, receiver operating characteristic (ROC) curve analysis was performed. Fisher's exact test was performed to test the different risk factor groups against the likelihood of a 10% WL. Stepwise regression analysis (a combination of forward selection and backward elimination) with the minimum corrected Akaike Information Criterion (AICc) was performed to select the optimal factors. Finally, the optimal risk factors were used in logistic regression analysis.

Results

Between January 2011 and December 2020, 95 patients with HNSCC were treated with IMRT, including VMAT, at our institution. Of these, 16 patients treated with three-dimensional radiotherapy and IMRT (hybrid radiotherapy) were excluded from the study. Finally, we retrospectively evaluated the remaining 79 patients with HNSCC (nasopharynx, 24; oropharynx, 18; hypopharynx, 30; larynx, 7) treated with IMRT using SIB methods. The details of these characteristics are shown in Table 1.

Table 1. Patients' characteristics

Characteristic		No. of patients	%
Age	**Median 64 years (25–92 years)**		
	< 65 years	44	55.7
	≥ 65 years	35	44.3
Sex	Male	67	84.8
	Female	12	15.2
Primary tumor sites	Nasopharynx	24	30.4
	Oropharynx	18	22.8
	Hypopharynx	30	38.0
	Larynx	7	8.9
Pretreatment BMI	**Median 20.4 (13.3–30.1)**		
	< 20	34	43,0
	≥ 20	45	57,0
PS	0	58	73.4
	≥1	21	26.6
TNM (UICC 7th)	**cStage**		
	< 3	16	20.3
	≥ 3	63	79.7
	cT		
	< 3	43	54.4
	≥ 3	36	45.6
	cN		
	0	26	32.9
	≥ 1	53	67.1
Systemic therapy	Yes	65	82.3
	No	14	17.7
Radiation dose	HRPTV	Median 70 Gy (66–70 Gy)	
	IRPTV	Median 60 Gy (60–63 Gy)	
	LRPTV	Median 54 Gy (54–56 Gy)	

BMI — body mass index; PS — performance status; TNM — tumor–node–metastasis; UICC — Union for International Cancer Control; HRPTV — high risk planning target volume; IRPTV — intermediate risk planning target volume; LRPTV — low risk planning target volume

The median WL and percentage of WL during IMRT treatment were 5.1 kg (range, 0–13.3 kg) and 8.5% (range, 0–18.2%), respectively. In addition, 31 patients (39%) had severe WL (≥ 10%) and 16 patients (20%) received nutritional support (percutaneous endoscopy gastrostomy, 3; nasogastric tube, 9; intravenous hyperalimentation, 4) due to disturbance of oral intake in the late phase of IMRT treatment.

Incidence of severe WL according to PTV volumes receiving ≥ 70 Gy, ≥ 60 Gy, and ≥ 54 Gy

The areas under the ROC curves for total PTV volumes receiving ≥ 70 Gy (PTV70Gy), ≥ 60 Gy (PTV60Gy), and ≥ 54 Gy (PTV54Gy) were 0.53 (sensitivity, 84%; specificity, 27%), 0.56 (sensitivity, 81%; specificity, 37%), and 0.59 (sensitivity, 94%; specificity, 37%), respectively. For severe WL, PTV54Gy, PTV70Gy, and PTV60Gy volumes of 615 cm^3, 90 cm^3, and 344 cm^3, respectively, correspond to the maximum sum of sensitivity and specificity.

The incidence of severe WL was 25.0% (6/24), 45.5% (25/55), 13.6% (3/22), 49.1% (28/57), 31.3% (5/16), and 41.3% (26/63) in patients with PTV70Gy < 90 cm^3, PTV70Gy ≥90 cm^3 ($p = 0.13$), PTV60Gy < 344 cm^3, PTV60Gy ≥ 344 cm^3 ($p < 0.01$), PTV54Gy < 615 cm^3, and PTV54Gy ≥ 615 cm^3 ($p = 0.57$), respectively (Tab. 2). In addition, the in-

Table 2. Incidence of severe weight loss (WL) during intensity-modulated radiation therapy (IMRT) treatment according to planning target volume (PTV)

Factors		> 10% WL	p
HRPTV + IRPTV + LRPTV (≥ 54 Gy)	< 615	31.3% (5/16)	0.06
	≥ 615	41.3% (26/63)	
HRPTV + IRPTV (≥60 Gy)	< 344	13.6% (3/22)	< 0.01
	≥ 344	49.1% (28/57)	
HRPTV (≥ 70 Gy)	< 90	25.0% (6/24)	0.13
	≥ 90	45.5% (25/55)	

SD — standard deviation; HRPTV — high risk planning target volume; IRPTV — intermediate risk planning target volume; LRPTV — low risk planning target volume

Table 3. Incidence of severe weight loss during intensity-modulated radiation therapy (IMRT) treatment according to each planning target volume (PTV)

Factors		PTV region of ≥ 70 Gy		PTV region of ≥ 60 Gy		PTV region of ≥ 54 Gy	
Lymphatic region		> 10% WL	p	> 10% WL	p	> 10% WL	p
Level I	No (control)	38.7% (29/75)	–	32.3% (10/31)	–	28.6% (4/14)	–
	Ipsilateral	0% (0/1)	> 0.99	34.5% (10/29)	> 0.99	36.0% (9/25)	0.73
	Bilateral	66.7% (2/3)	0.56	57.9% (11/19)	0.09	45.0% (18/40)	0.35
Level II	No (control)	34.6% (9/26)	–	13.3% (2/15)	–	–	–
	Ipsilateral	40.0% (10/25)	0.78	57.1% (8/14)	0.02	–	–
	Bilateral	42.9% (12/28)	0.59	42.0% (21/50)	0.04	39.2% (31/79)	–
Level III	No (control)	28.2% (13/34)	–	12.5% (2/16)	–	–	–
	Ipsilateral	37.8% (11/29)	> 0.99	55.0% (11/20)	0.01	–	–
	Bilateral	43.8% (7/16)	0.76	41.9% (18/43)	0.03	39.2% (31/79)	–
Level IV	No (control)	37.5% (24/64)	–	23.1% (6/26)	–	0% (0/4)	–
	Ipsilateral	55.6% (5/9)	0.47	33.3% (7/21)	0.56	–	–
	Bilateral	33.3% (2/6)	> 0.99	44.1% (15/34)	0.11	41.3% (31/75)	0.15
Level V	No (control)	39.5% (30/76)	–	25.7% (9/35)	–	21.4% (3/14)	–
	Ipsilateral	33.3% (1/3)	> 0.99	33.3% (7/21)	0.56	30.8% (4/13)	0.68
	Bilateral	–	–	65.2% (15/23)	0.01	46.2% (24/52)	0.13
Level VII	No (control)	36.8% (25/68)	–	20.0% (4/20)	-	33.3% (2/6)	–
	Ipsilateral	71.4% (5/7)	0.11	41.7% (10/24)	0.20	28.6% (2/7)	> 0.99
	Bilateral	25.0% (1/4)	> 0.99	48.6% (17/35)	0.05	40.9% (27/66)	> 0.99

cidence of severe WL was 28.3% (13/46) and 54.6% (18/33) in patients with IRPTV/PTV60Gy < 0.78 and IRPTV/PTV60Gy ≥ 0.78 (p = 0.02), respectively.

Site of the lymphatic region receiving ≥ 60 Gy and incidence of severe WL

The incidence of severe WL was 57.1% (8/14) in patients with PTV60Gy of ipsilateral level II neck, 13.3% (2/15) in patients with PTV60Gy of no level II neck (p = 0.02), 55.0% (11/20) in patients with PTV60Gy of ipsilateral level III neck, 12.5% (2/16) in patients with PTV60Gy of no level III neck (p = 0.01), 65.2% (15/23) in patients with PTV60Gy of bilateral level V neck, 25.7% (9/35) in patients with PTV60Gy of no level V neck (p = 0.01), 48.6% (17/35) in patients with PTV60Gy of bilateral level VII neck, and 20.0% (4/20) in patients with PTV60Gy of level VII neck (p = 0.05, Tab. 3).

Incidence of severe WL according to other factors

The incidence of severe WL was 52.4% (22/42) in patients with hypopharyngeal or laryngeal can-

Table 4. Incidence of severe weight loss (WL) during intensity-modulated radiation therapy (IMRT) according to other factors

Factors		> 10% WL	p
Age	< 65 years	40.9% (18/44)	0.82
	≥ 65 years	37.1% (13/35)	
Sex	Male	31.3% (21/67)	< 0.01
	Female	83.3% (10/12)	
Primary tumor sites	Nasopharynx/oropharynx	52.4% (22/42)	0.01
	Hypopharynx/larynx	24.3% (9/37)	
Pretreatment BMI	< 20	44.1% (15/34)	0.49
	≥ 20	35.6% (16/45)	
PS	0	41.4% (24/58)	0.61
	≥ 1	33.3% (7/21)	
cStage	<3	31.3% (5/16)	0.57
	≥ 3	41.3% (26/63)	
cT	< 3	39.5% (17/43)	> 0.99
	≥ 3	38.9% (14/36)	
cN	< 2	37.1% (13/35)	0.82
	≥ 2	40.9% (18/44)	
Systemic therapy	Yes	44.6% (29/65)	0.04
	No	14.3% (2/14)	
Dmean of parotid gland	< 25.9	30.6% (11/36)	0,17
	≥ 25.9	46.5% (20/43)	
Dmean of oral cavity	< 41.7	30.0% (12/40)	0.11
	≥ 41.7	48.7% (19/39)	

PTV — planning target volume; BMI — body mass index; PS — performance status; SD — standard deviation; Dmean — mean dose

cer and 24.3% (9/37) in those with nasopharyngeal or oropharyngeal cancer (p = 0.01, Tab. 4). In addition, sex (male *vs.* female) and systemic therapy (yes *vs.* no) were statistically significant factors (p < 0.01 and 0.04, respectively) (Tab. 4) for the incidence of severe WL.

Stepwise selection and multivariate analysis

Stepwise regression analysis with a cut-off p-value of 0.10 was performed including the abovementioned statistically significant clinical and PTV factors. The results revealed that three factors, primary site, PTV60Gy volume, and systemic therapy were selected for evaluation. In the multivariate analysis, primary site [odds ratio (OR): 3.0; 95% confidence interval (CI): 1.0–8.5; p = 0.04) and PTV60Gy ≥ 344 cm^3 (OR: 4.7; 95% CI: 1.0–24.4; p = 0.04, Tab. 5) were significant independent unfavorable factors for severe WL during IMRT treatment. Systemic therapy was not a significant unfavorable factor for severe WL (OR: 3.3; 95% CI: 0.6–19.3; p = 0.18, Tab. 5).

PTV60Gy ≥ 344 cm^3 was significantly correlated with radiation-induced mucositis ≥ Grade 3 of Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (p = 0.02); however, primary site was not correlated with radiation-induced mucositis ≥ Grade 3 (p = 0.62). In addition, the incidence of severe WL with mucositis ≥ Grade 3 *vs.* < Grade 3 was 57.9% (11/19) and 23.5% (4/17), respectively (p = 0.05).

Discussion

In our study, severe WL during IMRT treatment was associated with primary site and PTV60Gy volume. Sites of PTV60Gy were not the parameters that had a high correlation with the severe WL during IMRT treatment.

Mallick et al. investigated factors associated with WL during radiotherapy [8]. They mentioned

Table 5. Multiple logistic regression analysis of severe weight loss during intensity-modulated radiation therapy (IMRT)

Factors		OR (95% CI)	p
Primary site	Hypopharynx/larynx	3.0 (1.0–8.5)	0.04
	Nasopharynx/oropharynx		
HRPTV + IRPTV (≥ 60 Gy)	< 344	4.7 (1.0–24.4)	0.04
	≥ 344		
Systemic therapy	No	3.3 (0.6–19.3)	0.18
	Yes		

OR — odds ratio; CI — confidence interval; HRPTV — high risk planning target volume; IRPTV — intermediate risk planning target volume

that the total PTV (> 615 cm^3) and PTV70Gy (> 235 cm^3) were statistically significant factors for predicting WL during radiotherapy treatment. In contrast, our study suggested that a large PTV 60 Gy volume (≥ 344 cm^3) was a statistically significant factor for severe WL during IMRT. At present, the necessity of large IRPTV (60 Gy) regions in IMRT for head and neck cancer is unclear [10]. Lee et al. mentioned that the lymph node regions adjacent to the primary tumor and/or metastatic lymph nodes could be considered as IRPTV [9]. In contrast, Hansen et al. stated that the 5 mm margin to the primary tumor and/or metastatic lymph nodes should be considered as IRPTV [11]. Although dose reduction in the LRPTV (54 Gy) and range reduction of IRPTV have been attempted in recent clinical trials and guidelines [11–14], a smaller IRPTV seemed to be preferable in terms of severe WL during IMRT. Furthermore, it may not be necessary to perform IRPTV since there has been no data that indicates IRPTV affects the efficacy of IMRT for head and neck cancer.

In addition, Langius et al. reported the impact of PTV regions (ipsilateral or bilateral *vs*. no) on WL during radiotherapy [7]. However, in their study, two different types of irradiation techniques (IMRT and three-dimensional conformal radiotherapy) were used, which also included patients who received postoperative radiotherapy. Some studies have reported that these factors are important for WL during radiotherapy treatment [8, 15]. In our study, these two factors were excluded. In addition, the PTV regions were divided into lymphatic regions and analyzed to accommodate the IMRT era. Although PTV60Gy regions (ipsilateral level II or III and bilateral level V or VII) were statistically significant factors in univariate analysis, these PTV60Gy regions were not parameters that had the highest correlation with severe WL during IMRT treatment in stepwise and multivariate analyses. Furthermore, these PTV60Gy regions were thought to be confounding factors, and the PTV60Gy volume was found to be more important than the PTV 60 Gy region. In our study, severe mucositis (≥ Grade 3 of the CTCAE v4.0) was correlated with PTV60Gy ≥ 344 cm^3 and influenced severe WL during IMRT treatment. We believe that a large PTV60Gy volume increased mucositis and led to severe WL during IMRT. Although IRPTV was defined as 5 mm margins surrounding the lymph node region adjacent to the primary tumor and/or metastatic lymph nodes, this may have too large margins in terms of severe WL during IMRT.

In our study, the primary tumor site was the significant factor for severe WL during IMRT treatment. This has been reported to influence WL during radiotherapy in some studies [16, 17]. The primary tumor site was included in the abovementioned factor because it is part of the PTV60Gy regions. Because this factor was unchangeable in HNSCC treatment, this would be important as useful predictors for severe WL during IMRT treatment.

There were some limitations to our study owing to its retrospective nature. First, the sample size is small. Therefore, it was necessary to select factors for the multivariate analysis using a stepwise selection. However, because systemic therapy improved treatment outcomes even in elderly patients with HNSCC [18], systemic therapy should be combined with radiotherapy for HNSCC, even if it is a factor associated with severe WL. Second, although the use of nutritional support during IMRT treatment in our study was determined by each physician according to each case, the frequency was sufficiently low. This was important when considering the risk of true severe WL during IMRT treatment because some patients with head and neck cancer prefer to be treated on an outpatient basis. Because only a few reports have examined WL during radiotherapy treatment, we believe that our study showed an important finding in daily clinical practice. Furthermore, recently, dose calculation algorithms have been improved [19]. When dose calculation algorithm improves, it may also affect the dose distribution of IMRT plans. Therefore, updates will be needed regarding WL during IMRT treatment as dose calculation algorithm improves.

In conclusion, a large PTV60Gy (especially in level II or III neck regions) was associated with severe WL during IMRT treatment. Because one of the risk factors for severe WL during IMRT treatment was PTV60Gy, the range reduction of IRPTV seemed to be important in terms of severe WL.

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Conflict of interest

The authors declare that they have no conflict of interest.

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