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Early clinical outcomes by combination of intensity modulated radiation therapy and intensity modulated proton therapy in treating oropharynx cancer patients

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Abstract

Purpose: To report the early clinical outcomes of combining intensity-modulated radiation therapy (IMRT) and intensity-modulated proton therapy (IMPT) in comparison with IMRT alone in treating the oropharynx cancer (OPC) patients.

Materials and Methods: The medical records of 148 OPC patients were retrospectively reviewed, who underwent definitive radiotherapy (RT) with concurrent systemic therapy, from January 2016 till December 2019 at Samsung Medical Center. During the 5.5 weeks' RT course, the initial 16 (or 18) fractions were delivered by IMRT in all patients, and the subsequent 12 (or 10) fractions were either by IMRT in 81 patients (IMRT only) or by IMPT in 67 (IMRT/IMPT combination), respectively, based on comparison of adaptive re-plan profiles and availability of equipment. Propensity-score matching (PSM) was done on 76 patients (38 from each group) for comparative analyses.

Results: With the median follow-up of 24.7 months, there was no significant difference in overall survival and progression free survival between groups, both before and after PSM. Before PSM, IMRT/IMPT combination group experienced grade ≥3 acute toxicities less frequently: mucositis in 37.0% and 13.4% ($p<0.001$); and analgesic quantification algorithm (AQA) in 37.0% and 19.4% ($p=0.019$), respectively. The same trends were observed after PSM: mucositis in 39.5% and 15.8% ($p=0.021$); and AQA in 47.4% and 21.1% ($p=0.016$), respectively. In multivariate logistic regression, grade ≥3 mucositis was significantly less frequent in IMRT/IMPT combination group, both before and after PSM ($p=0.027$ and 0.024, respectively). AQA score ≥3 was also less frequent in IMRT/IMPT combination group, both before and after PSM ($p=0.085$ and 0.018, respectively).

Conclusions: In treating the OPC patients, with comparable early oncologic outcomes, more favorable acute toxicity profiles were achieved following IMRT/IMPT combination than IMRT alone.

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Keywords. Acute Toxicity, Oropharyngeal Cancer, Proton Beam Therapy, Radiation Therapy, Survival

Introduction

Radiation therapy (RT) has the capability of organ preservation, and plays a key role, with or without chemotherapy, in managing the oropharyngeal cancer (OPC) patients with non-metastatic disease extent [1-3]. With the technical advancement, intensity modulated radiation therapy (IMRT), when compared to the traditional 2- or 3-dimensional RT techniques, has enabled high enough radiation dose delivery to the targets at reduced risks of severe acute and delayed side effects. Though IMRT has currently become the most popular and recommended RT technique in treating most head and neck cancer (HNC) types, a significant proportion of HNC patients, however, still suffer from annoying side effects and lowered quality of life during and following high dose RT [4-7].

Proton beam therapy (PBT), by virtue of physical property of Bragg-Peak phenomenon, can generate more advantageous dose distribution profile than photon-based RT techniques, including IMRT, and has been in clinical use in treating several cancer types including HNC [8-11]. Nevertheless, more clinical evidences are still in need to confirm whether the physical advantage of PBT genuinely can lead to better therapeutic outcomes in real-world practice setting. Considering the substantial costs and resources needed for installation and operation of PBT facilities, answering this issue seems even more important.

With these theoretic backgrounds, we intended to apply PBT in treating the HNC patients since December of 2015, when our PBT facility began its operation [12]. However, the average waiting time interval before PBT to start after therapeutic decision has been about 4~6 weeks, because of limited PBT resources when compared to the clinical demands. It has been well addressed, however, that long waiting before treatment initiation in treating the HNC patients

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could result in significantly unfavorable oncologic outcomes [13,14]. In order to overcome this long waiting before treatment initiation, we developed our strategy to begin the RT course by IMRT (helical Tomotherapy, HT) and then to determine whether to continue IMRT or to switch into intensity modulated PBT (IMPT), based on the rival re-plan comparison, which corresponds to our adaptive re-plan policy. We previously reported the early clinical outcomes and acute toxicity profiles following IMRT only and IMRT/IMPT combination in treating the nasopharynx cancer (NPC) patients [15], and would report our experience in treating the OPC patients.

Results

Patients' characteristics

The characteristics of all patients and 76 matched patients based on the propensity scores (38 in each group) were summarized in **Table 1**. The median age of the whole patients was 60 years (range, 38~76 years), and the majority was male (137 patients, 92.6%). Among all patients, most characteristics were similarly distributed between groups, but the patients in IMRT/IMPT combination group more frequently had lower T stage (p=0.025) and received unilateral neck irradiation (p<0.001), respectively. Among 76 matched patients, however, all characteristics distributed similarly between groups.

Table 1. Baseline demographic and clinical characteristics.

Variables	All patients (N = 148)			Matched patients (N = 76)*		
	IMRT only (N = 81)	IMRT/IMPT (N = 67)	*p*-value	IMRT only (N = 38)	IMRT/IMPT (N = 38)	*p*-valu
Age	62.02 ± 8.74 years	59.90 ± 9.62 years	0.161	59.79 ± 7.17 years	58.08 ± 7.65 years	0.318
Gender			0.225†			0.358
Male	77 (95.1%)	60 (89.6%)		37 (97.4%)	34 (89.5%)	
Female	4 (4.9%)	7 (10.4%)		1 (2.6%)	4 (10.5%)	
ECOG PS			0.866†			0.615
0	4 (4.9%)	5 (7.5%)		3 (7.9%)	1 (2.6%)	
1	76 (93.8%)	61 (91.0%)		35 (92.1%)	37 (97.4%)	
2	1 (1.2%)	1 (1.5%)		-	-	
Current smoking			0.433			0.222
Yes	24 (29.6%)	16 (23.9%)		23 (60.5%)	28 (73.7%)	

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No	57 (70.4%)	51 (76.1%)		15 (39.5%)	10 (26.3%)	
HPV status			0.889			0.497
Positive	67 (82.7%)	56 (83.6%)		32 (84.2%)	34 (89.5%)	
Negative	14 (17.3%)	11 (16.4%)		6 (15.8%)	4 (10.5%)	
Clinical T stage			0.025			0.791
T1	15 (18.5%)	18 (26.9%)		8 (21.1%)	8 (21.1%)	
T2	36 (44.4%)	39 (58.2%)		22 (57.9%)	22 (57.9%)	
T3	18 (22.2%)	7 (10.4%)		7 (18.4%)	5 (13.2%)	
T4	12 (14.8%)	3 (4.5%)		1 (2.6%)	3 (7.9%)	
Clinical N stage			0.327†			0.130
N0	5 (6.2%)	8 (11.9%)		-	3 (7.9%)	
N1	10 (12.3%)	10 (14.9%)		4 (10.5%)	5 (13.2%)	
N2	61 (75.3%)	48 (71.6%)		31 (81.6%)	30 (78.9%)	
N3	5 (6.2%)	1 (1.5%)		3 (7.9%)	-	
Subsite			0.067†			0.783
Tonsil	55 (67.9%)	53 (79.1%)		29 (76.3%)	30 (78.9%)	
Base of tongue	23 (28.4%)	9 (13.4%)		9 (23.7%)	8 (21.1%)	
Others	3 (3.7%)	5 (7.5%)		-	-	
Neck irradiation			<0.001			1.000
Unilateral	15 (18.5%)	35 (52.2%)		10 (26.3%)	10 (26.3%)	
Bilateral	66 (81.5%)	32 (47.8%)		28 (73.7%)	28 (73.7%)	
Concurrent chemotherapy			0.673†			1.000
Cisplatin	69 (85.2%)	58 (86.6%)		38 (100.0%)	38 (100.0%)	
Cetuximab	5 (6.2%)	7 (10.4%)		-	-	
No chemotherapy	7 (8.6%)	2 (3.0%)		-	-	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMRT, Intensity-Modulated Radiation Therapy; IMPT, Intensity-Modulated Proton Therapy; HPV, Human Papillomavirus

* Two variables (T stage and bilateral neck irradiation) were used in the matching process. † Using Fisher's exact test.

Oncologic outcomes

The tumor response was excellent and the rates of overall and complete response, evaluated at 4 months of RT completion, were 99.3% and 85.1%, respectively. With the median follow-up of 24.7 months (range, 4.9~54.8 months), six patients (4.1%) succumbed to death while 28 (18.9%) experienced treatment failures. The failure sites were locoregional in 14 patients (9.5%), distant in 13 (8.8%), and combined locoregional and distant in one (0.7%), respectively. There were no significant differences of overall survival (OS) and progression-free survival (PFS) profiles between groups, both before and after propensity score matching (PSM) (**Figure 1**). Among all patients, the 2-year OS rates were 92.1% and 98.4% in IMRT only and IMRT/IMPT combination groups (p=0.235), and the 2-year PFS rates were 76.2% and 82.0% in IMRT only and IMRT/IMPT combination groups (p=0.533), respectively. The

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corresponding figures among the matched patients were 93.5% and 97.2% (p=0.861), and 86.0% and 78.3% (p=0.533), respectively.

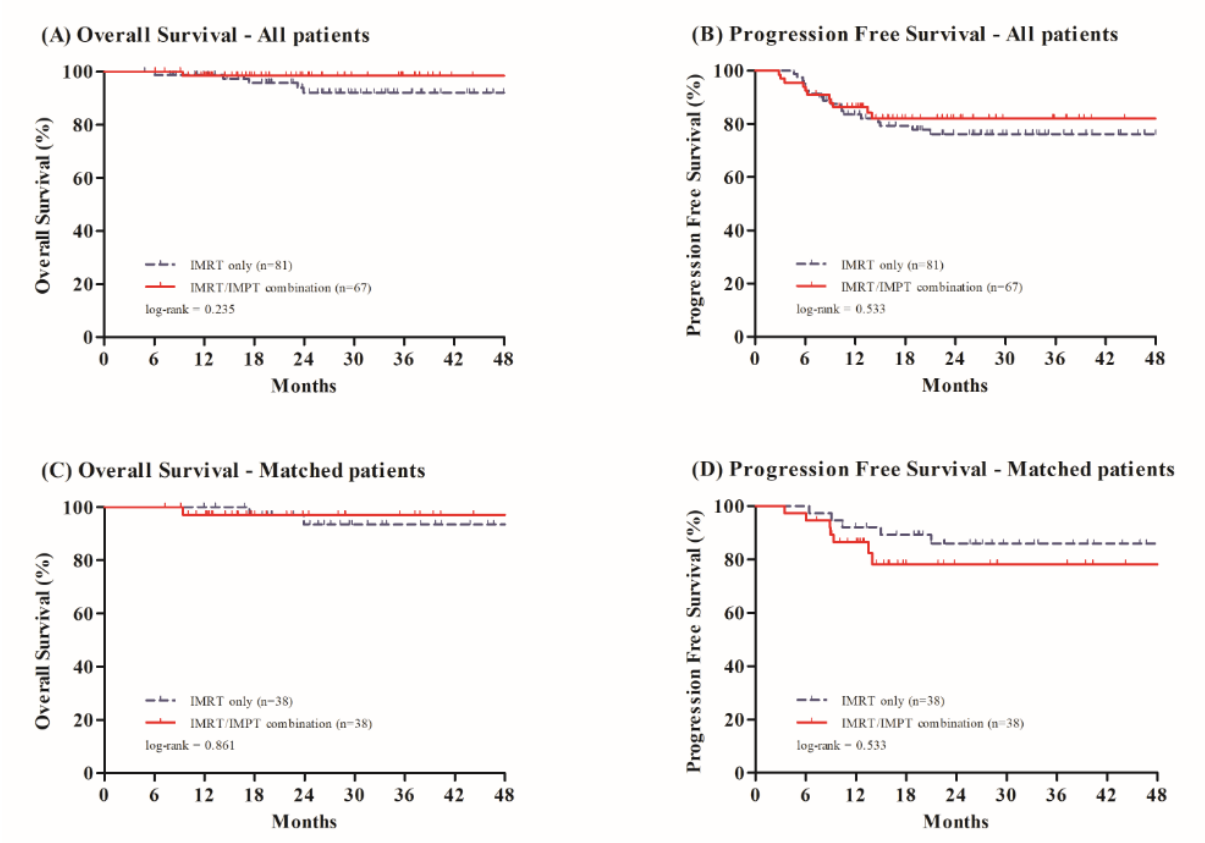

Figure 1. Overall survival and progression free survival among all patients (A, B) and matched patients (C, D) according to treatment group. IMRT, Intensity-Modulated Radiation Therapy; IMPT, Intensity-Modulated Proton Therapy

Acute toxicity profiles

Table 2 and **Figure 2** summarized the acute toxicity profiles. Among all patients, grade ≥3 dermatitis, mucositis, weight loss, and Analgesic Quantification Algorithm (AQA) score ≥3 (defined as need of strong opioids) occurred in five (3.4%), 39 (28.5%), 27 (18.2%) and 43 (29.1%), respectively (Table 2). Three patients underwent gastrostomy tube feeding during or after RT due to severe oral pain: two in IMRT only group; and one in IMRT/IMPT combination group, respectively. The patients in IMRT/IMPT combination group significantly less

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frequently experienced grade ≥3 mucositis (37.0% vs 13.4%, p<0.001) and AQA score ≥3 (37.0% vs 19.4%, p=0.019), respectively (**Figure 2A)**. Among the matched patients, the same trends were observed: the frequencies of grade ≥3 mucositis were 39.5 % and 15.8% (p=0.021); and those of AQA score ≥3 were 47.4 % and 21.1% (p=0.016), respectively (**Figure 2B**).

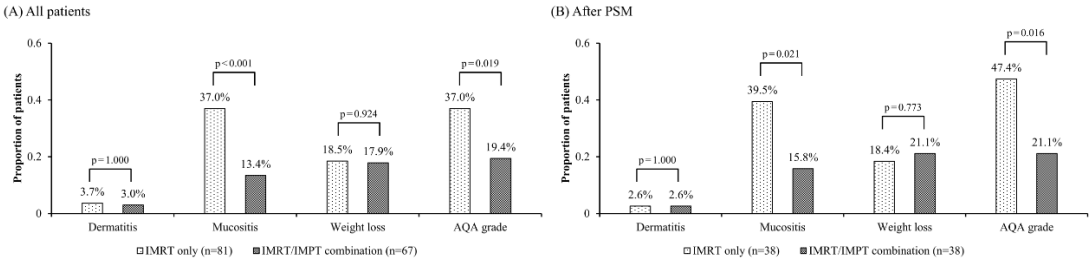

Figure 2. Grade 3 or higher toxicity distribution by treatment group among all patients (A), and matched patients (B). PSM, Propensity Score Matching; IMRT, Intensity-Modulated Radiation Therapy; IMPT, Intensity-Modulated Proton Therapy

Table 2. Acute toxicity profiles.

Toxicity	All patients (N = 148)			Matched patients (N = 76)		
	IMRT only (N = 81)	IMRT/IMPT (N = 67)	*p*-value	IMRT only (N = 38)	IMRT/IMPT (N = 38)	*p*-va
Dermatitis			0.969†			0.2
Grade 0	23 (28.4%)	21 (31.3%)		7 (18.4%)	14 (36.8%)	
Grade 1	35 (43.2%)	29 (43.3%)		19 (50.0%)	17 (44.7%)	
Grade 2	20 (24.7%)	15 (22.4%)		11 (28.9%)	6 (15.8%)	
Grade 3	3 (3.7%)	2 (3.0%)		1 (2.6%)	1 (2.6%)	
Mucositis			0.009†			0.0
Grade 0	-	-		-	-	
Grade 1	8 (9.9%)	12 (17.9%)		4 (10.5%)	6 (15.8%)	
Grade 2	43 (53.1%)	46 (68.7%)		19 (50.0%)	26 (68.4%)	
Grade 3	26 (32.1%)	8 (11.9%)		15 (39.5%)	5 (13.2%)	
Grade 4	4 (4.9%)	1 (1.5%)		-	1 (2.6%)	
Weight loss			0.245			0.4
Grade 0	12 (14.8%)	17 (25.4%)		4 (10.5%)	7 (18.4%)	
Grade 1	25 (30.9%)	23 (34.3%)		12 (31.6%)	14 (36.8%)	
Grade 2	28 (34.6%)	15 (22.4%)		15 (39.5%)	9 (23.7%)	
Grade 3	16 (19.8%)	12 (17.9%)		7 (18.4%)	8 (21.1%)	
AQA grade			0.042†			0.0

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Grade 0	4 (4.9%)	8 (11.9%)	2 (5.3%)	4 (10.5%)
Grade 1	42 (51.9%)	44 (65.7%)	17 (44.7%)	24 (63.2%)
Grade 2	5 (6.2%)	2 (3.0%)	1 (2.6%)	2 (5.3%)
Grade 3 or higher	30 (37.0%)	13 (19.4%)	18 (47.4%)	8 (21.1%)

IMRT, Intensity-Modulated Radiation Therapy; IMPT, Intensity-Modulated Proton Therapy; AQA, Analgesic Quantification Algorithm.

† Using Fisher's exact test.

Univariate and multivariate analyses for grade ≥3 mucositis and AQA score ≥3 were done, both before and after PSM, respectively (Table 3). The significant factors associated with grade ≥3 mucositis among all patients included three variables in univariate analyses: cT3-4 stage (HR=3.552, 95% CI 1.631~7.737, p=0.001); IMRT only (HR=3.791, 95% CI 1.646~8.733, p=0.002); and bilateral neck irradiation (HR=3.723, 95% CI 1.439~9.630, p=0.007), respectively. In multivariate analyses, however, IMRT only remained a significant factor for grade ≥3 mucositis (HR=2.725, 95% CI 1.123~6.615, p=0.027). The factor associated with AQA score ≥3 was IMRT only (HR=2.443, 95% CI 1.148~5.199, p=0.020) in univariate analyses, whose significance declined in multivariate analysis (HR=2.014, 95% CI 0.907~4.469, p=0.085).

Table 3. Univariate and multivariate logistic regression for grade ≥3 mucositis and analgesic quantification algorithm score ≥3.

Variables*	**All patients (N = 148)**				
	Univariate analysis		**Multivariate analysis**		**Univariate a**
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)
Grade ≥3 mucositis					
Clinical T stage					
T1-2	Ref	-	Ref	-	Ref
T3-4	3.552 (1.631 – 7.737)	0.001	2.328 (0.980 – 5.530)	0.056	1.800 (0.559 – 5.792
Neck irradiation					
Unilateral	Ref	-	Ref	-	Ref
Bilateral	3.723 (1.439 – 9.630)	0.007	1.846 (0.629 – 5.417)	0.264	1.744 (0.507 – 5.994
RT modality					
IMRT/IMPT combination	Ref	-	Ref	-	Ref
IMRT only	3.791 (1.646 – 8.733)	0.002	2.725 (1.123 – 6.615)	0.027	3.478 (1.172 – 10.323
Analgesic quantification algorithm score ≥3					
Age	1.007 (0.969 – 1.047)	0.731	Not included	-	1.070 (0.996 – 1.150
Clinical T stage					

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T1-2	Ref	-	Not included	-	Ref
T3-4	1.801 (0.841 – 3.853)	0.130	Not included	-	4.583 (1.433 – 14.660
Neck irradiation					
Unilateral	Ref	-	Ref	-	Ref
Bilateral	2.420 (1.052 – 5.566)	0.038	1.892 (0.784 – 4.567)	0.156	2.588 (0.764 – 8.766
RT modality					
IMRT/IMPT combination	Ref	-	Ref	-	Ref
IMRT only	2.443 (1.148 – 5.199)	0.020	2.014 (0.907 – 4.469)	0.085	3.375 (1.233 – 9.237

OR, Odds Ratio; CI, Confidence Interval; RT, Radiotherapy; IMRT, Intensity-Modulated Radiation Therapy; IMPT, Intensity-Modulated Proton Therapy.

* Variables with a p-value <0.1 on the univariate analysis of the entire or matched cohort were included in the table

Among the matched cohorts, grade ≥3 mucositis was more frequently encountered in IMRT only group both in univariate (HR=3.478, 95% CI 1.172~10.323, p=0.025) and multivariate (HR=3.567, 95% CI 1.186~10.725, p=0.024) analyses, respectively. AQA score ≥3 was also more commonly observed in IMRT only group in univariate (HR=3.375, 95% CI 1.233~9.237, p=0.018) and multivariate (HR=3.810, 95% CI 1.262~11.500, p=0.018) analyses, respectively.

Discussion

Radiation oral mucositis is very common and unavoidable acute side effect affecting most HNC patients who receive high dose RT. Oral mucositis typically causes oral soreness, swallowing difficulty, decreased oral intake, and subsequent weight loss. Severe oral pain usually necessitates taking pain-killers, sometimes narcotics, and the patients may become prone to various adverse effects of the medication. It was reported that RT-related complications, such as oral mucositis, can increase the treatment cost by up to 17,000 USD per patient, and its severity is proportionally associated with the incremental healthcare cost [16,17]. Moreover, the modification and/or interruption of the planned RT schedule occasionally is necessary, in order not to compromise the precision of RT and to compensate for the body contour change incurred by these sequence of events in addition to tumor shrinkage itself.

Considering these respects, IMPT, by virtue of Bragg-Peak phenomenon, can provide more effective sparing of the oral mucosa from moderate to high dose radiation exposure, especially

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when treating well-lateralized target lesions, and subsequently reduce the severity of oral mucositis, when compared to IMRT. Likewise, saving of anteriorly located oral cavity mucosal lining, if the target is posteriorly located as in most OPC patients, could be achieved more effectively by using IMPT.

Xiao et al. demonstrated that the detrimental effects by increased TTI was mediated by tumor progression during the waiting time [18], which was demonstrable by comparing the initial clinical stages and the surgical stages, and found that even 1 week's delay could be detrimental and suggested timely intervention within the first 4 weeks. Although induction chemotherapy before definitive local treatment modality could also be considered to bridge the gap, which, however, might increase the treatment-related morbidity risk and the care cost without significant clinical benefit [19]. Based on these backgrounds, we decided to begin upfront RT by starting by IMRT, instead of IMPT, in all OPC patients.

Adaptive re-plan during the RT course has been highly recommended in order to accommodate the body contour changes in treating most HNC patients [20,21]. The body contour change is usually more significant during the early CCRT course than during the later course. We previously measured the mean tumor volume reduction rates by the time of re-plan, which were 40.7% in the OPC patients and 41.9% in the NPC patients, respectively [22,23]. These clinically relevant data by the authors strongly endorse the adaptive re-plan strategy, which has long been our institutional policy. For the adaptive RT, we generated two rival plans, one by IMRT and the other by IMPT, and then to determine the subsequent RT modality (whether to continue IMRT or to switch into IMPT), based on the dosimetric profiles in addition to the availability of IMPT. By following these strategies, we could shorten the waiting from 4~6 weeks to a few days, avoid the break during the RT course due to significant and abrupt body contour changes, and determine optimal RT modality on the individual basis.

We previously reported the early clinical outcomes and acute toxicity profiles following IMRT

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only and IMRT/IMPT combination in treating the NPC patients [15], and found that combination of IMRT and IMPT was more advantageous in weight loss, analgesic use, with the equivalent oncologic outcomes. To the best of our knowledge, there have been only few retrospective studies on the OPC patients, which evaluated the causal relationship between of IMPT's dosimetric advantage and RT-related toxicities. Blanchard et al. performed a case-matched analysis comparing IMRT and IMPT for OPC patients, and reported reduced rates of gastrostomy tube dependency and severe weight loss (defined as >20% weight loss from the baseline) in IMPT group [24]. Sio et al., based on 81 OPC patients, demonstrated that patient-reported symptom burden was lower following IMPT than IMRT [25]. These two studies neither did thorough multivariate analyses, nor did quantitative measurement of the toxicities, including mucositis and analgesic usage. The current study intended to investigate whether similar effects as in the NPC patients could be obtained in the OPC patients by combining IMRT and IMPT. As described above, the oncologic outcomes of OS and PFS were not different between groups, while IMRT/IMPT combination, compared with IMRT only, resulted in more favorable acute toxicity profiles in terms of grade ≥3 mucositis and AQA score ≥3 through the quantitative measurement and multivariate analyses. Our study could have complemented the limitations of aforementioned studies and, at the same time, have supported the consistent finding of improved acute toxicity profiles in treating the OPC patients.

The current study has a weak point of uneven distribution of several characteristics between the treatment groups, mainly by virtue of the retrospective nature. We did propensity-score matching and multivariate logistic regression to mitigate this weakness. In addition to the main observations described above, our IMRT/IMPT combination regimen could reduce the direct RT cost up to 28% according to the Korean National Health Insurance plan, when compared with 30 fractions' IMPT only throughout the RT course.

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Materials and Methods

Patients

We retrospectively reviewed the medical records of 177 OPC patients who underwent definitive RT with or without concurrent chemotherapy from January of 2016 until December of 2019, after approval by our Institutional Review Board (IRB #2018-08-109). After excluding 29 patients, 148 were included in the current study. The reasons for exclusion were unknown human papillomavirus (HPV) status in 15 patients, different RT modalities other than IMRT only or IMRT-IMPT combination in 11, and previous history of receiving RT for the other head and neck cancer in three, respectively.

All patients underwent the initial evaluation including thorough physical examination, histologic confirmation, and routine diagnostic exams including computed tomography (CT) of the head and neck region and 18F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT). For the objective comparison purpose, the clinical stages were assessed according to the 7th edition American Joint Committee on Cancer staging manual, which mainly depended on the anatomic disease extent but not on the HPV status [26].

Treatment scheme

All patients underwent contrast enhanced CT-based simulation with the open mouth. According to our institutional "selective neck irradiation" policy, three target volumes were delineated: gross tumor volume (GTV); high-risk clinical target volume (HR-CTV) which included the tissue and lymphatics adjacent to GTV; and low-risk clinical target volume (LR-CTV), respectively [27]. LR-CTV was individually determined and did not include the clinically uninvolved lymphatics that were two stations away from GTV. The same target delineation policy was applied to all patients regardless of the actual RT modality assigned and/or the HPV

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status. The dose schedules varied along with the study period, which mainly reflected the resource allocation limitation at the authors' institute. The typical dose schedules to the GTV, HR-CTV, and LR-CTV were 66~68.4 Gy, 60 Gy, and 36 Gy over 30 fractions in 97 patients until January of 2018, while those were 67.2 Gy, 56 Gy, and 32~36 Gy over 28 fractions in 51 since after February of 2018, respectively. The differential dose delivery was possible by combining the simultaneous integrated boost and the adaptive re-plan and shrinking field concept, which eliminated LR-CTV during the later RT course.

All patients started RT by IMRT during the early RT course. At the time of adaptive re-plan, two rival plans on each patient, one by IMRT (TomoTherapy®, Accuray, Madison, WI, USA) and the other by IMPT (RayStation®, RaySearch Laboratories AB, Stockholm, Sweden), were generated under the same policy of target delineation and dose constraints for objective dosimetric comparison (**Figure 3**). We intended to assign RT modality during the later RT course based on the rival plan comparison. The actual RT modality assignment, however, did not solely depend on dosimetric superiority, but had to be allocated considering the practical resource limitation and availability. The patients who showed equivalence or superiority by IMRT plan were allocated to IMRT. Meanwhile, those who showed dosimetric superiority by IMPT but should have had RT break longer than a week for subsequent IMPT were allocated to IMRT in order to avoid the undesirable treatment interruption. Consequently, 81 patients (54.7%) continued to receive IMRT (IMRT only group) and 67 (45.3%) received IMRT + IMPT (IMRT/IMPT combination group), respectively (Table 1).

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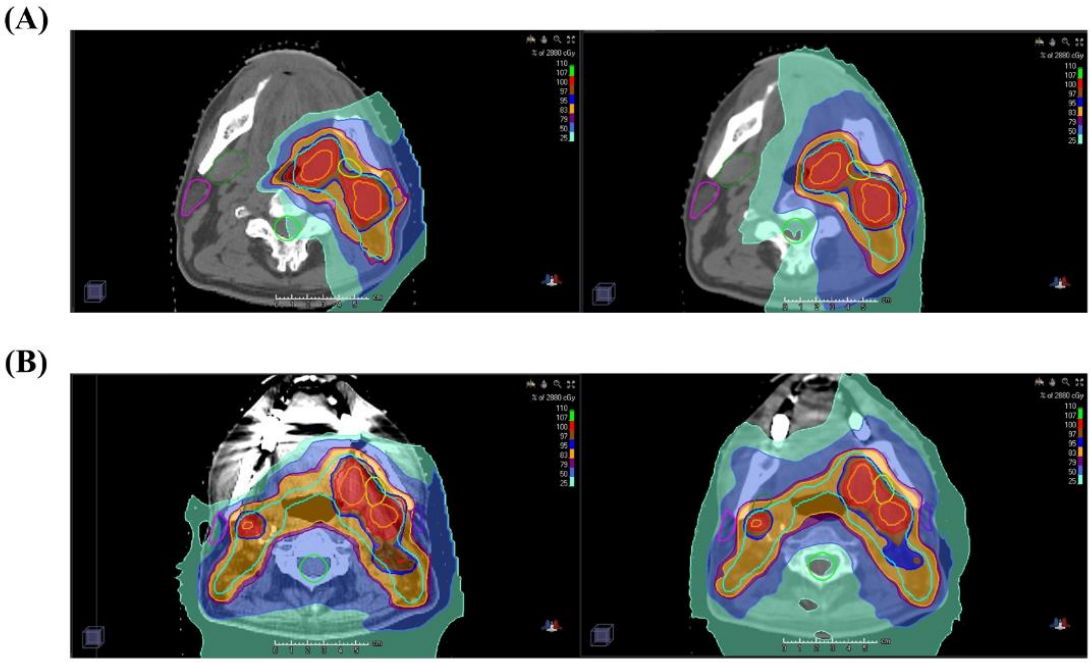

Figure 3. Comparison of dose distribution on axial view in unilateral (A) and bilateral (B) neck irradiation cases

Along with RT, 139 patients (93.9%) received concurrent chemotherapy during the RT course, while nine underwent RT alone. The intended chemotherapy regimens were 2 cycles of triweekly cisplatin (100 mg/m^2) in 118 patients (79.7%), 6 cycles of weekly cisplatin (35 mg/m^2) in nine (6,1%), and oral cetuximab (400 mg/m^2 loading dose followed by 5 weekly dose of 250 mg/m^2) in 12 (8.1%), respectively (Table 1). The vast majority of patients (130, 93.5%) were able to complete the planned chemotherapy cycles, while nine did not because of toxicity. Seven patients among 118 (5.9%) in whom 2 cycles of triweekly cisplatin was planned received only 1 cycle, and two among nine (22.2%) in whom weekly cisplatin were planned received <6 cycles, and all 12 in whom cetuximab was planned were able to complete the intended dose schedule, respectively.

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Propensity score matching

In order to adjust the differences in the baseline characteristics in groups, a PSM method was used. After building a multivariate logistic regression model including the variables with a p-value < 0.1 on the Chi-square test or Fisher's exact, two variables were considered significant (clinical T stage and bilateral neck irradiation). In order to guarantee the homogeneity, only the patients who receive cisplatin-based chemotherapy and the primary tumor site of tonsil or base of tongue were included at time of matching. Based on the calculated propensity score, the matching ratio was 1:1 with the caliper set at 0.2.

Assessment of acute side effects and response, and follow-up schedule after treatment

The acute toxicity profiles during RT were evaluated at least once a week on each patient by the radiation oncologist in charge: the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.03 [28] to monitor radiation dermatitis, oral mucositis, and weight loss; and the AQA scoring system to quantify the analgesic usage (Supplementary table 1) [29].

Response evaluation was done by neck CT taken 1 month of RT completion and PET-CT taken in 3 months thereafter, respectively. PET response criteria in solid tumors (PERCIST) was used to assess the early tumor response [30]. Subsequent follow-up evaluations, including neck CT, were regularly scheduled: at every 3-4 months' interval during the first 2 years; and at every 6 months' interval thereafter. Locoregional failure was defined as any development of new lesion or progression of preexisting lesion, either within or near the initial disease sites.

Statistical analysis

All statistical analyses were performed using the SPSS software version 24.0 (IBM Corporation, Armonk, NY) and R version 4.0.0 (R Development Core Team, Vienna, Austria, http://www.r-project.org). The OS and PFS rates of the two groups were calculated using the Kaplan-Meier

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estimate and compared by log-rank tests. To compare the patient characteristics and acute toxicity profiles between the two treatment groups, the Chi-square test or Fisher's exact test was used for categorical variables while the Student's t-test was used for continuous variables. Furthermore, multivariate logistic regression was performed in order to identify factors that are independently associated with acute toxicity. Factors with a p-value < 0.1 on the univariate analysis or factors considered clinically significant were included in the multivariate analysis, after exclusion of the possible confounding factors.

Conclusion

In summary, our strategy of combining IMRT and IMPT could avoid undesirable long waiting before treatment initiation, and lead to favorable acute toxicity profiles, at similar oncologic outcomes in treating the OPC patients. Further analyses with larger sample size and longer-term observation including the delayed side effect profiles would be needed.

Conflict of interest

None.

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