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Two-step Intensity-modulated Radiation Therapy for Oropharyngeal Cancer: Initial Clinical Experience and Validation of Clinical Staging

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Abstract. *Aim: To evaluate the clinical results of two-step intensity-modulated radiation therapy (IMRT) for oropharyngeal cancer. Patients and Methods: Eighty patients were treated with two-step IMRT between 2002 and 2014. Whole-neck radiotherapy (44.0-50.0 Gy/22-25 fractions) was delivered by IMRT, followed by boost IMRT to the high-risk clinical target volume (total dose of 70.0 Gy/35 fractions). Forty-seven patients received concurrent chemotherapy. Immunohistochemistry for human papillomavirus type 16 (HPV/p16) was performed for 64 patients. Results: The 5-year overall survival and locoregional control rates for stage I, II, III, and IVA-B disease were 80.0%, 75.0%, 78.0%, and 64.0% and 100.0%, 75.0%, 92.0%, and 82.0%, respectively. Overall survival was significantly higher in HPV/p16-positive patients than in HPV/p16-negative patients (p=0.01). Xerostomia of grade 2 or more was noted in 10 patients. Conclusion: Favourable overall survival and locoregional control rates with excellent salivary preservation were obtained using the two-step IMRT method for oropharyngeal cancer.*

Radiation therapy (RT) is the main treatment for head and neck cancer (HNC). Patients with locally advanced HNC who are treated with definitive RT have a 5-year survival rate of 40-60% (1-3). However, long-term late sequelae of RT are highly prevalent and have severe adverse effects on the quality of life (4-8). In particular, RT-induced xerostomia is the most prevalent late toxicity for HNC.

Highly conformal RT techniques, such as intensity-modulated RT (IMRT), allow the dose to the surrounding normal tissues to be reduced while maintaining the dose to the target volume. Several studies on IMRT have demonstrated promising locoregional tumour control, as well as, potential preservation of salivary function, swallowing, and quality of life (4-8).

Although IMRT methods vary according to each institution, most institutions use simultaneous integrated boost (SIB) techniques. SIB-IMRT consists of only one treatment plan: 33 fractions of 2.12 Gy and 1.7 Gy to the high- and low-risk planning target volumes (PTVs), respectively (9). Although SIB-IMRT is an exciting new technique for improving the therapeutic ratio, there remains a question of whether an initial IMRT plan can be used for the whole course of fractionated RT. As treatment planning and quality assurance of IMRT plans require considerable time to prepare, most investigators use the initial IMRT plan for the whole course of IMRT (4-6). However, significant anatomical changes, including shrinking of the primary tumour or nodal masses, and body weight loss have been reported during fractionated RT for HNC (4-6). In a previous study (6), we also revealed that the volume of the parotid glands had decreased by 26% during the course of IMRT. These changes in body contour, target volumes, and organs at risk during IMRT can affect the dose distribution to the target volume and organs at risk, which can lead to marginal recurrence or late toxicities (4-6).

In order to avoid changes in the dose distribution during the 7- to 8-week period of IMRT, in this study, a two-step IMRT method was adopted for HNC. For all patients, treatment planning computed tomography was performed before IMRT (CT1) and during the third or fourth week of

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IMRT (CT2) for the boost IMRT treatment planning. Whole-neck RT (44-50 Gy/22-25 fractions) was delivered by IMRT, followed by boost IMRT to the high-risk clinical target volume (CTV) to a total dose of 70 Gy/35 fractions.

We previously reported the clinical results of two-step IMRT for patients with nasopharyngeal cancer at our institution (4). The aim of this study was to retrospectively evaluate the clinical results of our adaptive RT scheme using a two-step IMRT method for treating patients with oropharyngeal cancer (OPC). In addition, we examined the relationship between human papillomavirus (HPV) status, which is considered a strong prognostic factor, and the clinical results.

Materials and Methods

Patients and study design. This retrospective study was conducted with Institutional Review Board approval (no. 26-262) and in accordance with the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, effective December 13, 2001. Informed written consent for IMRT as a new method of RT was obtained from all patients.

The clinical results of 80 consecutive patients with OPC who were treated with curative intent by two-step IMRT at our Institution between December 2002 and June 2014 were analyzed. The characteristics of the patients are summarised in Table I. The cohort comprised 59 men and 21 women, with a median age of 66 (range=35-85) years. Pre-treatment evaluations included a complete history and physical examination, routine blood tests, and a laryngoscopy. All patients were examined by gastrointestinal fibroscopy, whole-body computed tomographic (CT) scans with/without head and neck magnetic resonance imaging (MRI). From 2006, 51 patients (63.8%) also underwent ^{18}F-fluorodeoxyglucose positron-emission tomography (PET)/CT (n=17; 21.3%) or PET/CT simulation scans (n=34; 42.5%) (10, 11). Staging was performed according to the seventh edition of the tumour-node-metastasis (TNM) classification of malignant tumours (12). All patients were presented at our weekly Tumour Board meeting. Based on the joint recommendations from the multidisciplinary team meeting, patients were selected for RT alone or chemoradiation therapy. Forty-three patients (53.8%) had undergone ipsilateral or bilateral neck dissection before definitive RT. In addition, volume reduction surgery of the primary tumour was performed in 34 patients (42.5%) before RT.

Treatment. Eighty consecutive patients were treated with the two-step IMRT method. The median follow-up period of the surviving patients was 64 (range=28-134) months.

Between 2002 and 2014, 33 patients (41.3%) with early-stage OPC and major comorbidity or poor performance status were treated with RT alone. Concurrent chemotherapy was administered to 47 patients (58.8%). Based on the successive implementation of new treatment strategies during the study period, the concurrent chemotherapy regimen was modified. Between 2003 and 2005, eight patients (10.0%) were treated with RT (70.0 Gy) and concomitant weekly docetaxel (10.0-15.0 mg/m^2). Between 2005 and 2013, 27 patients (33.8%) were treated with RT (70.0 Gy) and three cycles of concomitant cisplatin (80.0 mg/m^2 every 3 weeks). Five patients (6.3%) with poor renal function were treated with weekly carboplatin (5 areas under the curve). Between 2013 and 2014, six elderly patients (7.5%) with poor renal function were treated with weekly cetuximab (250.0 mg/m^2). The treatment parameters are summarized in Table II.

Patients were immobilised with a thermoplastic mask covering the head, neck, and shoulders (Type-S thermoplastic-based system; MED-TEC, Orange City, IA, USA). Treatment planning CT scans were obtained with contrast medium at 2.0-mm slice intervals from the head through the aortic arch. For all patients, treatment planning CT was performed before IMRT (CT1) and during the third or fourth week of IMRT (CT2) for boost IMRT. In most instances, a new thermoplastic mask was made for CT2.

The gross tumour volume (GTV) included any visible disease on imaging studies (MRI, CT, or PET/CT) and physical examination (10, 11). The primary CTV encompassed a 5.0-10.0 mm margin with appropriate anatomical correction around the primary GTV. The nodal CTV was defined and delineated according to the Danish Head and Neck Cancer Group, European Organisation for Research and Treatment of Cancer, French Group of Radiation Oncology for Head and Neck Cancer, French Head and Neck Cancer Group, National Cancer Institute of Canada, and Radiation Therapy Oncology Group consensus guidelines (13). Cervical and retropharyngeal lymph nodes with the shortest axial diameters of 10 mm or more and 5 mm or more, respectively, on CT or MRI were defined as metastatic. Lymph nodes of borderline size with abnormal enhancement were also indications of malignancy. The oropharyngeal region, bilateral level II-IV nodes, and the retropharyngeal nodes were included in the initial CTV. Submandibular lymph nodes (level Ib) were only included in the CTV when involved lymph nodes were suspected in ipsilateral level Ib. Margins of 3.0-4.0 mm for treatment set-up and internal organ motion error were added to the CTV to determine the PTV. For the planning volume for organs at risk, a 3.0-mm margin was added to the spinal cord (14). For the parotid glands, no margin was added in treatment planning.

After whole-neck RT (44-50 Gy/22-25 fractions) was delivered by IMRT, boost IMRT (to a total dose of 70 Gy/35 fractions) was prescribed to PTV2, which included the GTV and appropriate margins based on CT2. The daily prescribed dose to the PTV was 2 Gy. The prescribed dose was normalised to the dose to 95.0% of the PTV.

Our goals on dose–volume histogram parameters were maximum PTV <120% of the prescribed dose, mean PTV <105% (usually 103-104%), maximum dose delivered to the spinal cord <50 Gy, maximum dose delivered to the brain <70.0 Gy, median dose <20 Gy, and mean dose <26 Gy for at least one parotid gland. The IMRT beam arrangements consisted of seven or nine coplanar beams. Treatment planning for IMRT was performed using inverse planning on commercial treatment planning systems (CadPlan-Helios; Varian Associates Ltd., Palo Alto, CA, USA and Eclipse; Varian Medical Systems International Inc., Baden, Switzerland). IMRT was delivered using dynamic multileaf collimation with one of two linear accelerators (Clinac 600C, Clinac 21EX; Varian Associates Ltd.) equipped with a 40-leaf dynamic multileaf collimator. Beam energy of 4 or 6 MV X-rays was used. The daily treatment time was 15-20 minutes. To verify the leaf motion of each beam, several quality assurance performance tests were conducted. For patient set-up verification, offline bony anatomy matching was performed using megavoltage imaging before the initial IMRT and boost treatments.

Immunohistochemistry. Immunohistochemistry (IHC) for HPV/p16 expression was performed for 64 (80.0%) out of the 80 patients included in this study. Tumour specimens were obtained during surgery or diagnostic biopsy. One representative paraffin block was

Table I. *Characteristics of patients with squamous cell oropharyngeal carcinoma (n=80) and their tumours.*

Characteristic	Value
Median age (range), years	66 (35-85)
Gender, n (%)	
Male	59 (73.8)
Female	21 (26.2)
PS, n (%)	
0	56 (70.0)
1	23 (28.8)
2	1 (1.2)
Tumour site, n (%)	
Lateral	50 (62.5)
Anterior	16 (20.0)
Superior	10 (12.5)
Posterior	4 (5.0)
TNM stage, n (%)	
Seventh edition	
I	5 (6.2)
II	8 (10.0)
III	14 (17.5)
IVA-B	53 (66.3)
Eighth edition	
HPV/p16-positive	
I	23 (28.8)
II	5 (6.2)
III	3 (3.7)
HPV/p16-negative	
I	4 (5.0)
II	6 (7.5)
III	9 (11.3)
IVA-B	30 (37.5)
HPV/p16 expression status, n (%)	
Positive	31 (38.7)
Negative	33 (41.3)
Unknown	16 (20.0)
Double cancer, n (%)	
Synchronous	5 (6.2)
Non-synchronous	23 (28.8)

HPV, Human papilloma virus; PS, performance status; TNM, tumour-node-metastasis classification (18, 19).

Table II. *Summary of treatment parameters for patients with squamous cell oropharyngeal carcinoma (n=80).*

Treatment	Value
Median RT dose (range), Gy[a]	70 (40-70)
Concurrent chemotherapy, n (%)	47 (58.8)
Docetaxel (15.0 mg/m^2 weekly)	8 (10.0)
Cisplatin (80.0-100.0 mg/m^2 every 3 weeks)	27 (33.8)
Carboplatin (5 AUC weekly)	5 (6.3)
5-FU (700.0 mg/m^2) and cisplatin (70.0 mg/m^2)	1 (1.2)
Cetuximab (250.0 mg/m^2 weekly)	6 (7.5)

5-FU, 5-Fluorouracil; AUC, area under the curve; RT, radiation therapy. [a]Delivered in 2 Gy per fraction.

selected for each tumour. Status for patients without tumour tissue available at Kindai University Hospital (Osaka, Japan) for HPV/p16 staining was defined as unknown.

For specimens obtained between 2002 and 2011, IHC for HPV/p16 was performed using a CINtec Histology Kit (MTM Laboratories AG, Heidelberg, Germany) based on the monoclonal antibody E6H4 (15). For specimens obtained between 2011 and 2014, IHC for HPV/p16 was based on the monoclonal anti-human p16INK4a (1H4) mouse IgG. HPV/p16 expression was scored as positive if strong diffuse nuclear and cytoplasmic staining was detected in >70.0% of the tumour cells (16, 17).

Outcomes. The probability of survival after commencing IMRT was estimated using the Kaplan–Meier method, with significance assessed by the log-rank test. Overall survival (OS) was defined as the time to death from any cause. Events for progression-free survival included locoregional or distant tumour progression and death from any cause. Primary tumour or regional lymph node recurrence were considered events for locoregional control (LRC). After IMRT, LRC and distant progression were evaluated every 3-4 months for more than 5 years by clinical examination and imaging studies (MRI, CT, and PET/CT). When tumour recurrence or distant metastasis was observed, salvage treatment was mandatory.

Toxicities. Late toxicities were graded 90 days after the commencement of IMRT according to the Common Terminology Criteria for Adverse Events, version 4.0 (18). Xerostomia was recorded as the highest score in the 90-day follow-up period.

Results

The 3- and 5-year OS and LRC rates of all 80 patients with OPC were 72.0% and 69.0%, and 89.0% and 85.0%, respectively. According to the TNM classification (seventh edition) (12), the 5-year OS and locoregional control rates for stage I, II, III, and IVA-B disease were 80.0%, 75.0%, 78.0%, and 64.0%, and 100.0%, 75.0%, 92.0% and 82.0% respectively (Figure 1a). As of March 2017, 28 patients (35.0%) had died. Fifteen patients (18.8%) died of their disease, including three treatment-related deaths (3.8%). Non-OPC-related mortality, including double cancer, myelodysplastic syndrome, anaplastic anaemia, pneumonia, and cerebral infarction, was observed in 13 patients (16.2%). At the time of the last follow-up, the remaining 52 patients (65.0%) were alive after a median follow-up period of 64 (range=28-134) months.

The 5-year LRC rates according to the seventh TNM classification (12) were 100.0%, 75.0%, 92.0%, and 82.0% for patients with stage I, II, III, and IVA-B disease, respectively (Figure 1b). Although there were 10 locoregional recurrences (12.5%), no marginal recurrence at the edge of the PTV was observed. All locoregional recurrences were detected in the PTV region receiving 66.0-70.0 Gy. Isolated distant failures were observed in four patients (5.0%) and one patient (1.2%) developed combined failures.

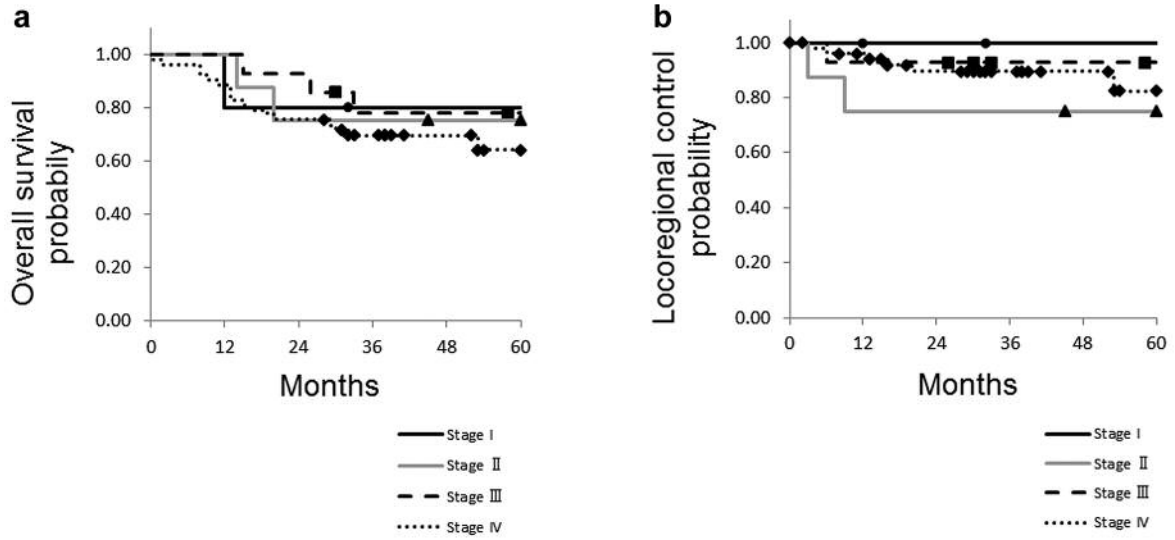

Figure 1. *Kaplan–Meier curves of overall survival (a) and locoregional control (b) of patients with oropharyngeal cancer (n=80) according to stage by the seventh edition of the tumour-node-metastasis classification (18).*

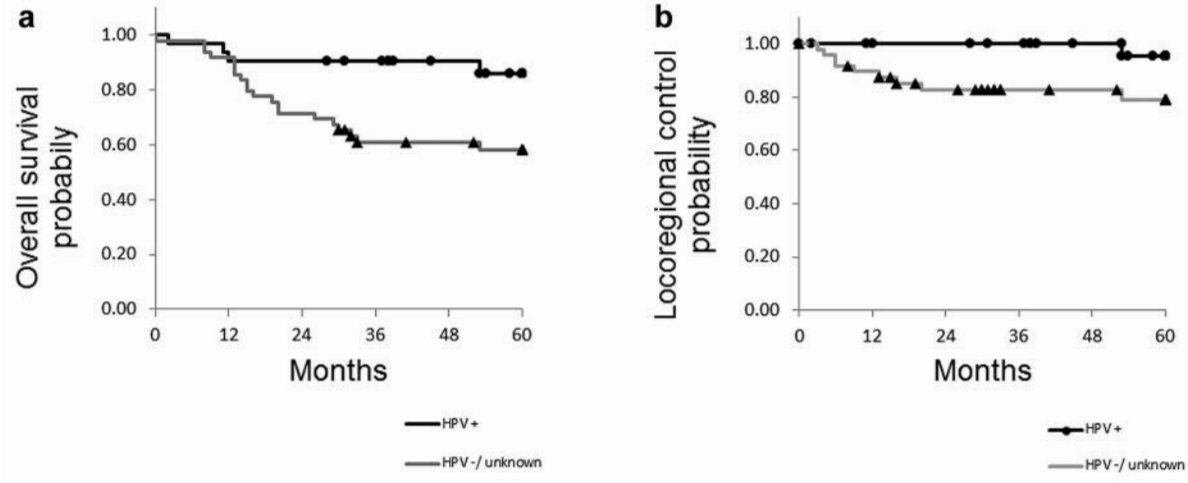

Figure 2. *Kaplan–Meier curves of overall survival (a) and locoregional control (b) of patients with oropharyngeal cancer (n=80) according to human papilloma virus (HPV)/p16 expression status.*

Thirty-one (48.4%) out of the 64 tumour specimens were HPV/p16-positive by IHC analysis. The 5-year OS and LRC rates were significantly higher for patients with HPV/p16-positive tumours compared with those with HPV/p16-negative ones or patients in whom IHC analysis was not performed (5-year OS: 86.0% *vs*. 58.0%, p=0.013 and 5-year LRC: 95.0% *vs*. 79.0%, p=0.038) (Figure 2). Of the 10 locoregional recurrences, one was HPV/p16-positive and seven were HPV/p16-negative. IHC analysis was not performed for the remaining two patients.

Restaging was performed according to the eighth edition of the TNM classification (19). Among the 31 HPV/p16-positive patients, 23 had stage I, five had stage II, and three had stage III disease. Among the 33 HPV/p16-negative patients, four had stage I, six had stage II, nine had stage III, and 30 had stage IVA-B disease. For the remaining 16 patients, IHC analysis was not performed. According to staging by the eighth edition of the TNM classification (19), the 5-year OS rates for patients with stage I, II, III, and IVA-B disease were 88.0%, 80.0%, 66.0%, and 48.0%, respectively (Figure 3a).

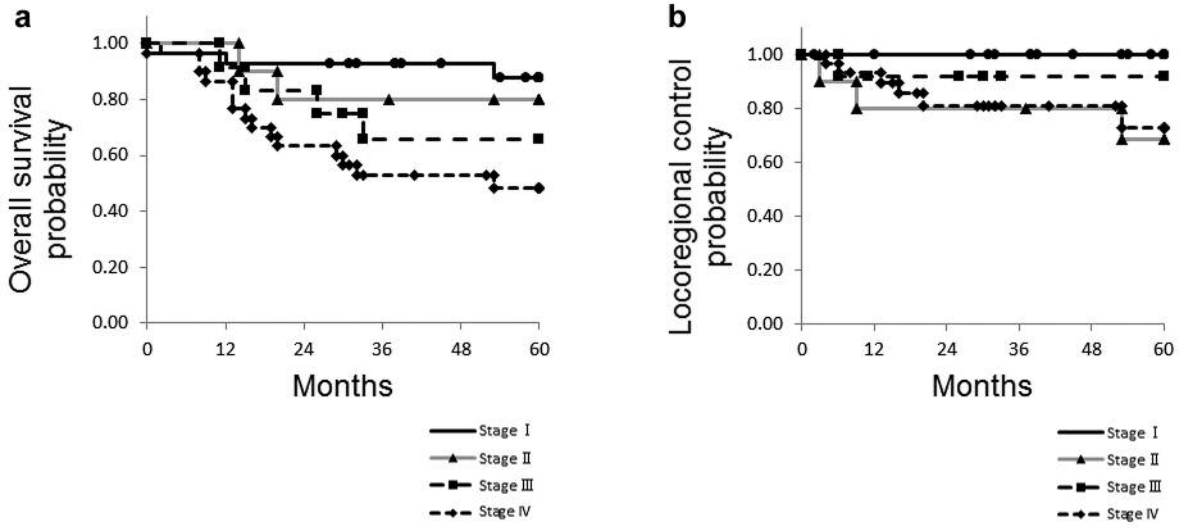

Figure 3. *Kaplan–Meier curves of overall survival (a) and locoregional control (b) of patients with oropharyngeal cancer (n=80) according to stage by the eighth edition of the tumour-node-metastasis classification (19).*

The corresponding 5-year LRC rates were 100.0%, 69.0%, 92.0%, and 73.0%, respectively (Figure 3b).

Late toxicities associated with IMRT with and without concurrent chemotherapy are summarized in Table III. Hypothyroidism and dysphagia were common late toxicities. Seventeen patients (21.3%) complained of dysphagia after treatment, with three (3.8%) requiring percutaneous endoscopic gastrostomy. Apparent treatment-related deaths were noted in three patients. One patient died of dysphagia due to severe mucositis. For this patient, RT was terminated at 64.0 Gy (32 fractions) due to grade 4 mucositis. However, persistent mucositis resulted in severe dysphagia, leading to nutritional deficiencies and a deterioration in performance status. One patient who was treated with 66.0 Gy RT and concomitant weekly docetaxel (15.0 mg/m^2) died of carotid artery rupture 74 months after treatment without recurrence. The rupture site involved the primary tumour. The final patient died of infectious pneumonia during IMRT.

Long-standing xerostomia of grade 2 or more was observed in 10 patients (12.5%). Excluding patients with early death (n=2), grade 0, 1, and 2 xerostomia at 2 years of treatment were observed in 49, 19, and 10 patients, respectively (Table III).

Table III. *Late toxicities (Common Terminology Criteria for Adverse Events, version 4.0) (18).*

Toxicity	Grade, no. of patients				
	G1	G2	G3	G4	G5
Skin	10	0	0	0	0
Middle ear inflammation	0	2	0	0	0
Dysphagia	11	2	3	0	1
Osteonecrosis of the jaw	0	1	1	0	0
Laryngeal oedema	0	0	1	0	0
Xerostomia at 24 months	19	10	0	–	–
Hypothyroidism	8	20	0	0	0
Vascular disorders	0	0	0	0	1

Discussion

IMRT has been increasingly adopted as an effective RT technique that provides excellent OS and LRC rates with fewer treatment-related toxicities. Most of the published data on IMRT for the treatment of HNC were collected using the SIB technique. Among the published studies, Huang *et al*. reported 3-year OS and LRC rates of 83% and 90%, respectively, for patients with stage III and IV OPC using SIB-IMRT (20). Similarly, Daly *et al*. reported 3-year OS and LRC rates of 83% and 92%, respectively, for SIB-IMRT-treated patients with OPC (21). These and several other studies (20-27) are summarised in Table IV. These institutions used the SIB technique and produced 3-year OS and LRC rates of approximately 84% and 90%, respectively. In this study, two-step IMRT was used to treat patients with OPC. The 3-year OS and LRC rates were 72% and 89%, respectively. Thus, the LRC rate was comparable to that of previous reports. However, the OS rate was slightly lower than that of previous reports. In this study, the HPV/p16-positive rate of patients with OPC was approximately 50%.

Table IV. *Summary of reported clinical results of intensity-modulated radiation therapy (IMRT) for oropharyngeal cancer.*

Study (Ref.)	Patients (n)	Median follow-up (months)	Stage (TNM edition)	IMRT	Dose/ fx	Adaptive replan	Xerostomia, grade (%)	LRC	OS
Huang *et al*. (20)	71	33	III-IV (6th)	SIB	70.0 Gy/33	–	2 (22%)	90% (3y)	83% (3y)
Daly *et al*. (21)	107	29	II-IV (6th)	SIB	66.0 Gy/30	–	–	92% (3y)	83% (3y)
Ward *et al*. (25)	156	22	I-IV (7th)	SIB	70.0 Gy/35	42%	2 (23%)	93% (2y)	88% (2y)
Masoud Rahbari *et al*. (26)	61	22	I-IV (7th)	SIB	70.0 Gy/35	–	1-2 (38%)	98% (2y)	90% (2y)
McBride *et al*. (22)	132	51	III-IV (6th)	SIB	70.0 Gy/33	–	1-2 (15%)	99% (5y)	79% (5y)
Setton *et al*. (23)	404	37	I-IV (5th)	SIB	70.0 Gy/33	–	2 (7%)	89% (3y)	85% (3y)
Garden *et al*. (24)	776	54	I-IV (6th)	SIB	66.0 Gy/33	–	–	90% (5y)	84% (5y)
Bird *et al*. (27)	177	26	I-IV (7th)	SIB	65.0 Gy/30	–	2 (38%)	88% (3y)	77% (3y)
Present series	80	64	I-IV (7th)	Two-step	70.0 Gy/35	100%	2 (12%)	85% (5y)	69% (5y)

Ref., Reference; fx, fractions; LRC, locoregional control; OS, overall survival; SIB, simultaneous integrated boost; y, years.

A recent study in America reported HPV/p16-positive rates as high as 70-80% (28). In Sweden, the HPV/p16-positive rate of OPC steadily increased over time to 93% in 2007 (29). This difference in the HPV/p16-positive rate of OPC may have contributed to the slightly lower OS rate in the present study. Notably, the 5-year OS and LRC rates for HPV/p16-positive patients were 86% and 95%, respectively.

For the SIB technique, most investigators use the initial IMRT plan for the whole course of IMRT. Anatomical changes, including shrinking of the primary tumour or nodal masses, and body weight loss during IMRT with/without concurrent chemotherapy have been reported (4-6). The two-step IMRT method may be adaptable to anatomical changes since all patients require re-planning during the third or fourth week of IMRT. However, the two-step IMRT method may lead to marginal recurrences due to insufficient target delineation. Chen *et al*. reported on the potential negative impact of contouring errors on the prognosis of HPV/p16-positive patients with OPC (30). Indeed, at our Institution, we have experienced several cases of early marginal recurrence in patients with nasopharyngeal cancer who were treated by two-step IMRT (4). In the present series of patients with OPC, no marginal recurrences were observed at the edge of the PTV. At our Institution, integrated PET/CT simulation scans have been performed from 2006 (9, 10). These PET/CT simulation scans are especially effective for visualising the GTV, and there is the potential for PET/CT simulation to reduce marginal recurrence (31). In addition, HPV/p16-positive OPC may be characterised by more rapid progression than HPV/p16-negative OPC (32). Overall, our two-step IMRT method may be useful for treating rapidly progressive HPV/p16-positive OPC.

In this series, three patients (3.8%) died of myelodysplasia or anaplastic anaemia. Recently, RT and chemotherapy were reported to be more likely to increase the risk of therapy-related myeloid neoplasms, including myelodysplasia (33, 34). These three cases may be therapy-related myeloid neoplasms influenced by RT with/without concurrent chemotherapy.

Only 10 (12.5%) out of the 80 patients in the current series developed grade 2 xerostomia. None of the patients developed grade 3 or more xerostomia. In our previous studies, we reported on the position and volume changes of the parotid glands during IMRT with and without concurrent chemotherapy (5, 6). The two-step IMRT method may be adjusted to anatomical changes, thereby preventing increases in the high-dose regions of the parotid glands (6). The incidence of grade 1-2 xerostomia using the SIB-IMRT method is reported to range from 7-38%, with a median of 22-23% (20-27) (Table IV). In this series, the rate of grade 2 xerostomia at 24 months was 12.5%. Thus, the effectiveness of the two-step IMRT method for preventing xerostomia was confirmed.

This study has several limitations, including its retrospective single-centre design and limited sample size. However, the treatment protocol of RT was kept constant in this study. In addition, we performed re-staging using the eighth edition of the TNM classification (19) of all analysed patients in order to update the outcomes according to the latest edition of the staging system. In the results, the updated staging system was validated to predict the clinical outcomes after two-step IMRT. The eighth edition of the TNM classification was recently reported to correlate prognosis of OPC better than the seventh edition (35). To our knowledge, this is the first report to describe the clinical results of IMRT for OPC with re-staging using the eighth edition of the TNM classification (19). Another limitation of this study is the lack of physical validation, such as study planning and dose–volume histogram analysis. However, we have already reported the superiority of the two-step IMRT method as an adaptive RT scheme in patients with nasopharyngeal cancer and performed a detailed analysis of the dose parameters for

the two-step IMRT method in patients with HNC (4, 6). Thus, we decided to use the two-step IMRT method in clinical practice. A prospective comparison study may be ethically challenging at our Institution. Therefore, we believe that our data are sufficiently reliable and could form the basis for future prospective clinical trials in order to directly compare these two different methods of IMRT (SIB and two-step) in combination with updated chemotherapy techniques, including targeted agents and immunotherapeutic approaches.

In conclusion, favourable OS and LRC rates with excellent salivary preservation were obtained using the two-step IMRT method for OPC. No marginal recurrence was detected at the edge of the PTV. Two-step IMRT may be the ideal method of adaptive RT for OPC. In addition, the eighth edition of the TNM classification predicted the clinical outcomes of patients treated with two-step IMRT better than the seventh.

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