Title page

Title: Detailed analysis of failure patterns using deformable image registration in hypopharyngeal cancer patients treated with sequential boost intensity-modulated radiotherapy (SQB-IMRT)

Running Head: Dosimetric analysis using DIR in hypopharyngeal cancer treated with SQB-IMRT

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Abstract

Introduction: Sequential boost intensity-modulated radiotherapy (SQB-IMRT) uses two different planning CTs (pCTs) and treatment plans. SQB-IMRT is a form of adaptive radiotherapy that allows for responses to changes in the shape of the tumour and organs at risk (OAR). On the other hand, dose accumulation with the two plans can be difficult to evaluate. The purpose of this study was to analyse patterns of locoregional failure using deformable image registration (DIR) in hypopharyngeal cancer patients treated with SQB-IMRT.

Methods: Between 2013 and 2019, 102 patients with hypopharyngeal cancer were treated with definitive SQB-IMRT at our institution. Dose accumulation with the 1st and 2nd plans was performed, and the dose to the locoregional recurrent tumour volume was calculated using the DIR workflow. Failure was classified as follows: (1) in-field (≥ 95% of the recurrent tumour volume received 95% of the prescribed dose), (2) marginal (20-95%), or (3) out-of-field (< 20%).

Results: After a median follow-up period of 25 months, locoregional failure occurred in 34 patients. Dose-volume histogram analysis showed that all locoregional failures occurred in the field within 95% of the prescribed dose, with no marginal or out-of-field recurrences observed.

Conclusion: The dosimetric analysis using DIR showed that all locoregional failures were within the high-dose region. More aggressive treatment may be required for gross tumours.

keywords

Head and Neck; Radiation Oncology

Text

Introduction

Hypopharyngeal cancer is a relatively rare disease, with an incidence of 84,000 new cases in 2020 worldwide [1, 2]. Most newly diagnosed patients present with locally advanced disease [3], which has the worst treatment outcomes among head and neck cancer (HNC) patients, with 5-year overall survival (OS) rates of 25-41% [2-4]. Since radiation therapy (RT) can preserve laryngeal function, it is one of the most important treatments for hypopharyngeal cancer.

Intensity-modulated radiation therapy (IMRT) is now considered the standard treatment for HNC. In clinical practice for HNC, there are two main IMRT approaches: sequential boost (SQB) and simultaneous integrated boost (SIB) IMRT. SQB-IMRT is similar to 3D conformal radiation therapy. SQB-IMRT consists of two plans: the gross tumour and prophylactic region are irradiated during the 1st plan, and a boost to the gross tumour is delivered during the 2nd plan. Although it is necessary to repeat the planning computed tomography (pCT) and create a boost plan, this allows for responses to changes in the shape of the tumour and organs at risk (OAR), allowing for a more accurate dose administration. Thus, SQB-IMRT is considered to be an adaptive therapy. Since SQB-IMRT uses two different pCTs and treatment plans, it can be challenging to evaluate the accumulated dose with the two plans. On the other hand, the SIB-IMRT approach requires only one plan for the entire treatment by using different doses per fraction for gross tumours and prophylactic regions. Because of its convenience, SIB-IMRT has been widely used. In hypopharyngeal cancer, most previous studies [5-10] have used SIB-IMRT, while reports of SQB-IMRT are lacking. Some studies [11-16] have reported the patterns of failure after IMRT for HNC using a rigid image registration (RIR) method. RIR is a simple image registration method using translation and rotation.

Deformable image registration (DIR) is a technique using a deformation vector field [17]. RIR can be accurate when the anatomy remains almost unchanged, for example, in intracranial lesions [17, 18]. However, RIR may be inadequate when the anatomy and patient setup change significantly due to weight loss or tumour regression [17, 18]. DIR does not move the image uniformly across the entire image as RIR does but rather allows voxel-by-voxel movement of the image in various directions. Using DIR, the anatomical correspondence points between images can be calculated even with differences in the imaging position and changes in body shape and organ geometry. On the other hand, DIR is prone to errors in regions where the difference between the target image and the deformed image is large. After DIR is conducted, the accuracy of registration should be confirmed by a validated DIR algorithm [19] using a quantitative physics approach and visual evaluation. In addition, DIR allows for dose accumulation and evaluation of the two plans when using SQB-IMRT. We evaluated the dosimetric features of locoregional recurrence with DIR. Since 2013, SQB-IMRT has been routinely used to treat hypopharyngeal cancer at our institution to address anatomical changes in the target volume and OARs. In this study, we retrospectively analysed the recurrence patterns of hypopharyngeal cancer patients treated with SQB-IMRT using DIR. The results of this study may provide evidence for a strategy to improve clinical outcomes by increasing the prescribed dose in areas prone to recurrence.

Methods

Ethical statement

This retrospective study was approved by the Ethics Committee of the University Hospital (020-0044); the informed consent requirement was waived.

Patients

We performed a retrospective analysis of patients who underwent definitive SQB-IMRT for hypopharyngeal cancer at our institution. Further details on the patients included in this study, such as the inclusion and exclusion criteria, are shown in Appendix 1.

Radiotherapy

The gross tumour volume (GTV) included the primary tumour (GTV-primary) and metastatic lymph nodes (GTV-node). The clinical target volume-primary tumour (CTV-primary) and CTV-metastatic lymph nodes (CTV-node) were created with a margin of 5-10 mm from the GTV to cover the risk areas of subclinical disease. If induction chemotherapy was given, the initial GTV before chemotherapy was included in the CTV-primary. The CTV-prophylactic lymph nodes (CTV-prophylactic) included bilateral levels II, III, IVa-b, Va-c, VIb, and VIIa. The planning target volume (PTV) was created with a margin of 3 mm from the CTV. PTV1 included PTV-primary tumour (PTV-primary), PTV-metastatic lymph nodes (PTV-node) and PTV-prophylactic lymph nodes (PTV-prophylactic) during the 1st plan. PTV2 included PTV-primary and PTV-node during the 2nd plan. PTV1 was delivered with a total dose of 46 Gy in 23 fractions (fr), and PTV2 was boosted with 24 Gy in 12 fr. Radiotherapy was performed once a day for five consecutive days per week. Other details on radiotherapy are shown in Appendix 2.

Follow-up

After the completion of radiotherapy, the patients were followed up every 1 month for the first year, 2 months for the second year, 3 months for the third year, and 4 to 6 months for the fourth to fifth years. Laryngoscopy was performed every follow-up visit, and CT

was conducted every 3 months. If recurrence was suspected, a tissue biopsy was performed. MRI or PET-CT was also performed to consider treatment options.

Evaluation of patterns of failure

The doses for the 1st and 2nd plans were accumulated and registered onto the 2nd pCT with the DIR workflow using MIM Maestro v7.0 (MIM Software, Cleveland, OH, USA). The recurrence tumour volume (V_{rec}) was delineated on follow-up CT at relapse (Recurrence_CT), with registered PET-CT and/or MRI, if available, as a reference. Autosegmentation was not performed. The accumulated dose on the 2nd pCT was propagated to Recurrence_CT with DIR. The workflow is shown in Fig. 1. The dose-volume histogram (DVH) of V_{rec} was analysed. The recurrences were classified according to the method of Dawson et al. [11]: (1) "in-field": more than 95% of V_{rec} received 95% of the prescribed dose; (2) "marginal": 20-95% of V_{rec} received 95% of the prescribed dose; and (3) "outside": less than 20% of V_{rec} received 95% of the prescribed dose. The recurrent tumour volume, maximum (D_{max}), minimum (D_{min}), and mean dose (D_{mean}) of V_{rec}, and volume of 95% of the prescribed dose were evaluated. The updated recurrence classification by Mohamed published in 2016 [20] was also used. It is based on the dose and the original planning target volume (TV) using centroid-based approaches. Recurrences were classified into five types, the details of which are shown in Appendix 3.

Detailed process and assessment of the accuracy of DIR

The details of DIR were as follows: Basically, two DICOM images were imported into MIM, and the default semiautomatic workflow for DIR was applied. First, RIR was automatically performed; after visual confirmation, intensity-based DIR was automatically conducted. Finally, the region of interest and/or radiotherapy dose

were propagated to the target image. For the 1st and 2nd plan dose accumulation, the area of the entire neck was set as the volume of interest (VOI); for the propagation of the accumulated dose to the Recurrence_CT, the area around the recurrent tumour was set as the VOI.

To assess the accuracy of DIR, the mean distance to agreement (MDA) and Dice similarity coefficient (DSC) were used [21]. Details of the process are provided in Appendix 4.

Statistical analysis

OS, locoregional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) were estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using Cox proportional hazards models to investigate risk factors for OS and LRPFS. Variables with P <0.10 in the univariate analysis were included in the multivariable analysis. Statistical analysis was performed using JMP software version 14 (SAS Institute Inc., Cary, NC, USA). Patients with less than 6 months of follow-up were excluded from the survival analysis.

Results

Between 2013 and 2019, 102 patients met the inclusion criteria. The characteristics of these patients are summarized in Table 1. The median age at diagnosis was 66 (range, 40 to 89) years old. The majority of the patients had stage IV disease (56 cases, 55%). We usually contoured the targets using fused MRI (35%) and/or PET (92%). The IMRT delivery techniques were mostly step-and-shoot (84 cases, 82%), some were VMAT (13 cases, 13%), and 5 cases (4.9%) were a combination of step-and-shoot and VMAT. Ninety-seven patients (95%) received 70 Gy/35 fr. Five patients (4.9%)

received 71 Gy/33 fr, which consisted of a 1st plan of 46 Gy/23 fr and a 2nd plan of 25 Gy/10 fr, to compensate for treatment interruption due to public holidays. The median overall treatment time for radiotherapy was 51 (47-62) days. Before radiotherapy, 2 patients (2.0%) underwent neck dissection without resection of the primary site. Details of chemotherapy are shown in Appendix 5.

Clinical outcomes

Of the 102 patients, survival was analysed for 84 patients who were followed up for more than 6 months. The median follow-up periods for the 84 patients and the surviving 63 patients were 25 (6.1-82) months and 27 (6.1-82) months, respectively. The 2-year OS, LRPFS, DMFS, and PFS rates were 79% (95% confidence interval, 68-87%), 57% (46-68%), 71% (60-80%), and 54% (43-64%), respectively (Fig. 2). The 3-year OS, LRPFS, DMFS, and PFS rates were 76% (64-85%), 54% (43-66%), 69% (58-79%), and 49% (38-61%), respectively. The 5-year OS, LRPFS, DMFS, and PFS rates were 55% (37-72%), 39% (24-55%), 55% (38-71%), and 40% (26-56%), respectively. The univariate and multivariate analyses of OS and LRPFS are summarized in Appendix 6. Adverse events are shown in Appendix 7.

Accuracy of DIR

The MDA and DSC results are shown in Appendix 4. After quantitative and qualitative evaluation, the accuracy of the DIR workflow in dose accumulation was determined to be level 0 in all 32 cases. The accuracy of the DIR workflow in V_{rec} analysis was determined to be level 1 in 17 cases, level 2 in 11 cases and level 3 in 4 cases.

Patterns of failure

The patterns of failure are shown in Fig. 3. Forty-one patients were identified; of them, 34 (33%) had locoregional failure, and 19 had distant metastases. Of the patients experiencing locoregional recurrence, 26 experienced local failure, 15 experienced regional failure, and 7 experienced both local and regional failure. The median time to recurrence after radiotherapy was 5.8 (2.7-34) months. Fourteen patients with local regional recurrence underwent salvage surgery.

We performed dosimetric analysis for 32 out of 34 patients with locoregional failure. For the other 2 patients, images of recurrence were not available. The results of the dosimetric analysis are shown in Table 2. The median value of V_{rec} was 4.7 (0.3-60.5) cm^3. The median of the mean dose of V_{rec} was 72.5 (71.6-74.1) Gy. All DVH curves of V_{rec} are shown in Fig. 4. In the 32 patients, the prescribed dose was 70 Gy, and the 95% dose was calculated to be 66.5 Gy. The median $V_{66.5\ Gy}$ of V_{rec} was 100% (95.2-100%). All recurrences were classified as "in-field" and not "marginal" or "out-field". The location of all failure centroids was within the CTV-primary or CTV-node. All V_{rec}s were classified as Type A (central high dose). Representative cases are shown in Appendix 8. The mean doses of the CTV-primary and CTV-node were 72.4 Gy (71.5-74.1 Gy), and the mean CTV-prophylactic was 60.1 Gy (54.4-68.4 Gy).

Discussion

We retrospectively analysed the patterns of failure and the dose for locoregional recurrence in hypopharyngeal cancer patients treated with SQB-IMRT using DIR. All locoregional failures were in the field within the high-dose region; there were no cases of marginal or outfield recurrence. Several previous studies have also reported that most cases of locoregional failure occurred in the high-dose region, although those analyses did not use DIR [11-16]. For

example, Tandon et al. [15] analysed 39 failures of HNC after definitive SIB-IMRT using RIR and reported that 27 (69%) of failures were located within the high-dose region and 12 (31%) were located in other areas. Mohamed et al. [20] conducted a detailed comparison of DIR vs. RIR for analysing patterns of failure for HNC. They found that out of 26 cases, 22 cases were in-field failures in DIR vs. 18 cases in RIR, while 1 case was a marginal failure in the high dose region in DIR vs. 5 cases in RIR. They concluded that DIR was more accurate and highly recommended for evaluating locoregional failure for HNC. Since the anatomy of HNC often changes significantly due to weight loss and tumour regression, it is reasonable to assume that DIR, which can compensate for these changes, is more accurate than RIR. According to the previous study by Mohamed et al. [20], if the recurrence cases in this study were analysed by RIR instead of DIR, they would have been incorrectly assessed to have occurred more peripherally. An inaccurate judgment can affect management afterward. Recurrence from the centre indicates biologic radiotherapy resistance, and increased radiation doses or intensified chemotherapy should be considered. However, recurrence from the margins implies an error in the radiotherapy process. Improvement in the accuracy of contouring and dose administration should be considered. Thus, the accurate classification of recurrence is important to improve radiotherapy outcomes. We believe that a more accurate DIR-based recurrence assessment is important, as recommended by Mohamed et al.

Our results using DIR strongly suggest that recurrence occurs within high-dose regions. Since SQB-IMRT uses two CTs and two treatment plans, dose accumulation is usually difficult to evaluate, but DIR allowed us to analyse the DVH of recurrent tumours. Since all locoregional failures were within the high-dose region, more aggressive therapy for the GTV may be necessary. Network analysis

[22] for locally advanced HNC showed that hyperfractionated radiotherapy with concomitant chemotherapy had the highest OS rate, and this approach may be worth exploring in hypopharyngeal cancer.

We usually use PET-CT (92%) and MRI (35%) to delineate the target volume. Some publications [23, 24] have reported that coregistration of PET-CT or MRI with pCT could improve the delineation of the target volume. Delineation with PET-CT and/or MRI can be important for the accurate identification of high-dose regions.

In this study, the mean accumulated dose to the CTV-prophylactic was 60.1 Gy (54.4-68.4 Gy). This was analysed only in patients with locoregional recurrence (N=32), but we believe it is an overall trend. The CTV-prophylactic received 46 Gy during the 1st plan, and another low dose was added around the GTV during the 2nd plan, resulting in an accumulated dose of 60 Gy to the CTV-prophylactic. Dose accumulation over two plans using different CTVs requires special equipment, such as DIR software, and is time consuming. Therefore, in actual clinical practice, we may tend to ignore the effect of a low dose on CTV-prophylactic during the 2nd plan without dose accumulation. We should be aware of the risk of unexpectedly high doses being administered to the elective nodal region.

The 2-year rates of OS and LRPFS were 79% and 57%, respectively. Our literature search did not identify any study mentioning the treatment outcomes of SQB-IMRT only for hypopharyngeal cancer. Previous reports of hypopharyngeal cancer patients treated with definitive IMRT are listed in Table 3 [5-10]. Our results seem to be comparable to or slightly worse than those of previous reports. In the multidisciplinary HNC board in our institution, patients with stage III/IV disease are usually recommended for surgery; therefore, patients with more complications, who might have a poor

prognosis, could have received radiotherapy. In fact, the age of the patients tended to be older than that in other reports. However, it is difficult to make exact comparisons between these retrospective studies because of some critical limitations, such as our short follow-up period.

In our study, acute G3 toxicities of mucositis and dysphagia were observed in 34% and 24% of the patients, respectively. At 2 years after the completion of radiotherapy, late G2 or higher toxicities (dysphagia and xerostomia) were observed in 22% and 15%, respectively, and any G3 toxicity was observed in 6%. These are roughly in the range of previous reports, and it is difficult to make direct comparisons in retrospective analyses.

Previous studies [25-29] have reported that SQB-IMRT is equivalent to SIB-IMRT in terms of treatment outcomes for patients with HNC. A few prospective randomized trials [27-29] have been conducted, and comparable treatment outcomes were reported. We believe that the findings in our study are consistent with these results and provide evidence to support that the clinical outcomes of SQB and SIB-IMRT are comparable, even in patients with hypopharyngeal cancer. There is one report indicating the benefit of SQB-IMRT in terms of dose reduction to the parotid gland for distant tumours [30]. This may indicate the potential benefit of SQB-IMRT, but it should be verified in a prospective study specifically exploring this aspect. In recent years, the benefits of SIB over SQB with respect to OS have been reported [31]. Although the methodology was retrospective and not described in detail, the study was noteworthy, as it potentially indicated the usefulness of SIB. In fact, SIB-IMRT has been adopted worldwide with the theoretical strengths of greater conformality and higher intratumour doses. The contour guidelines and institution and trial protocols almost exclusively use SIB.

The DIR workflow could be adapted to SIB-IMRT. The doses and contours of SIB could be deformed to match the 2nd pCT performed during treatment. Dose accumulation would be more complex in SIB. This DIR workflow might then be more closely related to the currently high interest area of biomarker PET-driven treatment adaptation and response assessment [32-34]. Dose adaptation to the GTV or subvolumes within the GTV according to biomarkers during treatment may be more accurate with the use of DIR, and DIR dose accumulation may better represent voxels receiving high doses.

DIR has the limitation of being time consuming, but it is an important procedure in adaptive radiotherapy for HNC. One of the purposes of adaptive radiotherapy is to increase the radiation dose to the target. On the other hand, some studies have aimed to decrease adverse effects and improve local control through frequent adaptations [35, 36]. Prospective clinical trials are needed to clarify the benefits of adaptive radiotherapy with DIR.

In addition to the limitations mentioned above, (1) this study was a retrospective study at a single institution, (2) the follow-up period was as short as 25 months, and (3) we evaluated adverse events only by a radiation oncologist. Patient-reported outcomes (PROs) and quality of life (QOL) were not assessed. In future prospective studies planning to compare SQB and SIB-IMRT, these evaluations would be necessary.

Conclusion

In hypopharyngeal cancer patients treated with SQB-IMRT, the analysis using DIR showed that all locoregional failures were within the high-dose region; therefore, more aggressive therapy may be required for the GTV.

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Appendices

Appendix 1. Details on the patients included in this study

Inclusion criteria
(1) Patients with histologically diagnosed squamous cell carcinoma (2) Stage I to IVb according to the 7th-8th edition of the UICC TNM classification (3) Definitive SQB-IMRT with a total dose of 66 Gy or higher
Exclusion criteria
(1) Patients who underwent surgery at the primary site before RT (2) SIB-IMRT (3) Conventional 3D conformal radiation therapy
Staging system
• The 7th edition of the UICC TNM classification (between 2013 and 2017) • The 8th edition of the UICC TNM classification (from 2018)
Workup before radiation therapy
• Laryngoscopy • Biopsy of the primary site • CT • With/without magnetic resonance imaging (MRI) • With/without ^{18}F-fluorodeoxyglucose positron emission tomography/ computed tomography (FDG-PET/CT)
Decision making on treatment policy
• All cases were discussed with the multidisciplinary HNC board before treatment to determine the TNM stage and treatment strategy.

Abbreviations: 3D= 3-dimensional, CT= computed tomography, HNC=head and neck cancer, IMRT=intensity-modulated radiotherapy, RT=radiation therapy, SQB=sequential boost, UICC=Union for International Cancer Control

599 **Appendix 2.** Details on radiotherapy

600

CT scans

- 2 to 2.5 mm slice thickness
- Usually with contrast enhancement

Radiation treatment planning system

- Pinnacle v9.0 (Phillips, Medical Systems, WI)

Contouring

- Manually contoured by radiation oncology residents based on the guidelines [1, 2]
- Reviewed by radiation oncologists with more than 10 years of experience

Plan optimization

- Optimized such that 95% of the PTV received the prescribed dose (PTV D95%)

Dose constraints for target volumes and OARs

Structures		Criteria	Acceptable Criteria
PTV1 or PTV2	D_{95}	= 70 Gy	
	D_{98}	> 65.1 Gy	> 63 Gy
	D_{15}	< 77 Gy	< 80.5 Gy
	D_{max}	< 84 Gy	< 87.5 Gy
Brainstem + 3 mm	D_{max}	< 60 Gy	< 64 Gy
	D_{1cc}		< 60 Gy
Spinal cord + 3 mm	D_{max}	< 50 Gy	< 54 Gy
	D_{1cc}		< 50 Gy
Brain	D_{max}	< 70 Gy	< 74 Gy
	D_{1cc}		< 70 Gy
Parotid gland	D_{mean}	< 26 Gy	< 30 Gy
Submandibular gland	D_{mean}	< 39 Gy	
Oral cavity	D_{mean}	< 45Gy	
Larynx	D_{mean}	As low as possible	
PCM	D_{mean}	As low as possible	
Thyroid gland	D_{mean}	As low as possible	

IMRT methods

- A step-and-shoot method with 7 static ports (until 2017) or volumetric modulated arc therapy (VMAT) with two arcs (since 2018)

Treatment delivery

- Clinac iX linear accelerators or TrueBeam (Varian Medical Systems, Palo Alto, CA, USA) with 6 MV photons
- Image-guided radiation therapy using daily cone-beam CT and a 6-degree-of-freedom couch for rotational error correction

Abbreviations: D_{1cc}=minimum dose received by the highest irradiated volumes of 1 cc, D_{max}=maximum dose, D_{mean}=mean dose, D_{XX}=dose to XX% of the highest irradiated volume of the target, OAR=organs at risk, PCM=pharyngeal constrictor muscle, PTV1=PTV of 1st plan, PTV2=PTV of 2nd plan

608 **Appendix 3.** Details of the updated recurrence classification by
609 Mohamed
610

Type	Description
A, Central high dose	The centroid of V_{rec} originated in a high-dose TV, and the dose to 95% volume (D95%) of V_{rec} was > 95% of the dose prescribed to the corresponding TV of origin
B, Peripheral high dose	The centroid of V_{rec} was in a high-dose TV, but D95% of V_{rec} was <95% of the dose to this TV
C, Central elective dose	The centroid of V_{rec} was in an intermediate or low-dose TV, D95% of V_{rec} was > 95% of the dose to the respective TV
D, Peripheral elective dose	The centroid of V_{rec} was in an intermediate- or low-dose TV, but D95% of V_{rec} was < 95% of the dose to the respective TV
E, Extraneous dose	The centroid of V_{rec} was outside all TVs

611

612 Abbreviations: TV=target volume, V_{rec}=recurrence tumour volume

613

Appendix 4. Assessment of DIR accuracy and the MDA and DSC results

In the DIR workflow for dose accumulation using the first and second plans, six anatomical structures were identified—the brainstem, right and left parotid glands, mandible, oral cavity, and spinal cord—to assess the accuracy across the entire irradiated field. In the DIR workflow for the analysis of V_{rec} using Recurrence_CT and a 2nd pCT (with the accumulated dose), three anatomic structures were identified—the hyoid bone, cricoid cartilage, and cervical spinal cord—for accuracy around the recurrent tumour. With reference to TGA 132 [3], we basically set the tolerances for quantitative evaluation as 3 mm or less for MDA and 0.8 or greater for DSC on the average of each structure. Finally, a qualitative evaluation was performed by two radiation oncologists, and the accuracy levels were categorized [3] as follows:

0: Whole scan aligned
1: Locally aligned
2: Useable with risk of deformation
3: Useable for diagnosis only
4: Alignment not acceptable

The MDA and DSC results are shown in the following table.

DIR workflow for dose accumulation using the first and second plans									
MDA					DSC				
Average	Median	SD	Min	Max	Average	Median	SD	Min	Max
1.45	1.36	0.56	0.56	2.81	0.84	0.84	0.05	0.74	0.93
DIR workflow for analysis of V_{rec} using Recurrence_CT and a 2nd pCT									
MDA					DSC				
Average	Median	SD	Min	Max	Average	Median	SD	Min	Max
1.57	1.32	0.79	0.64	4.48	0.67	0.70	0.11	0.35	0.84

Abbreviations: MDA=mean distance to agreement, DSC=Dice similarity coefficient, SD=standard deviation

Appendix 5. Chemotherapy

	N	(%)
Induction chemotherapy	**18***	**(18%)**
TPF (75/75/750 mg/m^2) x3 **	16	(16%)
Others	2	(2%)
Concurrent chemotherapy	**83**	**(81%)**
Cisplatin-based chemotherapy	73	(72%)
Weekly cisplatin (40 mg/m^2) x6	68	(67%)
Tri-weekly cisplatin (100 mg/m^2) x3	3	(3%)
Others	2	(2%)
(median cumulative dose of cisplatin: 240 (120-300) mg/m^2)		
Cetuximab (400-250 mg/m^2) ***	6	(6%)
Weekly carboplatin (AUC 1.5) x7	4	(4%)
No chemotherapy	**19**	**(19%)**

* All 18 patients also received concurrent chemotherapy.
** Docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-fluorouracil 750 mg/m^2 on days 1 through 5, administered every 3 weeks
*** 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly for 6 cycles

Abbreviations: AUC=area under the curve, N=number of patients

Appendix 6. Univariate and multivariate analyses of overall survival and locoregional progression-free survival

		Univariate analysis		Multivariate analysis	
		hazard ratio (95% CI)	p value	hazard ratio (95% CI)	p value
Overall survival					
Age	(65 ≤ y vs. 65 > y)	0.98 (0.41-2.32)	0.959		
Sex	(male vs. female)	0.53 (0.16-1.81)	0.314		
T stage**	(T1/2 vs. T3/4)	0.20 (0.08-0.52)	0.001*	0.28 (0.11-0.74)	0.010*
N stage**	(N0/1 vs. N2/3)	0.21 (0.07-0.63)	0.006*	0.34 (0.11-1.05)	0.061
CCRT	(yes vs. no)	0.58 (0.22-1.50)	0.261		
ICT	(yes vs. no)	3.24 (1.34-7.87)	0.009*	2.15 (0.88-5.28)	0.094
Locoregional progression-free survival					
Age	(65 ≤ y vs. 65 > y)	0.53 (0.26-1.09)	0.084	0.49 (0.24-0.97)	0.042*
Sex	(male vs. female)	0.50 (0.19-1.27)	0.144		
T stage**	(T1/2 vs. T3/4)	0.61 (0.31-1.20)	0.154		
N stage**	(N0/1 vs. N2/3)	0.42 (0.19-0.93)	0.033*	0.31 (0.14-0.66)	0.002*
CCRT	(yes vs. no)	0.39 (0.16-0.97)	0.042*	0.36 (0.15-0.88)	0.026*
ICT	(yes vs. no)	2.01 (0.95-4.27)	0.067	2.01 (0.95-4.26)	0.070

* Statistical significance of difference at $p < .05$

** According to the UICC TNM classification, 7^{th}-8^{th} edition.

Abbreviations: CCRT=concurrent chemotherapy, CI=confidence interval, ICT=induction chemotherapy

Appendix 7. Adverse events of all 102 patients

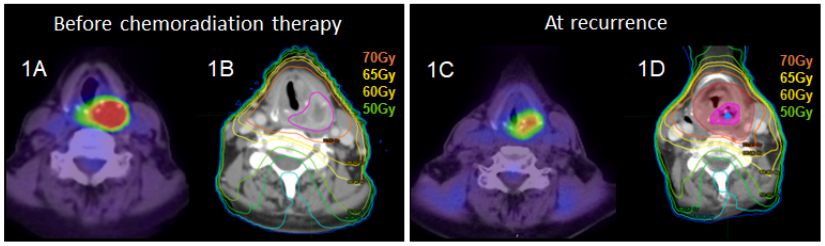
		Grade 2	Grade 3	Grade 4
Acute adverse events[*] (number of at risk)		N (%)	N (%)	N (%)
Any	(N=78)	37 (47%)	38 (49%)	3 (4%)
Nonhematologic				
dermatitis	(N=102)	81 (79%)	10 (10%)	0 (0%)
mucositis	(N=102)	63 (62%)	35 (34%)	0 (0%)
dysphagia	(N=102)	22 (22%)	24 (24%)	0 (0%)
dysgeusia	(N=85)	65 (76%)	ND	ND
dry mouth	(N=82)	33 (40%)	4 (5%)	ND
Hematologic				
leukopenia	(N=102)	40 (39%)	27 (26%)	2 (2%)
neutropenia	(N=102)	26 (25%)	17 (17%)	1 (1%)
anemia	(N=102)	35 (34%)	7 (7%)	0 (0%)
thrombocytopenia	(N=102)	11 (11%)	5 (5%)	0 (0%)
Late adverse events				
At 6 months after RT				
Any	(N=34)	13 (38%)	1 (3%)	0 (0%)
dysphagia	(N=37)	9 (24%)	1 (3%)	0 (0%)
dysgeusia	(N=42)	1 (2%)	ND	ND
dry mouth	(N=40)	10 (25%)	0 (0%)	ND
At 2 years after RT				
Any	(N=17)	4 (24%)	1 (6%)	0 (0%)
dysphagia	(N=18)	3 (17%)	1 (6%)	0 (0%)
dysgeusia	(N=21)	0 (0%)	ND	ND
dry mouth	(N=20)	3 (15%)	0 (0%)	ND

[*] Evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria

Abbreviations: N=number of patients, ND=not defined, RT=radiation therapy

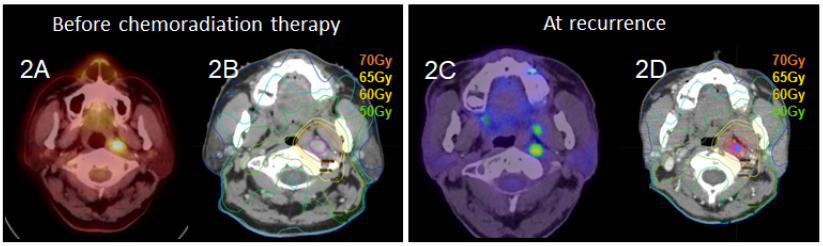
672 **Appendix 8.** Recurrence patterns and dose distribution in
673 representative cases

Case 1 : local recurrence, in-field failure, type A recurrence.



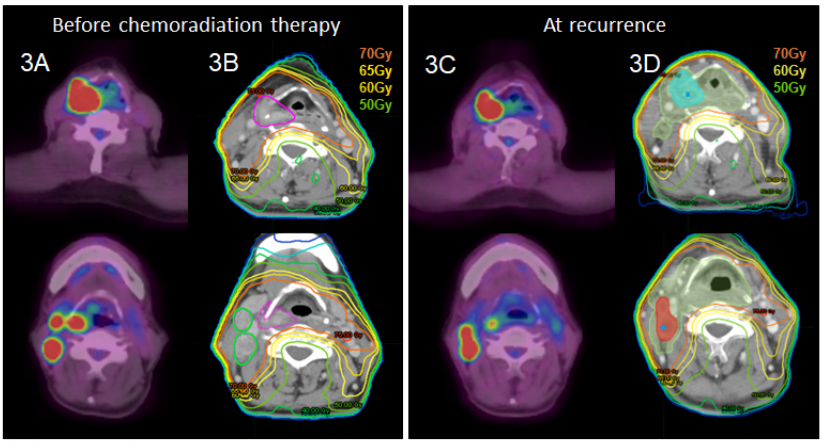
(1A) FDG-PET/CT of primary tumor before chemoradiation therapy
(1B) GTV-primary on planning CT (pink)
(1C) Recurrence of primary site on FDG-PET/CT
(1D) Recurrence of primary site (pink) on Recurrence_CT and isodose line using DIR. Recurrence tumors was within high-dose region. Centroid (blue) was located in CTV2 (red).

Case 2 : regional recurrence, in-field failure, type A recurrence.



(2A) FDG-PET/CT of metastatic lymph node before chemoradiation therapy
(2B) GTV-node on planning CT (pink)
(2C) Recurrence of metastatic lymph node on FDG-PET/CT
(2D) Recurrence of metastatic lymph node (pink) on Recurrence_CT and isodose line using DIR. Recurrence lymph node were within high-dose region. Centroid (blue) was located in CTV2 (red).

Case 3 : local and regional recurrence, in-field failure, type A recurrence.



(3A) FDG-PET/CT of primary tumor and metastatic lymph nodes before chemoradiation therapy
(3B) GTV-primary (pink) and GTV-node (green) on planning CT
(3C) Recurrence of primary site and lymph node on FDG-PET/CT
(3D) Recurrence of primary site (blue) and lymph node (red) on Recurrence_CT and isodose line using DIR. Centroids (blue) were located in CTV2 (green). Recurrence tumors were within high-dose region.

674
675

References (Appendix)

1. Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumor Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncolog. *Radiother Onco*l 2018; **126**: 3–24.

2. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, 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**: 172–81.

3. Brock KK, Mutic S, McNutt TR, Li H, Kessler ML. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM Radiation Therapy Committee Task Group No. 132. *Med Phys* 2017; **44**: e43–76.

Figure Legends

Fig. 1. Schematic of the DIR workflow for analysing the dose to recurrent tumours.
Abbreviations: pCT = planning computed tomography, DIR = deformable image registration, fr = fractions

Fig. 2. Kaplan–Meier curves for (a) overall survival, (b) locoregional progression-free survival, (c) distant metastasis-free survival and (d) progression-free survival.
Abbreviations: OS = overall survival, LRPFS = locoregional progression-free survival, DMFS = distant metastasis-free survival, PFS = progression-free survival

Fig. 3. Patterns of failure.

Fig. 4. DVH analysis for the recurrent tumours of 32 locoregional recurrences.
Abbreviations: DVH = dose-volume histogram

Tables

Table 1. Characteristics of all 102 patients

Characteristic (N=102)		N (%)
Age	≤ 65 y	59 58%)
	> 65 y	43 (42%)
Sex	Male	93 (91%)
	Female	9 (9%)
KPS	≤ 80 KPS	100 (98%)
	> 80 KPS	2 (2%)
Anatomic subsite	Pyriform sinus	80 (78%)
	Posterior wall	18 (18%)
	Postcricoid region	4 (4%)
ICT	Yes	18 (18%)
	No	84 (82)
CCRT	Yes	83 (81%)
	No	19 (19%)
T classification*	1	4 (4%)
	2	57 (56%)
	3	31 (30%)
	4	10 (10%)
N classification*	0	35 (34%)
	1	12 (12%)
	2	48 (47%)
	3	7 (7%)
Stage group*	I	3 (3%)
	II	23 (23%)
	III	20 (20%)
	IV	56 (55%)
IMRT delivery technique	Step-and-shoot	84 (82%)
	VMAT	13 (13%)
	Step-and-shoot and VMAT	5 (5%)
Diagnostic image used for IMRT planning	MRI	36 (35%)
	FDG-PET/CT	94 (92%)

* According to the UICC TNM classification, 7-8th edition.

Abbreviations: KPS=Karnofsky performance status, ICT=induction chemotherapy, CCRT=concurrent chemotherapy, IMRT=intensity-modulated radiotherapy, VMAT=volumetric modulated arc therapy,

MRI=magnetic resonance imaging, FDG-PET/CT=^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

Table 2. Dosimetric analysis for recurrent tumours in 32 patients

Recurrent tumour (N=32)		Median	(Range)
Volume		4.7 cm^3	(0.3-60.5 cm^3)
D_{max}		73.8 Gy	(72.3-76.5 Gy)
D_{min}		71.0 Gy	(50.8-72.6 Gy)
D_{mean}		72.5 Gy	(71.6-74.1 Gy)
$V_{66.5\ Gy}$		100%	(95.2 -100%)
> 95%	(in-field)	N=32 (100%)	
20-95%	(marginal)	N=0 (0%)	
≤ 20%	(outside)	N=0 (0%)	
Location of centroid			
CTV-primary/node		N=32 (100%)	
CTV-prophylactic		N=0 (0%)	
Outside CTVs		N=0 (0%)	

Abbreviations: D_{max}=maximum dose, D_{min}=minimum dose, D_{mean}=mean dose, $V_{66.5\ Gy}$=the volume receiving more than 66.5 Gy

730 **Table 3.** Reports of clinical outcomes and adverse events of
731 hypopharyngeal cancer patients treated with definitive IMRT
732

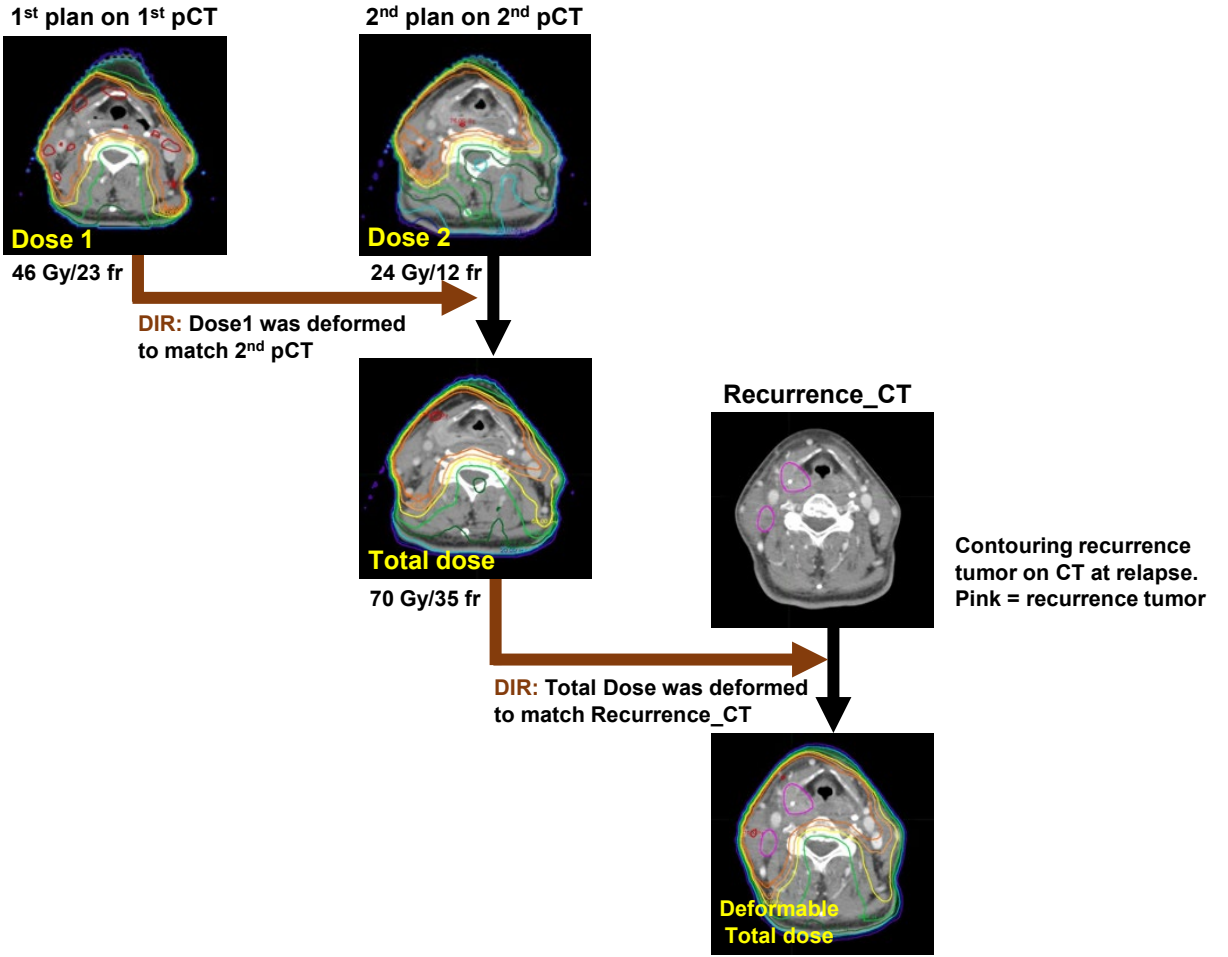
Study	IMRT	N	Median age	FU	Dose/fractions	OS	LRPFS
Studer (2006)	SIB	29	60.8	16	60-71 Gy (2.0-2.2 Gy/fr)	NA	NA
Liu (2010)	SIB	27	60.7	36	T2/3: 72.6 Gy/35 fr T4: 76.8 Gy/37 fr	52%, at 3y	LRPFS 68%, at 3y
Huang (2010)	SIB	33	57	19	70 Gy (1.8-2.0 Gy/fr)	44%, at 5y	LRPFS 53%, at 5y
Mok (2014)	SIB	91	67	50	60-70 Gy/25-40 fr	50%, at 3y	NA
Edson (2016)	SIB	98	63.5	35	70 Gy/33-35 fr	74%, at 2y	NA
Katsoulakis (2016)	SIB	100	63	48	70 Gy/33 fr	49%, at 3y	NA
Current study	SQB	84	66	25	70 Gy/35 fr	79%, at 2y	LRPFS 57%, at 2y

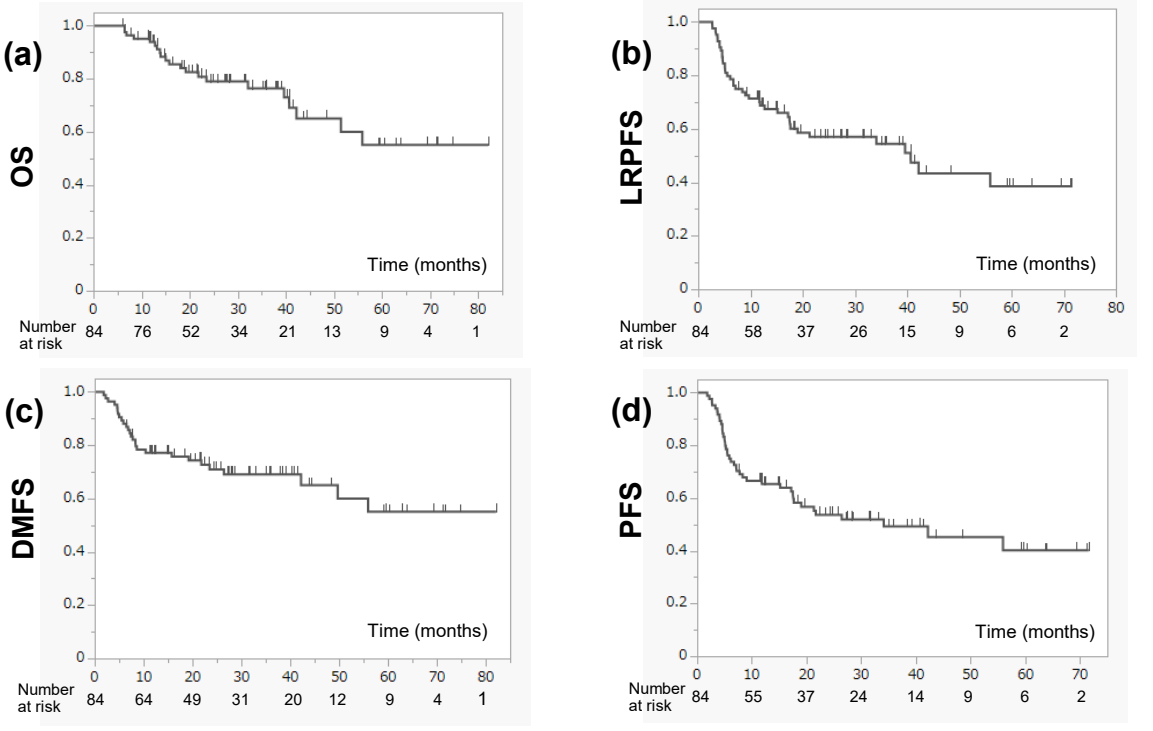
733

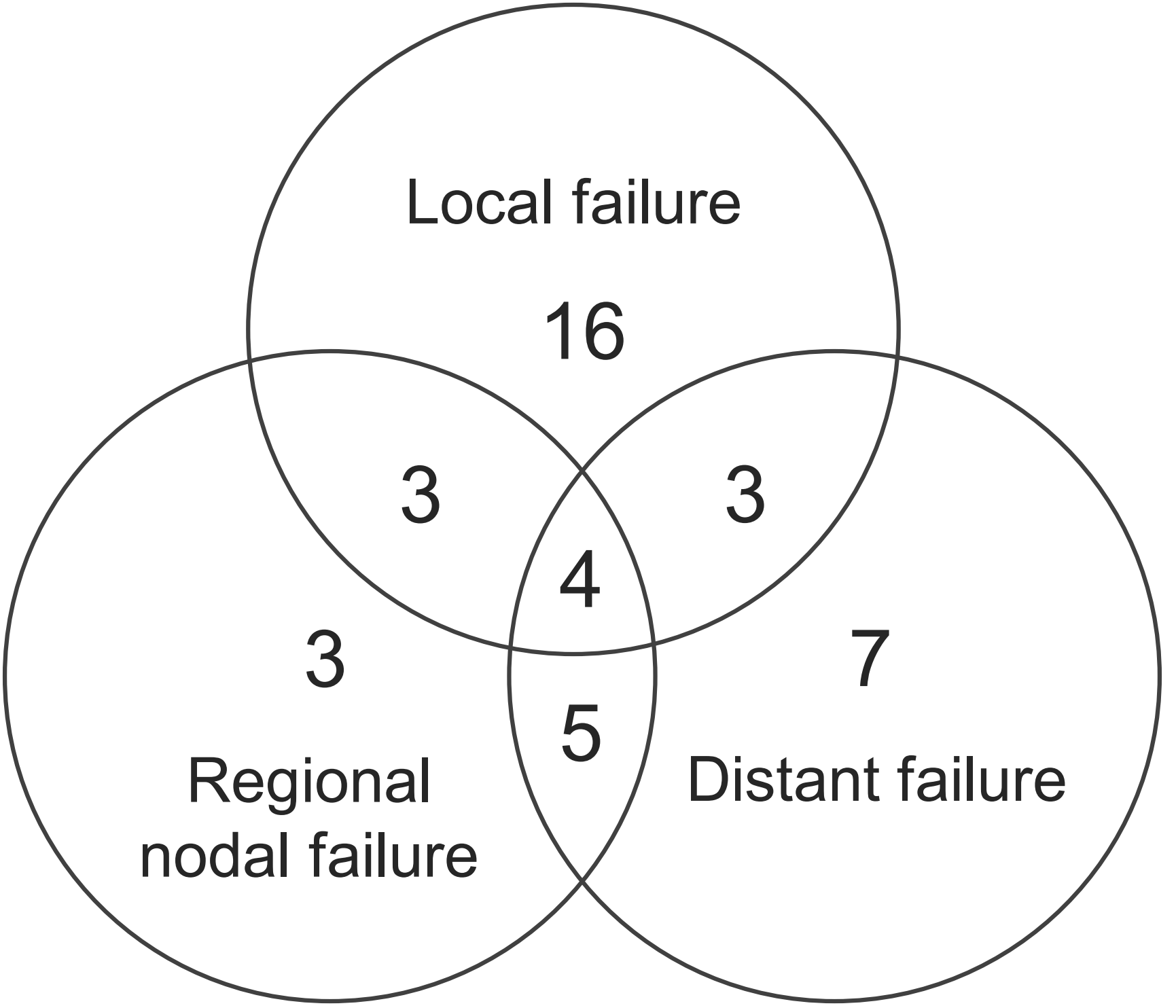
Study	Acute Toxicities	Late Toxicities
Studer (2006)	G3 mucositis; 21%	G3/4 dysphagia; 7%
Liu (2010)	≥G3 mucositis; 35% ≥G3 dysphagia; 63%	≥G2 dysphagia (stricture); 26% ≥G2 dry mouth; 48%
Huang (2010)	≥G2 mucositis; 39% ≥G3 dysphagia (pharyngitis); 30%	≥G2 dysphagia; 6% ≥G2 dry mouth; 0%
Mok (2014)	NA	G3 dysphagia at 2y (feeding tube); 19% Any G3 toxicity; 22.6% (at 2y)
Edson (2016)	≥G3 dysphagia (feeding tube); 66%	G3 dysphagia at 2y (feeding tube); 3% Any G3 toxicity; 23% (at 2y)
Katsoulakis (2016)	G3 mucositis or dysphagia; 26%	G3 dysphagia (feeding tube); 6% Any G3 toxicity; 32%
Current study	≥G3 mucositis; 34% ≥G3 dysphagia; 24% Any G3 toxicity; 49%	≥G2 dysphagia at 2y; 22% ≥G2 dry mouth at 2y: 15% Any G3 toxicity; 3% (at 6m), 6% (at 2y)

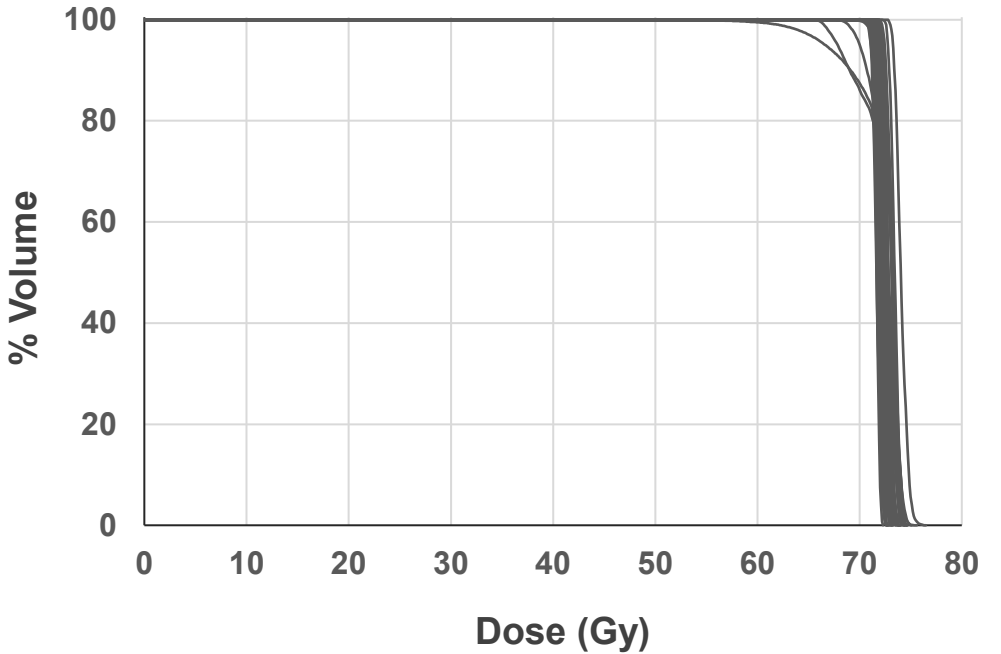
734

735 Abbreviations: IMRT=intensity-modulated radiotherapy, N=number
736 of patients, FU=follow-up period, m=months, OS=overall survival,
737 LRPFS=locoregional progression-free survival, SIB=simultaneous-
738 integrated boost, fr=fractions, NA=not available, SQB=sequential
739 boost, G=grade, y=year


1st plan on 1st pCT
2nd plan on 2nd pCT
Dose 1
46 Gy/23 fr
Dose 2
24 Gy/12 fr
DIR: Dose1 was deformed to match 2nd pCT
Total dose
70 Gy/35 fr
Recurrence_CT
Contouring recurrence tumor on CT at relapse. Pink = recurrence tumor
DIR: Total Dose was deformed to match Recurrence_CT
Deformable Total dose


(a)
OS
1.0
0.8
0.6
0.4
0.2
0
Time (months)
0 10 20 30 40 50 60 70 80
Number at risk 84 76 52 34 21 13 9 4 1
(b)
LRPFS
1.0
0.8
0.6
0.4
0.2
0
Time (months)
0 10 20 30 40 50 60 70 80
Number at risk 84 58 37 26 15 9 6 2
(c)
DMFS
1.0
0.8
0.6
0.4
0.2
0
Time (months)
0 10 20 30 40 50 60 70 80
Number at risk 84 64 49 31 20 12 9 4 1
(d)
PFS
1.0
0.8
0.6
0.4
0.2
0
Time (months)
0 10 20 30 40 50 60 70
Number at risk 84 55 37 24 14 9 6 2


Local failure
16
3
3
4
3
7
5
Regional
nodal failure
Distant failure


100
80
60
40
20
0
% Volume
0
10
20
30
40
50
60
70
80
Dose (Gy)