ONLINE FIRST

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

Impact of upgraded radiotherapy system on outcomes in postoperative head and neck squamous cell carcinoma patients

Authors: Keiichiro Koiwai, Dai Hirasawa, Miyu Sugimura, Yuuki Endo, Kai Mizuhata, Hironobu Ina, Ayumu Fukazawa, Ryosuke Kitoh, Hironori Sakai, Yasunari Fujinaga

DOI: 10.5603/RPOR.a2022.0120

Article type: Research paper

Published online: 2022-11-09

Impact of upgraded radiotherapy system on outcomes in postoperative head and neck squamous cell carcinoma patients

Running head: Upgraded postoperative RT for head and neck SCC

10.5603/RPOR.a2022.0120

Keiichiro Koiwai[1], Dai Hirasawa[1], Miyu Sugimura[1], Yuuki Endo[1], Kai Mizuhata[1], Hironobu Ina[1], Ayumu Fukazawa[1], Ryosuke Kitoh[2], Hironori Sakai[3], Yasunari Fujinaga[1]

[1]*Department of Radiology, Shinshu University, School of Medicine, Matsumoto, Japan*

[2]*Department of Otorhinolaryngology, Shinshu University, School of Medicine, Matsumoto, Japan*

[3]*Department of Dentistry and Oral Surgery, Shinshu University, School of Medicine, Matsumoto, Japan*

Corresponding author: Keiichiro Koiwai, MD, Department of Radiology, Shinshu University, School of Medicine, 3-1-1, Asahi, Matsumoto, Japan; e-mail:

kkoiwai@shinshu-u.ac.jp

Abstract

Background: This study was performed to evaluate the impact of upgrade of radiotherapy system, including launch of intensity-modulated radiation therapy (IMRT), on the therapeutic outcomes.

Materials and methods: Patients with head and neck (H&N) squamous cell carcinoma (SCC) who underwent postoperative radiotherapy at our hospital between June 2009 and July 2019 were retrospectively reviewed. In July 2014, we converted the radiotherapy technique for these patients from a 3-dimensional conformal radiotherapy (3D-CRT) to IMRT, along with the adoption of a meticulous planning policy and a few advanced procedures, including online imaging guidance.

Results: A total of 136 patients (57 treated with the previous system and 79 treated with the upgraded system) were reviewed. There were significantly more patients with extracapsular extension in the upgraded-system group than the previous-system group ($p = 0.0021$). There were significantly fewer patients with ≥ Grade 2 acute and late adverse events in the upgraded-system group than the previous-system group. The

differences in progression-free survival (PFS), distant metastasis-free survival (DFFS), locoregional progression-free survival (LRPFS), and overall survival (OS) between the two groups were not statistically significant (p = 0.8962, 0.9926, 0.6244, and 0.4827, respectively). Multivariate analysis revealed that the upgrade had neither positive nor negative impact on survival outcomes. Extracapsular extension was independently associated with decreased LRPFS and OS (p = 0.0499 and 0.0392, respectively).

Conclusions: The IMRT-centered upgrade was beneficial for the postoperative patients with H&N SCC, because survival outcomes were sustained with less toxicities.

Key words: head and neck squamous cell carcinoma; postoperative radiotherapy; intensity-modulated radiation therapy

Introduction

Postoperative radiotherapy for head and neck squamous cell carcinoma (H&N SCC) was introduced in the 1950s [1] and has been performed with or without chemotherapy as a standard of care in patients with risk factors for recurrence [2]. Intensity-modulated radiation therapy (IMRT) has been widely applied for head and neck cancers because of its superiority to the conventional 3-dimensional conformal

radiotherapy (3D-CRT) technique in terms of preventing severe xerostomia [3, 4]. However, there is controversy regarding its effectiveness on survival outcomes, especially in a postoperative setting [4, 5]. Our hospital upgraded its radiotherapy system in July 2014. The radiotherapy technique for postoperative H&N SCC patients was converted from 3D-CRT to IMRT. Since then, we have meticulously planned and performed IMRT, which has been accompanied by newly incorporated procedures. This study was performed to evaluate the impact of our IMRT-centered upgrade on the therapeutic outcomes by comparing patients treated with the upgraded system with those treated with the previous system.

Materials and methods

Patients

As mentioned above, our hospital started treating patients with the upgraded system in July 2014, prior to which we used the previous system. The study period was set in order to compare the clinical outcomes of patients with H&N SCC who underwent postoperative radiotherapy at our hospital during the 5 years after the upgrade (the upgraded-system era) with those treated during the 5 years before the upgrade (the

previous-system era). Hence, the patients treated between June 2009 and July 2019 were retrospectively reviewed. Patients with any histological type other than SCC were excluded from the study.

This retrospective study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. Our Institutional Review Board approved the study (approval number: 5353) and waived the requirement for informed consent.

Treatment

All patients underwent physical examinations, endoscopy, and computed tomography (CT) as pre-treatment workups. Magnetic resonance imaging (MRI) was added if necessary. Almost all the patients underwent 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET).

Combinations of platinum agents and taxanes were administered as pre-operative chemotherapy at the discretion of the attending physicians. Definitive resection of primary lesion with neck dissection was routinely performed for the patients throughout the study period. Prophylactic neck dissection for the patients with no lymph node metastasis was omitted if the primary site was either the nasal or the

paranasal cavity.

Regardless of the radiotherapy technique, treatment volumes were determined based on preoperative imaging examinations, operative findings, and pathological review of surgical specimens. However, we were aware of the risk of geographical misses in implementing IMRT [6], so we intensified both pre- and postoperative discussion at the institutional multidisciplinary H&N Cancer Board consisting of radiation oncologists, head and neck surgeons, dentists, and medical oncologists at the beginning of the upgraded-system era. We deepened the understanding of each patient's condition through discussion to maintain the quality of IMRT planning.

For patients in the previous-system group, a non-opposed pair of fields was used for initial whole-neck irradiation. Then, the spinal cord was shielded by reduction in the posterior border of the fields. This posterior neck tissue was typically supplemented with 6–12 MeV electron fields matched at the skin surface and prescribed to achieve the desired dose. Boost fields were subsequently delivered when needed. By this sequential cone-down technique, the following doses were delivered to the clinical target volumes (CTVs): 57.6 Gy for low-risk CTVs (elective lymph node levels), 63 Gy for intermediate-risk CTVs (entire tumor beds and nodal levels containing

metastatic lymph nodes), and 70.2 Gy for high-risk CTVs (positive surgical margins) at 1.8 Gy per fraction, 5 days per week [7]. Extracapsular extension wasn't taken into account when deciding radiation doses.

Patients in the upgraded-system group were treated with volumetric modulated arc therapy with a simultaneous integrated boost consisting of 35 fractions with single doses of 1.6 Gy (low-risk CTVs), 1.8 Gy (intermediate-risk CTVs), and 2 Gy (high-risk CTVs), 5 days per week, up to a total dose of 56 Gy/63 Gy/70 Gy. A boost of 7.4 Gy in four fractions was added to the 63 Gy if a surgical margin was revealed to be positive after initiating radiotherapy. As well as 3D-CRT, extracapsular extension wasn't considered when deciding radiation doses. Although the CTVs were determined according to a policy similar to that used in 3D-CRT planning, we made more efforts to delineate precise target volumes in IMRT planning compared with 3D-CRT planning. The results of the clinical assessment described above were fully incorporated into the delineation, although image registration wasn't routinely used. Lymph node levels were routinely delineated according to the consensus guidelines [8, 9].

In 3D-CRT, we prescribed a radiation dose to the isocenter or a nearby point, at the

discretion of the attending physicians. In IMRT, we prescribed a dose covering 95% ($D_{95\%}$) of the representative planning target volume (PTV).

The radiotherapy planning system (RTPS) was Eclipse (Varian Medical Systems, Palo Alto, CA, United States) throughout the study period, but dose calculation in 3D-CRT planning was mostly performed using the pencil-beam convolution (PBC) algorithm, which is equivalent to the Clarkson method, with heterogeneity correction using the Batho power law. We updated the RTPS when we upgraded the radiotherapy system. The dose calculation algorithm was replaced by the anisotropic analytical algorithm (AAA).

Most of the patients in the previous-system group were treated with a linear accelerator that did not have any online imaging guidance functions. On the other hand, the linear accelerator which we obtained for the upgraded system was equipped with an ExacTrac X-ray online imaging guidance system (Brainlab, Munich, Germany), and we routinely corrected the patient's position in each session of IMRT.

We usually started radiotherapy no later than 6 weeks after surgery [10], and concurrent chemotherapy was administered to patients with risk factors, such as extracapsular extension of lymph node metastases and positive surgical margins [11],

regardless of radiotherapy technique. A tri-weekly cisplatin regimen was uniformly adopted.

Patients were examined at least weekly during radiotherapy to monitor radiation-induced acute toxicity. They were followed once a month for the first one or two years. Then, the intervals were gradually prolonged. Radiological image examinations were performed every 3 to 6 months during the follow-up period. Routine follow-up usually ended 5 years after treatment but continued as needed or requested.

Statistical analysis

Statistical comparisons between the previous-system and upgraded-system groups were performed using Fisher's exact test and the Mann-Whitney *U* test. Survival analyses were then performed. Any cases of treatment failure or death due to any cause were counted as events in progression-free survival (PFS) analysis. Either distant metastasis or death due to any cause was counted as an event in distant metastasis-free survival (DMFS) analysis. Either locoregional failure or death due to any cause was counted as an event in locoregional progression-free survival (LRPFS) analysis. Death due to any cause was counted as an event in overall survival (OS) analysis. These

survival rates of each of the groups were calculated from the day of surgery, and the survival curves were calculated by the KaplaniMeier method. Statistical comparisons between the curves of the previous-system and upgraded-system groups were performed by the log-rank test. A multivariate analysis was performed based on the Cox proportional-hazards regression model to identify the prognostic factors for the survivals. All statistical analyses were performed with JMP version 14.2.0 (SAS Institute Inc., Cary, NC, United States). In all analyses, $p < 0.05$ was taken to indicate statistical significance. Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 5.0 (National Cancer Institute, Rockville, MD, United States).

Results

A total of 136 patients with H&N SCC who received postoperative radiotherapy at our hospital between June 2009 and July 2019 were identified as appropriate for this study. Fifty-seven were treated with the previous system and 79 were treated with the upgraded system. Table 1 shows the characteristics of both groups. Performance status was evaluated with the Eastern Cooperative Oncology Group scale [13], and geriatric assessment was performed with the Charleston Comorbidity Index (CCI) [13]. The

stages were harmonized according to the current 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system [14]. There were significantly more patients who underwent pre-treatment MRI in the upgraded-system group than the previous-system group. There were significantly more patients with extracapsular extension in the upgraded-system group than the previous-system group. Hence, significantly more patients received concurrent chemotherapy in the upgraded-system group than the previous-system group. The mean follow-up period in the upgraded-system group was significantly shorter than that in the previous-system group.

Most of the patients underwent their treatment as planned. Table 2 shows the acute adverse events in both groups. There were significantly fewer patients with dermatitis, mucositis, and dysphagia ≥ Grade 2 in the upgraded-system group than the previous-system group ($p = 0.0003$, 0.0067, and < 0.0001, respectively). Table 3 shows the late adverse events in both groups. There were significantly fewer patients with xerostomia, dysphagia, and osteonecrosis of the jaw ≥ Grade 2 in the upgraded-system group than the previous-system group ($p = 0.0006$, < 0.0001, and 0.0429, respectively).

By the time of the last follow-up, treatment failures occurred in 60 patients (24 with

distant metastases alone, 26 with locoregional failures alone, and 10 with combined failures) and 27 patients died. Figure 1 shows the PFS, DFFS, LRPFS, and OS curves of the previous-system and upgraded-system groups. Three-year PFS, DFFS, LRPFS, and OS rates in the previous-system and upgraded-system groups were 59.6% [95% confidence interval (CI): 46.5–71.5] and 65.0% (95% CI: 53.7–74.8), 61.4% (95% CI: 48.3–73.1) and 70.2% (95% CI: 58.8–79.6), 66.3% (95% CI: 53.0–77.4) and 71.4% (95% CI: 60.3–80.4), and 67.6% (95% CI: 54.6–78.6) and 76.6% (95% CI: 65.5–85.0), respectively. The differences in PFS, DFFS, LRPFS, and OS between the two groups were not statistically significant ($p = 0.8962$, 0.9926, 0.6244, and 0.4827, respectively).

A multivariate analysis was performed. Based on prior knowledge including results of the previous studies [11, 15], radiotherapy system and other 5 potential prognostic factors were selected as variables from the dichotomized characteristics listed on Table 1. The selected variables were as follows: radiotherapy system (upgraded vs previous), age (≥ 75 *vs.* < 75), sex (male vs female), pathological stage (I–II *vs.* III–IV), pathological margin (positive *vs.* negative), extracapsular extension (positive vs negative). The results of the multivariate analysis are shown in Table 4. Radiotherapy

system was not an independent prognostic factor for the survivals. Higher age was independently associated with decreased DMFS and OS ($p = 0.0184$ and 0.0414, respectively), pathological positive margin was independently associated with decreased OS ($p = 0.0404$), and extracapsular extension was independently associated with decreased LRPFS and OS ($p = 0.0499$ and 0.0392, respectively).

Discussion

This study showed that the postoperative survival outcomes of patients with H&N SCC was sustained after upgrading the radiotherapy system, which is IMRT-centered, along with less toxic profiles. Although multivariate analysis revealed that the upgrade had neither positive nor negative impact on survival outcomes, the survival rates of the upgraded-system group, which contained more high-risk patients (i.e., with extracapsular extension) than the previous-system group, weren't deteriorated.

Meta-analyses have shown that IMRT reduces adverse events, especially xerostomia, in patients with H&N cancers [3]. Organs at risk, such as the salivary glands, can be spared effectively by this method [4]. In this study, adverse events other than xerostomia were also reduced in the upgraded-system group. As a result of intensification of the multidisciplinary approach at the beginning of the upgraded-

system era, oral care was routinely given to patients treated with IMRT, which may have been responsible for the reduction in the adverse events [16].

On the other hand, there have been only a few studies showing that IMRT is effective in improving survival outcomes. In a study using the Surveillance, Epidemiology, and Results-Medicare database, Beadle et al. reported that IMRT improved cause-specific survival in patients with H&N cancers [5]. In contrast, a meta-analysis by De Felice et al. reported that IMRT did not necessarily have survival benefits in these patients [4].

There have been only a few studies regarding survival outcome of postoperative H&N cancer patients who had IMRT. Most of them were non-comparison studies [17–19], and there is substantial inconsistency among the results of the comparison studies. Chen et al. compared postoperative patients with SCC of the oral cavity receiving IMRT with those receiving conventional radiotherapy in terms of survival, and reported that the 3-year locoregional control and disease-free survival rates were significantly increased in the IMRT group [20]. In contrast, Turaka et al. reported that IMRT was associated with increased recurrence in postoperative H&N cancer patients [21].

Reasons for the inconsistency cannot be easily explained, but differences in the

procedures accompanying IMRT may be one source of inconsistency [4]. From that point of view, there are a few possible explanations for the results in our study. We endeavored to reduce geographical misses in IMRT planning by meticulously tailored target delineation. This may have avoided the geographical misses and contributed to the sustained survival outcomes. Online positional correction with imaging guidance, which was routinely used in the upgraded system but not in the previous system, was also thought to avoid the incidence of geographical misses in delivery of radiation [22]. We adopted a suitable prescribing method and a dose-calculation algorithm for IMRT planning. $D_{95\%}$ prescription ensures consistent dosimetric coverage [23], and AAA is a more accurate algorithm than PBC [24]. These factors could also have contributed to the observed sustainment in the survival outcomes. By the time of the upgrade, we had developed fundamental skills, such as patient immobilization, through the previous system. This may have been an important factor for the outcomes with the upgraded system. The procedures described above, in a combined manner, are thought to have yielded better therapeutic outcome (sustained survivals with less toxicity).

Comparing therapeutic outcomes before and after conversion of the therapeutic technique in a single institution, as in the present study, is a reasonable way to evaluate

the impact of newly incorporated methodologies on the outcomes. Especially, IMRT is already widely used because of its ability to reduce adverse events [3], so randomized controlled trials are not easily applicable to such evaluations.

This study had some limitations. First, it had a retrospective design, and the actual relations between outcomes and interventions may have been masked by unknown biases. Second, the sample size was small because it was from a single institution. Third, the follow-up period was significantly different between the upgraded-system group and previous-system group. This may have affected the difference of the outcomes, such as the late adverse events. Fourth, although the upgrade was IMRT-centered, there was a possibility that IMRT per se had only a limited effect, because the upgrade included a few other newly incorporated interventions and the effect of each of them could not be quantified. Fifth, we also could not exclude the possibility that advances in treatments other than radiotherapy, such as surgery and chemotherapy, affected the outcomes, because patients in the upgraded-system group were treated in a later period than the previous-system group.

Conclusions

Our 10-year experience of postoperative radiotherapy for H&N SCC using the

previous system in the first half and the upgraded system in the second half was retrospectively reviewed. We found that the upgrade, which was IMRT-centered, was beneficial, because survival outcomes were sustained with less toxicities.

Acknowledgements

The authors are grateful to Ms. M. Hazama and Mrs. Y. Ogawa for their support.

Conflicting interests

None declared.

Funding

None declared.

Figure 1. Survival curves of the previous-system group and the upgraded-system group. **A.** Progression-free survival; **B.** Distant metastasis-free survival; **C.** Locoregional progression-free survival; **D.** Overall survival

References

1. Maccomb WS, Fletcher GH. Planned combination of surgery and radiation in treatment of advanced primary head and neck cancers. Am J Roentgenol Radium Ther Nucl Med. 1957; 77(3): 397–414, indexed in Pubmed: 13403033.

2. Amdur R, Parsons J, Mendenhall W, et al. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys. 1989; 16(1): 25–36, doi: 10.1016/0360-3016(89)90006-0, indexed in Pubmed: 2912947.

3. Marta GN, Silva V, de Andrade Carvalho H, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 2014; 110(1): 9–15, doi: 10.1016/j.radonc.2013.11.010, indexed in Pubmed: 24332675.

4. DE Felice F, Pranno N, Papi P, et al. Xerostomia and Clinical Outcomes in Definitive Intensity Modulated Radiotherapy (IMRT) Three-dimensional Conformal Radiotherapy (3D-CRT) for Head and Neck Squamous Cell Carcinoma: A Meta-analysis. In Vivo. 2020; 34(2): 623–629, doi: 10.21873/invivo.11816, indexed in Pubmed: 32111762.

5. Beadle BM, Liao KP, Elting LS, et al. Improved survival using intensity-modulated radiation therapy in head and neck cancers: a SEER-Medicare analysis. Cancer. 2014; 120(5): 702–710, doi: 10.1002/cncr.28372, indexed in Pubmed: 24421077.

6. Chen AM, Farwell DG, Luu Q, et al. Marginal misses after postoperative intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2011; 80(5): 1423–1429, doi: 10.1016/j.ijrobp.2010.04.011, indexed in Pubmed: 20656416.

7. Rosenthal DI, Mohamed ASR, Garden AS, et al. Final Report of a Prospective Randomized Trial to Evaluate the Dose-Response Relationship for Postoperative Radiation Therapy and Pathologic Risk Groups in Patients With Head and Neck Cancer. Int J Radiat Oncol Biol Phys. 2017; 98(5): 1002–1011, doi: 10.1016/j.ijrobp.2017.02.218, indexed in Pubmed: 28721881.

8. Grégoire V, Levendag P, Ang KK, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. Radiother Oncol. 2003; 69(3): 227–236, doi: 10.1016/j.radonc.2003.09.011, indexed in Pubmed: 14644481.

9. Grégoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI,

RTOG, TROG consensus guidelines. Radiother Oncol. 2014; 110(1): 172–181, doi: 10.1016/j.radonc.2013.10.010, indexed in Pubmed: 24183870.

10. Mantravadi RV, Haas RE, Liebner EJ, et al. Postoperative radiotherapy for persistent tumor at the surgical margin in head and neck cancers. Laryngoscope. 1983; 93(10): 1337–1340, doi: 10.1002/lary.1983.93.10.1337, indexed in Pubmed: 6621234.

11. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005; 27(10): 843–850, doi: 10.1002/hed.20279, indexed in Pubmed: 16161069.

12. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5(6): 649–655, indexed in Pubmed: 7165009.

13. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011; 173(6): 676–682, doi: 10.1093/aje/kwq433, indexed in Pubmed: 21330339.

14. Zanoni DK, Patel SG, Shah JP. Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer: Rationale and Implications. Curr Oncol Rep. 2019; 21(6): 52, doi: 10.1007/s11912-019-0799-x, indexed in Pubmed: 30997577.

15. Cooper J, Pajak T, Forastiere A, et al. Precisely defining high-risk operable head and neck tumors based on rtog #85-03 and #88-24: Targets for postoperative radiochemotherapy? Head Neck. 1998; 20(7): 588–594, doi: 10.1002/(sici)1097-0347(199810)20:7<588::aid-hed2>3.0.co;2-f, indexed in Pubmed: 9744457.

16. Leu M, Patzer C, Guhlich M, et al. Postoperative Radiochemotherapy Using Modern Radiotherapy Techniques in Elderly Patients with Head and Neck Squamous Cell Carcinoma: The Challenge of Weighing Up Benefits and Harms of Treatment

Modalities in Clinical Practice. Cancers (Basel). 2021; 13(14), doi: 10.3390/cancers13143384, indexed in Pubmed: 34298599.

17. Hsieh CH, Shueng PW, Wang LY, et al. Clinical effectiveness, toxicity, and failure patterns of helical tomotherapy for postoperative oral cavity cancer patients. Onco Targets Ther. 2014; 7: 405–414, doi: 10.2147/OTT.S59998, indexed in Pubmed: 24648744.

18. Ooishi M, Motegi A, Kawashima M, et al. Patterns of failure after postoperative intensity-modulated radiotherapy for locally advanced and recurrent head and neck cancer. Jpn J Clin Oncol. 2016; 46(10): 919–927, doi: 10.1093/jjco/hyw095, indexed in Pubmed: 27511989.

19. Studer G, Furrer K, Davis BJ, et al. Postoperative IMRT in head and neck cancer. Radiat Oncol. 2006; 1: 40, doi: 10.1186/1748-717X-1-40, indexed in Pubmed: 17052346.

20. Chen PY, Chen HHW, Hsiao JR, et al. Intensity-modulated radiotherapy improves outcomes in postoperative patients with squamous cell carcinoma of the oral

cavity. Oral Oncol. 2012; 48(8): 747–752, doi: 10.1016/j.oraloncology.2012.02.010, indexed in Pubmed: 22401870.

21. Turaka A, Li T, Sharma NK, et al. Increased recurrences using intensity-modulated radiation therapy in the postoperative setting. Am J Clin Oncol. 2010; 33(6): 599–603, doi: 10.1097/COC.0b013e3181c4c3cc, indexed in Pubmed: 21063195.

22. Prabhakar R, Laviraj MA, Haresh KP, et al. Impact of patient setup error in the treatment of head and neck cancer with intensity modulated radiation therapy. Phys Med. 2010; 26(1): 26–33, doi: 10.1016/j.ejmp.2009.05.001, indexed in Pubmed: 19576833.

23. Yaparpalvi R, Hong L, Mah D, et al. ICRU reference dose in an era of intensity-modulated radiation therapy clinical trials: correlation with planning target volume mean dose and suitability for intensity-modulated radiation therapy dose prescription. Radiother Oncol. 2008; 89(3): 347–352, doi: 10.1016/j.radonc.2008.07.025, indexed in Pubmed: 18762345.

24. Ueki N, Matsuo Y, Shibuya K, et al. Differences in the dose-volume metrics with heterogeneity correction status and its influence on local control in stereotactic body radiation therapy for lung cancer. J Radiat Res. 2013; 54(2): 337–343, doi: 10.1093/jrr/rrs084, indexed in Pubmed: 22984280.

Table 1. Patient characteristics

Characteristics	**Radiotherapy system**		**p-value**
	Previous (%)	**Upgraded (%)**	
Number of patients	57	79	
Age (years)	26–88 (M: 66)	24 – 86 (M: 67)	0.9419
Age (≥ 75/< 75)	16 (28.1)/41 (71.9)	19 (24.1)/60 (75.9)	0.6917
Sex (male/female)	45 (78.9)/12 (21.1)	64 (81.0)/15 (19.0)	0.8290
Primary site (tongue and oral cavity/others)	33 (57.9)/24 (42.1)	50 (63.3)/29 (36.7)	0.5941
Primary site (details)			
Nasal and paranasal cavity	4 (7.0)	3 (3.8)	
Tongue and oral cavity	33 (58.0)	50 (63.3)	
Oropharynx	2 (3.5)	3 (3.8)	
Hypopharynx	8 (14.0)	9 (11.4)	
Larynx	10 (17.5)	14 (17/7)	
PS (0–1/≥ 2)	55 (96.5)/2 (3.5)	75 (94.9)/4 (5.1)	1.0000
PS (details)			
0	44 (77.1)	49 (62.0)	
1	11 (19.3)	26 (32.9)	
2	1 (1.8)	4 (5.1)	
3	1 (1.8)	0 (0)	
CCI (≤ 3/≥ 4)	54 (94.7)/3 (5.3)	77 (97.5)/2 (2.5)	0.6494
CCI (details)			
2	51 (89.4)	75 (94.9)	
3	3 (5.3)	2 (2.5)	

4	2 (3.5)	1 (1.3)	
5	1 (1.8)	1 (1.3)	
Pre-treatment MRI (yes/no)	36 (63.2)/21 (36.8)	70 (88.6)/9 (11.2)	0.0007
Pathological stage (I–II/III–IV)	4 (7.0)/53 (93.0)	5 (6.3)/74 (93.7)	1.0000
Pathological stage (details)			
I	2 (3.5)	1 (1.3)	
II	2 (3.5)	4 (5.1)	
III	7 (12.3)	6 (7.6)	
IV	46 (80.7)	68 (86.0)	
Pathological margin (positive/negative)	10 (17.5)/47 (82.5)	14 (17.7)/65 (82.3)	1.0000
Extracapsular extension (positive/negative)	8 (14.0)/49 (86.0)	30 (38.0)/49 (62.0)	0.0021
Preoperative chemotherapy (yes/no)	7 (12.3)/50 (87.7)	13 (16.5)/66 (83.5)	0.6257
Concurrent chemotherapy (yes/no)	8 (14.0)/49 (86.0)	28 (35.0)/51 (65.0)	0.0058
Radiation dose [Gy]	57.6–70.2 (M: 63)	14.4–70.2 (M: 63)	0.6435
Follow-up period [months]	6.0–147.6 (M: 63.8)	4.1–89.6 (M: 42.2)	0.0071

CCI — Charleston Comorbidity Index; M — median; PS — performance status; MRI — magnetic resonance imaging

Table 2. Acute adverse events (≥ Grade 2)

Events	Previous-system group	Upgraded-system group	p-value
Dermatitis	46/57 (80.7%)	40/79 (50.6%)	0.0003
Mucositis	48/57 (84.2%)	49/79 (62.0%)	0.0067
Xerostomia	26/57 (45.6%)	23/79 (29.1%)	0.0698
Dysphagia	40/57 (70.2%)	8/79 (10.1%)	< 0.0001

Table 3. Late adverse events (≥ Grade 2)

Events	Previous-system group	Upgraded-system group	p-value
Xerostomia	26/57 (45.6%)	14/79 (17.7%)	0.0006
Dysphagia	31/57 (54.4%)	5/79 (6.3%)	< 0.0001
Osteonecrosis of the jaw	9/57 (15.8%)	4/79 (5.1%)	0.0429

Table 4. Multivariate analysis for survivals

Variables	PFS		DMFS		LRPFS		OS	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Radiotherapy system (upgraded *vs.*	0.97 (0.58–1.64)	0.9136	0.89 (0.50–1.57)	0.6863	0.75 (0.42–1.33)	0.3207	0.66 (0.32–1.28)	0.2199

previous)								
Age (≥ 75 *vs.* < 75)	1.55 (0.92–2.54)	0.1001	1.96 (1.12–3.31)	0.0184	1.44 (0.80–2.48)	0.2169	1.91 (1.03–3.45)	0.0414
Sex (male *vs.* female)	1.44 (0.79–2.85)	0.2427	1.29 (0.68–2.71)	0.4607	1.58 (0.81–3.38)	0.1861	1.37 (0.66–3.19)	0.4163
Pathological stage (I–II *vs.* III–IV)	0.79 (0.34–2.31)	0.6395	0.86 (0.34–2.92)	0.7918	0.58 (0.24–1.72)	0.2984	0.57 (0.22–1.96)	0.3381
Pathological margin (positive *vs.* negative)	1.55 (0.84–2.69)	0.1573	1.68 (0.86–3.06)	0.1204	1.86 (0.98–3.36)	0.0589	2.10 (1.04–4.00)	0.0404
Extracapsular extension (positive	1.73 (0.98–2.98)	0.0578	1.74 (0.93–3.18)	0.0829	1.88 (1.01–3.46)	0.0499	2.12 (1.04–4.19)	0.0392

vs. negative)								

PFS — progression-free survival; DMFS — distant metastasis-free survival; LRPFS — locoregional progression-free survival; OS — overall survival; HR — hazard ratio; CI — confidence interval; p — p-value