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Single-Institute Clinical Experiences Using Whole-Field Simultaneous Integrated Boost (SIB) Intensity-Modulated Radiotherapy (IMRT) and Sequential IMRT in Postoperative Patients With Oral Cavity Cancer (OCC)

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Abstract

This study aimed to review clinical experiences using whole-field simultaneous integrated boost (SIB) intensity-modulated radiotherapy (IMRT) and sequential IMRT in postoperative patients with oral cavity cancer (OCC). From November 2006 to December 2014, a total of 182 postoperative patients with OCC who underwent either SIB-IMRT (n = 63) or sequential IMRT (n = 119) were enrolled retrospectively and matched randomly according to multiple risk factors by a computer. The differences were well balanced after patient matching ($P = .38$). The median follow-up time was 65 months. For patients treated with the SIB technique and the sequential technique, the respective mortality rates were 36.8% and 20.0% ($P = .04$). The primary recurrence rates were 26.3% and 10.0% ($P = .02$), respectively. The respective marginal failure rates were 26.7% and 16.7%. A multivariate logistic regression analysis showed that patients who received the SIB technique had a 2.74 times higher risk of death than those who received the sequential technique (95% confidence interval = 1.10-6.79, $P = .03$). Sequential IMRT provided a significantly lower dose to the esophagus (5.2 Gy, $P = .02$) and trachea (4.6 Gy, $P = .03$) than SIB-IMRT. For patients with locally advanced OCC, postoperative sequential IMRT may overcome an unpredictable geographic miss, potentially with a lower marginal failure rate in the primary area. Patients treated by sequential IMRT show equal overall survival benefits to those treated by SIB-IMRT and a lower mortality rate than those treated by SIB-IMRT. Additionally, a reduced dose to the esophagus and trachea compared to sequential IMRT was noted.

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Introduction

The simultaneous integrated boost (SIB) and sequential techniques are 2 common strategies used in daily practice. "Sequential intensity-modulated radiation therapy (IMRT)" is defined as the delivery of the same fraction size of 2 Gy as a single fraction per day, 5 days a week, for 7 weeks to initially treat the elective volume and finally to treat the boost volume in a sequential manner using a "shrinking-field" technique.[1-3] In contrast, if different dose levels are delivered simultaneously during IMRT to different target volumes within a single treatment fraction, that procedure is known as the "SIB-IMRT" technique.[2,4]

Patients with head and neck squamous cell carcinoma (HNSCC) tend to undergo changes in soft tissues and body weight throughout the course of radiotherapy (RT),[5,6] causing great deviation in the dose delivered to the planning target volume (PTV) and normal tissues outside the PTV,[7] which may result in an unpredictable geographic miss.[8] Additionally, SIB-IMRT might present a risk of locoregional failure due to the low marginal doses when the doses given to the adjacent critical structures or other normal tissues are the major concern in the high-dose region.[3,9] The percentage of marginal failure for patients with nasopharyngeal carcinoma (NPC) treated using the SIB technique has been reported to be 12% to 43%.[10,11] The above results suggest that the possibility of a geographic miss using the SIB technique may increase the probability of margin failure more than that using the sequential technique throughout the course of RT.

In the current study, we compared the clinical outcomes of patients who received SIB-IMRT with the outcomes of those who received sequential IMRT after surgery for locally advanced oral cavity cancer (OCC).

Materials and Methods

Patient Characteristics

From December 2006 to December 2014, 196 patients with OCC underwent IMRT with or without SIB at the Far Eastern Memorial Hospital. Of those patients, 182 without a history of disease recurrence after surgery who received RT with or without concurrent chemotherapy were retrospectively enrolled. The data were collected after receiving approval from the institutional review board of the Far Eastern Memorial Hospital (FEMH-IRB, 104008-E). All patients were initially evaluated by a multimodality treatment team consisting of an otolaryngologist, an oral surgeon, a medical oncologist, and a radiation oncologist. Staging investigations included a complete medical history and physical examination, a fiber-optic endoscopic evaluation, complete blood cell counts, liver function tests, a chest X-ray, preoperative magnetic resonance imaging (MRI) of the head and neck region, and a dental evaluation. Bone scans and computed tomography (CT) scans of the chest and abdomen were obtained whenever possible before the beginning of treatment. All tumor specimens were staged according to the tumor-node-metastasis staging system (*American Joint Committee on Cancer Staging Manual, Seventh Edition*).

Radiation Therapy

Computed tomography-based, intensity-modulated RT with 6-MV photons (Tomotherapy, Accuray, Inc, Madison, Wisconsin; Versa HD, Elekta, Crawley, West Sussex, United Kingdom) was employed at our institution. Radiation therapy with or without concurrent chemoradiation therapy (CCRT) was initiated 4 to 6 weeks after surgery using 6-MV photon beams and IMRT with the SIB or sequential technique comprising 1.8- or 2-Gy fractions on 5 consecutive days a week for 7 weeks. The choices of dose and treatment techniques were made at the discretion of the primary oncologist. There were 3 radiation oncologists (Drs A, B, and C) in our department who belonged to the head and neck cancer subspecialty. The percentages of patients treated by Dr A versus Dr B versus Dr C in the SIB and sequential groups were 34.9% versus 6% versus 58.7% and 62.2% versus 8.4% versus 29.4%, respectively. Target regions and normal structures were contoured using the Pinnacle 3 Treatment Planning System (Philips Healthcare, Madison, Wisconsin). The preoperative magnetic resonance images were retrieved on a Pinnacle workstation and fused with the CT images by rigid image registration to contour the postoperative flap and confirm the location of the preoperative gross tumor to avoid miscontouring the gross tumor due to structural changes caused by surgery.

Delineation of Target Volumes

The clinical target volumes (CTVs) were determined as previously reported.[8,12] Briefly, CTV1 was defined as the area encompassing the preoperative gross tumor and postoperative flap plus a 0.8- to 1-cm margin, which included the resection bed along with soft tissue invaded by the tumor or extracapsular extension (ECE) of metastatic neck nodes, lymph nodes if positive, truncating air, and uninvolved bones. CTV2 was defined as a high-risk subclinical area. CTV3 was designated a low-risk area of potential subclinical disease. To account for organ motion and patient setup errors, a margin was added to the CTVs to construct the PTVs. A margin of 3 to 5 mm was added to CTV1 and CTV2 to form PTV1 and PTV2,

respectively, while PTV3 consisted of CTV3 plus a margin of 5 to 7 mm. For SIB-IMRT, PTV1, PTV2, and PTV3 received 66, 59.4, and 54 Gy, respectively, in 33 fractions. For sequential IMRT, PTV1 in high-risk patients with OCC received 64 to 66 Gy, and PTV1 in intermediate-risk patients with OCC received 60 Gy. The PTV2 dose comprised 60 Gy in 30 fractions, and the PTV3 dose comprised 46 Gy in 23 fractions.

Additionally, no more than 20% of any PTV received more than 110% of its prescribed dose, and no more than 1% of any PTV received less than 93% of its prescribed dose. The dose constraints for the organs at risk (OARs) were as follows: (1) a maximum dose of 54 Gy for the brainstem; (2) a maximum dose of 45 Gy for the spinal cord; (3) a maximum dose of 45 Gy for the optic chiasm and optic nerve; (4) a mean dose < 30 Gy for the bilateral parotid glands with a median dose < 26 Gy, for parotid glands with a volume larger than 20 mL, the median dose was < 20 Gy; (5) a mean dose of < 50 Gy for two-thirds of the glottic larynx; (6) a mean dose of < 50 Gy for the inner ear; and (7) a maximum dose of 70 Gy for the mandible.

Chemotherapy

Studies have shown that a close or positive resection margin, extracapsular spread (ECE), perineural invasion (PNI), lymphovascular space involvement (LVSI), primary tumor stage T3 and T4, and 2 or more positive lymph nodes are significant predictors of poor overall survival (OS) and local control in patients with head and neck cancer.[13-15] Patients with any of these prognostic factors underwent concurrent chemotherapy. Concurrent chemotherapy comprised the weekly intravenous administration of cisplatin (30 mg/m^2) plus fluorouracil (425 mg/m^2) and leucovorin (30 mg/m^2).[16-18]

Definition of Relapse and Delineation of Locoregional Failure

When available, images delineating the site of locoregional failure were fused with the treatment planning CT scan. Otherwise, anatomic landmarks were used to determine the failure site. Failure was defined as infield if >95% of the volume of the recurrent tumor fell within the CTV, marginal if 20% to 95% of the volume was within the CTV, and out of field if 20% fell within the CTV.[4]

Follow-Up

All the patients were evaluated at least once a week during RT. Upon the completion of radiation treatment, patients were evaluated every 3 months for the first 2 years. Posttreatment MRI of the oral cavity and neck was performed 1, 3, and 6 months after the completion of RT. Acute toxicities (occurring <90 days after the initiation of RT) were defined and graded according to the Common Terminology Criteria for Adverse Events v3.0. The earliest date of detecting grade 3 or worse toxicity was recorded.

Statistical Methods

Data on demographic characteristics, treatment features, toxicities, and clinical outcome were collected. The follow-up started on November 1, 2006, and ended on December 31, 2014, with a median follow-up period of 65 months (4-96 months). To make the 2 groups of samples similar, the subsite, pathological stage (eg, tumor stage and primary tumor stage) and resection margin status were matched, and then a computer was used to randomly divide patients into 2 groups, and differences were compared after matching. Pearson chi-square/Fisher exact tests were used to compare differences in categorical variables between the SIB and sequential groups. Student *t* test was used to compare continuous variables. Multivariate logistic regression analyses were performed to explore risk factors for death (eg, positive lymph nodes, margin status, and group (SIB vs sequential)) and to determine the relative contribution of each dependent variable to survival. A P value <.05 was considered statistically significant. All analyses were performed using SPSS software (version 20.0, IBM Corporation, Armonk, New York).

Results

Patient Characteristics

A total of 176 men and 6 women were included in this study. As shown in Table 1, the incidences of oral cancers of the tongue and buccal mucosa in the SIB versus sequential groups were 41.3% and 34.9% versus 33.6% and 36.1%, respectively. There were no significant differences between the 2 groups of patients. However, the percentage of patients with a positive resection margin status was significantly higher in the sequential group than in the SIB-IMRT group (23% vs 11%, $P = .012$) before matching (Table 1). The rates of lung, skin, bone, and liver metastasis in the SIB group versus those in the sequential group were 11.7% versus 10.1%, 1.6% versus 2.5%, 3.2% versus 3.4%, and 1.6% versus 0.8%, respectively. The differences were well balanced after patient matching ($P = .38$).

Treatment Outcomes

For patients treated with the SIB and sequential techniques after matching, the mortality rates were 36.8% and 20.0% ($P = .04$), respectively; the primary recurrence rates were 26% and 10% ($P = .02$), respectively. There were no significant differences in other outcomes between the 2 groups (Table 2).

The multivariate logistic regression analysis of death after adjusting for ECE, PNI, LVSI, 2 or more positive lymph nodes, surgical margins, T3, T4, package of overall treatment time (POTT), interval between operation and postoperation RT, and overall treatment time of radiotherapy (OTTRT) showed that patients who received the SIB technique had a 2.74 times higher risk of death than those who received the sequential technique (95% confidence interval [95% CI] = 1.10-6.79, $P = .03$); those with 2 or more positive lymph nodes had a 2.77 times higher risk than those with less than 2 positive

Table 1. Patient Characteristics Before and After Matching.[a]

	Before Matching			After Matching		
	SIB (n = 63)	Sequential (n = 119)		SIB (n = 57)	Sequential (n = 60)	
Variable	n (%)	n (%)	*P* Value	n (%)	n (%)	*P* Value
Age (mean ± SD, years)	51.29 ± 10.71	52.37 ± 0.88	.49	51.05 ± 11.05	52.00 ± 9.99	.63
Sex						
Male	61 (96.8%)	115 (96.6%)	.95	55 (96.5%)	60 (96.8%)	.61[b]
Female	2 (3.2%)	4 (3.4%)		2 (3.5%)	1 (1.7%)	
Subsite						
Oral tongue	26 (41.3%)	40 (33.6%)	.61	26 (45.6%)	23 (38.3%)	.66
Buccal mucosa	22 (34.9%)	43 (36.1%)		22 (38.6%)	28 (46.7%)	
Alveolar ridge	9 (14.3%)	21 (17.6%)		9 (15.8%)	9 (15.0%)	
Resection margin status						
Positive	7 (11.1%)	27 (22.7%)	.012	5 (8.8%)	10 (16.7%)	.38
Close	16 (25.4%)	43 (36.1%)		14 (24.6%)	16 (26.7%)	
Negative	40 (63.5%)	49 (32.8%)		38 (66.7%)	34 (56.7%)	
Extracapsular spread						
Positive	11 (17.5%)	32 (26.9%)	.15	11 (19.3%)	11 (18.3%)	.89
Negative	52 (82.5%)	87 (73.1%)		46 (80.7%)	49 (81.7%)	
Perineural involvement						
Positive	49 (77.8%)	86 (72.3%)	.42	43 (75.4%)	42 (70.0%)	.51
Negative	14 (22.2%)	33 (27.7%)		14 (24.6%)	18 (30.0%)	
Lymphovascular space involvement						
Positive	33 (52.4%)	66 (55.5%)	.76	29 (50.9%)	30 (50.0%)	.92
Negative	30 (47.6%)	53 (44.5%)		28 (49.1%)	30 (50.0%)	
Pathology stage						
Tumor stage						
Stage I	4 (6.3%)	11 (9.2%)	.23	3 (5.3%)	5 (8.3%)	.45
Stage II	8 (12.7%)	22 (18.5%)		7 (12.3%)	11 (18.3%)	
Stage III	19 (30.2%)	21 (17.6%)		18 (31.6%)	12 (20.0%)	
Stage IVA	32 (50.8%)	65 (54.6%)		29 (50.9%)	32 (53.3%)	
Primary tumor stage						
T1	9 (14.3%)	20 (16.8%)	.69	8 (14.0%)	8 (13.3%)	.98
T2	18 (29.0%)	42 (35.3%)		17 (29.8%)	20 (33.3%)	
T3	14 (22.6%)	21 (17.6%)		12 (21.1%)	12 (20.0%)	
T4a	22 (34.9%)	36 (30.3%)		20 (35.1%)	20 (33.3%)	
Regional lymph node stage (LN ≥ 2)						
No	42 (66.7%)	78 (65.6%)	.96	37 (64.9%)	43 (71.7%)	.43
Yes	21 (33.3%)	41 (34.4%)		20 (35.2%)	17 (28.3%)	
Adjuvant concurrent chemotherapy						
Yes	57 (90.5%)	111 (84.9%)	.18	51 (89.4%)	52 (86.7%)	.19
No	6 (9.5%)	18 (15.1%)		6 (10.5%)	8 (13.3%)	
Modality of radiotherapy						
IMRT	32 (50.8%)	64 (53.8%)	.76	28 (49.1%)	32 (53.3%)	.65
HT	31 (49.2%)	55 (46.2%)		29 (50.9%)	28 (46.7%)	
RT dose						
Mean ± SD	64.7 ± 2.9 Gy	65.6 ± 2.9 Gy	.08	64.62 ± 2.9 Gy	65.06 ± 2.9 Gy	.41
POTT						
≤ 13 weeks	46 (73.0%)	78 (65.5%)	.30	42 (73.7%)	43 (71.7%)	.81
> 13 weeks	17 (27.0%)	41 (34.5%)		15 (26.3%)	17 (28.3%)	
IBOR						
≤ 6.5 weeks	47 (74.6%)	101 (84.9%)	.11	42 (73.7%)	50 (83.3%)	.20
> 6.5 weeks	16 (25.4%)	18 (15.1%)		15 (26.3%)	10 (16.7%)	
OTTRT						
≤ 8 weeks	55 (87.3%)	89 (74.8%)	.06	50 (87.7%)	47 (78.3%)	.19
> 8 weeks	8 (12.3%)	30 (25.2%)		7 (12.3%)	13 (21.7%)	

Abbreviations: IBOR, interval between operation and postoperation radiotherapy; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; LN, lymph node; OTTRT, overall treatment time of radiotherapy; POTT, package of overall treatment time. SD, standard deviation; SIB, simultaneous integrated boost.

[a]The *P* value was determined by Fisher's exact test.

[b]Fisher exact test.

Table 2. Pearson's Chi-Square Test Was Used to Compare Differences Between the SIB and Sequential Groups After Matching.

Control rate	SIB (n = 57) n (%)	Sequential (n = 60) n (%)	*P* Value
Mortality rate			
Yes	21 (36.8%)	12 (20.0%)	.04[a]
No	36 (63.2%)	48 (80.0%)	
Disease-free rate			
No	28 (49.1%)	21 (35.0%)	.12
Yes	29 (50.9%)	39 (65.0%)	
Locoregional recurrent rate			
Yes	23 (40.4%)	17 (28.3%)	.17
No	34 (59.6%)	43 (71.7%)	
Region recurrent rate			
Yes	11 (19.3%)	12 (20.0%)	.92
No	46 (80.7%)	48 (80.0%)	
Primary recurrent rate			
Yes	15 (26.3%)	6 (10.0%)	.02[a]
No	42 (73.7%)	54 (90.0%)	

Abbreviation: SIB, simultaneous integrated boost.
[a]$P < .05$.

lymph nodes (95% CI = 1.13-6.77, P =0.03); and those with a POTT of more than 13 weeks had a 2.61 times higher risk than those with a POTT of less than 13 weeks (95% CI = 1.03-6.64, $P = .04$). There was also a trend for an association between death and positive margins (odds ratio = 3.24, 95% CI = 0.94-11.18, $P = .06$).

The Cox regression model showed no difference between the sequential and SIB techniques (hazard ratio [HR] = 0.54, 95% CI = 0.25-1.16, $P = .11$). However, patients with 2 or more positive lymph nodes (HR = 2.32, 95% CI = 1.15-4.67, $P = .02$), positive margins (HR = 3.61, 95% CI = 1.47-8.87, $P = .005$), and an OTTRT of more than 8 weeks (HR = 2.93, 95% CI = 1.15-4.67, $P = .02$) had a significantly higher HR of death.

Local Failure in the Primary Tumor Area for Both Groups

The rate of local failure in the primary tumor area was 27.0% (17/63) with the SIB technique and 13.4% (16/119) with the sequential technique ($P = .028$). After matching, the rate of local failure in the primary tumor area was 26.3% (15/57) with the SIB technique and 10.0% (6/60) with the sequential technique ($P = .02$). Of the 15 patients in the SIB group with local failure, 46.7% (n = 7) had infield failure, 26.7% (n = 4) had marginal failure, and 26.7% (n = 4) had out-of-field failure. Of the 6 patients in the sequential technique group with local failure, 50.0% (n = 3) had infield failure, 16.7% (n = 1) had marginal failure, and 33.3% (n = 2) had out-of-field failure. There was no difference in regional failure between the SIB and sequential technique groups ($P = .92$; Table 2).

Table 3. Dosimetric Comparison of Organs at risk in Patients With High-Risk Oral Cavity Cancer Treated With Simultaneous Integrated Boost and Sequential Intensity-Modulated Radiotherapy With or Without Concurrent Chemoradiation Therapy After Matching.[a,b,c]

	Average dose (mean ± SD, Gy)		
	SIB (n = 57)	Sequential (n = 60)	*P* Value
Maximal spinal cord dose (D1 cm^3)	36.4 ± 3.9	36.8 ± 4.8	.75
Maximal brain stem dose (D1 cm^3)	31.4 ± 7.1	29.4 ± 9.0	.44
Mean dose to the right parotid gland	31.0 ± 7.9	30.6 ± 10.8	.87
Mean dose to the left parotid gland	30.9 ± 9.4	31.4 ± 12.3	.85
Oral pharynx	51.7 ± 6.8	50.2 ± 6.8	.40
Larynx	42.1 ± 7.6	42.5 ± 8.5	.86
Esophagus	33.7 ± 7.4	28.5 ± 9.1	.02
Trachea	35.9 ± 7.2	31.3 ± 9.0	.03

Abbreviations: SD, standard deviation; SIB, simultaneous integrated boost.
[a]Mean ± SD.
[b]Esophagus: Contouring from the cricopharyngeus muscle at the level of the cricoid cartilage superiorly to the cranial edge of the sternal manubrium.
[c]Trachea: Contouring from the bottom of the larynx to the cranial edge of the sternal manubrium.

Dosimetric Comparison of OARs

Dosimetric comparisons of OARs for patients treated with SIB and sequential IMRT with or without CCRT after matching are presented in Table 3. There were no significant differences between the groups in the maximal dose to the spinal cord and brain stem or the mean dose to the bilateral parotid glands, oropharynx, and larynx. However, sequential IMRT provided a significantly lower dose to the esophagus (5.2 Gy, $P = .02$) and trachea (4.6 Gy, $P = .03$) than the SIB technique.

Toxicities

The data on acute toxicities in both groups of patients with and without chemotherapy are detailed in Table 4. The SIB group had more grade 3 dysphagia (26.3% vs 15.0%, $P = .13$), $\geq$ grade 2 body weight loss (29.8% vs 16.7%, $P = .09$), and normal thrombocytopenia (15.8% vs 53.3%, $P < .001$) than the sequential group.

Discussion

In the current study, there was no significant difference in the OS, disease-free survival, or locoregional survival rate between the 2 techniques. However, patients who received the SIB technique had a 2.74 times higher risk of death than patients who received the sequential technique. Additionally, the respective primary recurrence rates were 26.3% and 10.0%. The respective marginal failure rates in the SIB and sequential groups were 26.7% and 16.7%. Additionally, sequential IMRT provided a significantly lower dose to the esophagus and trachea than the SIB technique.

Table 4. Acute Toxicities in Patients With High-Risk Oral Cavity Cancer Treated With Simultaneous Integrated Boost and Sequential Intensity-Modulated Radiotherapy With or Without Concurrent Chemoradiation Therapy After Matching.

[a]Toxicity	SIB (n = 57) n (%)	Sequential (n = 60) n (%)	*P* Value
[b]Xerostomia (acute)			
Gr. 1	36 (63.2%)	46 (76.7%)	.11
Gr. 2	21 (36.8%)	14 (23.3%)	
Mucositis			
Gr. 1	3 (5.3%)	6 (10.0%)	.39
Gr. 2	31 (54.4%)	36 (60.0%)	
Gr. 3	23 (40.4%)	18 (30.0%)	
Dermatitis			
Gr. 1	26 (45.6%)	29 (48.3%)	.96
Gr. 2	23 (40.4%)	23 (38.3%)	
Gr. 3	8 (14.0%)	8 (13.3%)	
Body weight loss			
Gr. 1	40 (70.2%)	50 (83.3%)	.09
≥ Gr. 2[c]	17 (29.8%)	10 (16.7%)	
Dysphagia			
Gr. 0-2	42 (73.7%)	48 (85.0%)	.13
Gr. 3	15 (26.3%)	9 (15.0%)	
Fistula formation or superficial cases of skin dehiscence			
Yes	2 (3.5%)	1 (1.7%)	.53
No	55 (96.5%)	59 (98.3%)	
Anemia			
Normal	50 (87.7%)	55 (91.7%)	.48
Abnormal	7 (12.3%)	5 (8.3%)	
Leucopenia			
Normal (Hb > 8)	46 (80.7%)	46 (76.7%)	.82
Gr. 2 (Hb 6-8)	7 (12.3%)	8 (13.3%)	
≥ Gr. 3[c] (Hb <8)	4 (7.0%)	6 (10.0%)	
Thrombocytopenia			
Normal	9 (15.8%)	32 (53.3%)	<.001[d]
Gr. 1	48 (84.2%)	26 (43.3%)	
≥Gr. 2	0 (0%)	2 (3.3%)	

Abbreviations: Gr, grade; Hb, hemoglobin; SIB, simultaneous integrated boost.
[a]Toxicity grade was determined according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0).
[b]Acute xerostomia: Acute toxicity was defined as occurring < 90 days after beginning radiotherapy.
[c]There were no grade 5 adverse events, and when <5 adverse events occurred, the variables were merged.
[d]P < .001.

Vlacich et al reported no significant difference in the 4-year OS rates between patients with locally advanced HNSCC who received either the sequential or SIB technique (69% vs 77%, $P = .13$).[19] Recently, a meta-analysis also noted that the sequential and SIB techniques provided comparable outcomes in the treatment of patients afflicted by HNSCC.[20] Similarly, patients with NPC treated with either technique also showed no difference in progression-free survival (PFS) or OS.[21-23] In the current study, our data also showed no difference between the sequential and SIB techniques ($P = .11$).

Nevertheless, there are certain prognostic factors that could influence the outcomes of patients with HNSCC who undergo surgery.[14,15] One of the independent predictors of OS for HNSCC is the Eastern Cooperative Oncology Group (ECOG) performance status.[24,25] Although there was no significant difference in the OS rate of patients with HNSCC who received either the sequential or SIB technique according to Vlacich et al,[19] there were 4 times as many patients with ECOG 2 in the sequential group than in the SIB group (13% vs 3%).[19] Additionally, Yao et al indicated that patients with oropharyngeal cancer had a significantly better OS rate than patients with OCC.[26] The percentages of OCC and oropharynx cases in the SIB versus sequential group in Vlacich's study were 1% versus 4% and 58% versus i71%, respectively.[19] As mentioned earlier, these factors may affect the OS of patients with HNSCC. Therefore, it is not reasonable to apply the results from the Vlacich study to postoperative patients with OCC receiving adjuvant CCRT.

In the current study, all patients were postoperative patients having OCC with prognostic factors who received adjuvant treatment. After adjusting for prognostic factors in the multivariate logistic regression model, patients who received the SIB technique had a 2.74 times higher risk of death than those who received the sequential technique ($P = .03$) and a 17% higher mortality rate than those who received the sequential technique ($P = .04$). Interestingly, in the study by Songthong et al,[21] the 2-year PFS rate for patients with NPC in the group receiving sequential treatment was 15% higher than that of patients in the SIB group. Similarly, our data also showed that postoperative patients with OCC treated with sequential IMRT had a 13% higher 5-year local progression-free survival (LPFS) rate than those treated with SIB-IMRT (65%), although the difference was not statistically significant. After matching for a close or positive resection margin, there was no significant difference in the rate of resection. Nevertheless, the rate of local failure in the primary tumor area for the SIB group was 16% higher than that for the sequential group (10%, $P = .02$). Moreover, the respective marginal failure rates were 17% and 27%.

Mohan et al[3] found that the volume of normal tissues outside the target regions that received the prescribed dose for the PTV boost was 34% larger with 2-phase IMRT. Miyazaki et al demonstrated that the D99 (the minimum relative dose that covers 99% of the volume of the PTV) for a PTV boost was significantly higher with the sequential technique than with SIB-IMRT.[27] Stromberger et al demonstrated that the sequential technique showed a significantly higher D95 for PTV1 (the volume including the tumor bed and high-risk areas) of 98.5% compared with 94.4% using the SIB technique.[28] Fogliata et al[29] reported that the mean dose to PTV1, volume receiving at least 95% of the prescribed dose (V95), and equivalent uniform dose were higher using the sequential regimen than the SIB regimen. Stromberger et al also noted higher V95% in PTV1 (281 cm^3) and a better homogeneity index (1.04) with the sequential technique than with the SIB technique (138 cm^3 and 1.10) in similar patients.[28] The dose distributions with IMRT-based SIB plans are more conformal than those with simple sequential plans according to Mohan et al.[3] Nevertheless, the biological dose correction for altered fractionation modifies the result, leading to a more homogeneous dose

distribution with the sequential technique than with the SIB technique.[29] It is apparent that the boost area or PTV_{high} may receive a higher mean dose when using the sequential technique, thereby potentially decreasing the risk of marginal and local failure and increasing LPFS for postoperative patients with OCC.

Patients with OCC tend to experience changes in the soft tissue and flap throughout the course of RT, along with interfractional anatomic changes that may result in an unpredictable geographic miss.[5-8,30] Miyazaki et al reported that SIB with a sequential re-SIB plan had a significantly lower spinal cord Dmax than that of the initial SIB plan.[27] Additionally, the degree of dose inhomogeneity inside PTV1 was analyzed using the standard deviation parameter, demonstrating better homogeneity for the sequential technique and worse homogeneity for the SIB technique.[29] Therefore, when a patient exhibits interfractional anatomic changes during the entire course of RT or CCRT according to one plan for SIB-IMRT and receives a replanned SIB, geometric changes in the dose distribution are possible and may be prone to uncertainties related to the replanned SIB-IMRT and delivery.

Compared with the SIB technique, sequential plans can better account for the changes in body shape when a new CT scan is obtained for field planning due to shrinkage. Additionally, the V95% of the PTV with the sequential technique for the same group is larger than that with the SIB technique,[28] and a more homogeneous dose distribution is observed with the sequential technique than with the SIB technique.[29] In contrast to the SIB technique, the sequential technique allows a consistent dose per fraction between all treatment volumes and throughout the course of treatment.

Mohan et al compared IMRT techniques and concluded that SIB-IMRT achieved greater normal tissue sparing than the sequential planning of an IMRT boost after whole-neck IMRT.[3] Notably, the adverse effects observed in the clinic are not always consistent with the concepts mentioned above. For instance, there were no significant differences in acute toxicities between the 2 IMRT techniques for NPC.[21] In addition, a meta-analysis suggested that SIB-IMRT and sequential IMRT might confer a similar risk of acute and severe side effects in patients with head and neck cancer.[20] Additionally, 2 articles showed that IMRT with the sequential technique had more advantages than SIB-IMRT in protecting OARs and that SIB-IMRT induced a higher rate of severe dermatitis and dysphagia.[19,23] In the current study, patients treated with SIB-IMRT had higher levels of grade 3 dysphagia (by 11%) and showed a trend of $\geq$ grade 2 body weight loss (by 13%) than patients treated with the sequential technique, although the difference was not statistically significant.

In the current study, sequential IMRT resulted in a lower dose to the esophagus than the SIB technique ($P = .02$), and the esophageal area in our contouring included part of the inferior pharyngeal constrictor (from the inferior aspect of the hyoid to the inferior end of the cricoid cartilage).[31,32] Interestingly, the glottic/supraglottic larynx and inferior pharyngeal constrictors are strongly correlated with dysphagia.[33-35] In fact, similar tumor control rates have been reported with 1.6 Gy/fraction and 2.0 Gy/fraction.[36] In other words, with a similar α/β ratio for the tissues, there may be similar degrees of damage from treatment and recovery between SIB fractions.[37] Moreover, 2 articles demonstrated significantly higher mean laryngeal and pharyngoesophageal axis doses with whole-field IMRT.[38,39] Accordingly, compared with the SIB technique (35 fractions), during sequential treatment, the lower neck and pharyngeal constrictors may have decreased severity of acute toxicity due to fewer irradiation fractions (23-25 fractions).

There were several limitations to the current study, namely, the retrospective nature of the analysis, the relatively small number of patients analyzed, and the fact that the total dose and technique were left to the discretion of the treating doctor, which could have significantly confounded the results. These patients were not selected or treated based on a prospective protocol, leading to heterogeneity in patient management. However, all the patients were reviewed by a multidisciplinary tumor board, and thus, all individuals were treated with a consistent treatment philosophy. Second, the treatment modalities at our hospital were IMRT and helical tomotherapy (HT). Helical tomotherapy has better uniformity and conformal indices, as well as better critical organ-sparing properties, than IMRT.[40,41] However, there were no differences in the percentage of patients treated by IMRT or HT between the 2 groups. Finally, the toxicity data were not prospectively collected but rather extracted from the medical records. Therefore, all these potential differences must be accounted for, and findings need to be confirmed in a formal, prospective manner.

Conclusion

For patients with locally advanced OCC, postoperative sequential IMRT may allow a consistent dose per fraction for all treatment volumes to overcome an unpredictable geographic miss potentially with a low marginal failure rate in the primary area. Patients treated by sequential IMRT show equal OS benefits to those treated by SIB-IMRT and a lower mortality rate than those treated by SIB-IMRT. Additionally, a reduced dose to the esophagus and trachea compared to that with the sequential technique was noted. These data warrant further evaluation in a prospective study to confirm the benefit of sequential IMRT.

Authors' Note

CHH contributed to conception/design; PWS, LJL, WCL, and LJW contributed to provision of study material or patients; HPY contributed to collection and/or assembly of data; CHH, LYW, and HLC contributed to data analysis and interpretation; and CHH contributed to manuscript writing. The current study was approved by the institutional review board of the Far Eastern Memorial Hospital (approval no. FEMH-IRB, 104008-E). The institutional review board of the Far Eastern Memorial Hospital waived the need to obtain consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this noninterventional study. All authors read and approved the final manuscript.

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