



Title	Detailed analysis of failure patterns using deformable image registration in hypopharyngeal cancer patients treated with sequential boost intensity-modulated radiotherapy
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Citation	Journal of Medical Imaging and Radiation Oncology, 67(1), 98-110 <a href="https://doi.org/10.1111/1754-9485.13491">https://doi.org/10.1111/1754-9485.13491</a>
Issue Date	2023-02
Doc URL	<a href="http://hdl.handle.net/2115/91127">http://hdl.handle.net/2115/91127</a>
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Type	article (author version)
File Information	JMIRO_1754-9485.13491.pdf



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1 **Title page**  
2 **Title: Detailed analysis of failure patterns using deformable**  
3 **image registration in hypopharyngeal cancer patients treated**  
4 **with sequential boost intensity-modulated radiotherapy**  
5 **(SQB-IMRT)**

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7  
8 ***Running Head: Dosimetric analysis using DIR in***  
9 ***hypopharyngeal cancer treated with SQB-IMRT***

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52 **Funding:** This work was supported by the Japan Society for the  
53 Promotion of Science (JSPS), Japan, during the conduct of the study  
54 (Grant Number 19K08088).

55 **Conflict of interest:** The authors declare that there are no  
56 conflicts of interest.

57 **Ethical approval:** This retrospective study was approved by the  
58 institutional ethics review board of Hokkaido University (020-0044).

59 **Consent to participate:** Informed consent was waived because of  
60 the retrospective study design.

61 **Type of manuscript:** Original article.

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64

65 **Abstract**

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

75 **Methods:** Between 2013 and 2019, 102 patients with  
76 hypopharyngeal cancer were treated with definitive SQB-IMRT at  
77 our institution. Dose accumulation with the 1st and 2nd plans was  
78 performed, and the dose to the locoregional recurrent tumour  
79 volume was calculated using the DIR workflow. Failure was  
80 classified as follows: (1) in-field ( $\geq 95\%$  of the recurrent tumour  
81 volume received 95% of the prescribed dose), (2) marginal (20-  
82 95%), or (3) out-of-field ( $< 20\%$ ).

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

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

91

92 **keywords**

93 Head and Neck; Radiation Oncology

94

95

96

97 **Text**

98 **Introduction**

99 Hypopharyngeal cancer is a relatively rare disease, with an  
100 incidence of 84,000 new cases in 2020 worldwide [1, 2]. Most newly  
101 diagnosed patients present with locally advanced disease [3], which  
102 has the worst treatment outcomes among head and neck cancer  
103 (HNC) patients, with 5-year overall survival (OS) rates of 25-41%  
104 [2-4]. Since radiation therapy (RT) can preserve laryngeal function,  
105 it is one of the most important treatments for hypopharyngeal  
106 cancer.

107 Intensity-modulated radiation therapy (IMRT) is now considered the  
108 standard treatment for HNC. In clinical practice for HNC, there are  
109 two main IMRT approaches: sequential boost (SQB) and  
110 simultaneous integrated boost (SIB) IMRT. SQB-IMRT is similar to  
111 3D conformal radiation therapy. SQB-IMRT consists of two plans:  
112 the gross tumour and prophylactic region are irradiated during the  
113 1st plan, and a boost to the gross tumour is delivered during the  
114 2nd plan. Although it is necessary to repeat the planning computed  
115 tomography (pCT) and create a boost plan, this allows for responses  
116 to changes in the shape of the tumour and organs at risk (OAR),  
117 allowing for a more accurate dose administration. Thus, SQB-IMRT  
118 is considered to be an adaptive therapy. Since SQB-IMRT uses two  
119 different pCTs and treatment plans, it can be challenging to  
120 evaluate the accumulated dose with the two plans. On the other  
121 hand, the SIB-IMRT approach requires only one plan for the entire  
122 treatment by using different doses per fraction for gross tumours  
123 and prophylactic regions. Because of its convenience, SIB-IMRT has  
124 been widely used. In hypopharyngeal cancer, most previous studies  
125 [5-10] have used SIB-IMRT, while reports of SQB-IMRT are lacking.  
126 Some studies [11-16] have reported the patterns of failure after  
127 IMRT for HNC using a rigid image registration (RIR) method. RIR is  
128 a simple image registration method using translation and rotation.

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

155

## 156 **Methods**

### 157 Ethical statement

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

161

162 Patients

163 We performed a retrospective analysis of patients who underwent  
164 definitive SQB-IMRT for hypopharyngeal cancer at our institution.

165 Further details on the patients included in this study, such as the  
166 inclusion and exclusion criteria, are shown in Appendix 1.

167

168 Radiotherapy

169 The gross tumour volume (GTV) included the primary tumour (GTV-  
170 primary) and metastatic lymph nodes (GTV-node). The clinical  
171 target volume-primary tumour (CTV-primary) and CTV-metastatic  
172 lymph nodes (CTV-node) were created with a margin of 5-10 mm  
173 from the GTV to cover the risk areas of subclinical disease. If  
174 induction chemotherapy was given, the initial GTV before  
175 chemotherapy was included in the CTV-primary. The CTV-  
176 prophylactic lymph nodes (CTV-prophylactic) included bilateral  
177 levels II, III, IVa-b, Va-c, VIb, and VIIa. The planning target volume  
178 (PTV) was created with a margin of 3 mm from the CTV. PTV1  
179 included PTV-primary tumour (PTV-primary), PTV-metastatic lymph  
180 nodes (PTV-node) and PTV-prophylactic lymph nodes (PTV-  
181 prophylactic) during the 1st plan. PTV2 included PTV-primary and  
182 PTV-node during the 2nd plan. PTV1 was delivered with a total dose  
183 of 46 Gy in 23 fractions (fr), and PTV2 was boosted with 24 Gy in  
184 12 fr. Radiotherapy was performed once a day for five consecutive  
185 days per week. Other details on radiotherapy are shown in Appendix  
186 2.

187

188 Follow-up

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

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

196

#### 197 Evaluation of patterns of failure

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

218

#### 219 Detailed process and assessment of the accuracy of DIR

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



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

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

233

### 234 Statistical analysis

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

245

## 246 **Results**

247 Between 2013 and 2019, 102 patients met the inclusion criteria.  
248 The characteristics of these patients are summarized in Table 1. The  
249 median age at diagnosis was 66 (range, 40 to 89) years old. The  
250 majority of the patients had stage IV disease (56 cases, 55%). We  
251 usually contoured the targets using fused MRI (35%) and/or PET  
252 (92%). The IMRT delivery techniques were mostly step-and-shoot  
253 (84 cases, 82%), some were VMAT (13 cases, 13%), and 5 cases  
254 (4.9%) were a combination of step-and-shoot and VMAT. Ninety-  
255 seven patients (95%) received 70 Gy/35 fr. Five patients (4.9%)

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

262

### 263 Clinical outcomes

264 Of the 102 patients, survival was analysed for 84 patients who were  
265 followed up for more than 6 months. The median follow-up periods  
266 for the 84 patients and the surviving 63 patients were 25 (6.1-82)  
267 months and 27 (6.1-82) months, respectively. The 2-year OS,  
268 LRPFS, DMFS, and PFS rates were 79% (95% confidence interval,  
269 68-87%), 57% (46-68%), 71% (60-80%), and 54% (43-64%),  
270 respectively (Fig. 2). The 3-year OS, LRPFS, DMFS, and PFS rates  
271 were 76% (64-85%), 54% (43-66%), 69% (58-79%), and 49%  
272 (38-61%), respectively. The 5-year OS, LRPFS, DMFS, and PFS  
273 rates were 55% (37-72%), 39% (24-55%), 55% (38-71%), and  
274 40% (26-56%), respectively. The univariate and multivariate  
275 analyses of OS and LRPFS are summarized in Appendix 6. Adverse  
276 events are shown in Appendix 7.

277

### 278 Accuracy of DIR

279 The MDA and DSC results are shown in Appendix 4. After  
280 quantitative and qualitative evaluation, the accuracy of the DIR  
281 workflow in dose accumulation was determined to be level 0 in all  
282 32 cases. The accuracy of the DIR workflow in  $V_{rec}$  analysis was  
283 determined to be level 1 in 17 cases, level 2 in 11 cases and level 3  
284 in 4 cases.

285

### 286 Patterns of failure

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

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

309

## 310 **Discussion**

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

318 example, Tandon et al. [15] analysed 39 failures of HNC after  
319 definitive SIB-IMRT using RIR and reported that 27 (69%) of  
320 failures were located within the high-dose region and 12 (31%)  
321 were located in other areas. Mohamed et al. [20] conducted a  
322 detailed comparison of DIR vs. RIR for analysing patterns of failure  
323 for HNC. They found that out of 26 cases, 22 cases were in-field  
324 failures in DIR vs. 18 cases in RIR, while 1 case was a marginal  
325 failure in the high dose region in DIR vs. 5 cases in RIR. They  
326 concluded that DIR was more accurate and highly recommended for  
327 evaluating locoregional failure for HNC. Since the anatomy of HNC  
328 often changes significantly due to weight loss and tumour  
329 regression, it is reasonable to assume that DIR, which can  
330 compensate for these changes, is more accurate than RIR.  
331 According to the previous study by Mohamed et al. [20], if the  
332 recurrence cases in this study were analysed by RIR instead of DIR,  
333 they would have been incorrectly assessed to have occurred more  
334 peripherally. An inaccurate judgment can affect management  
335 afterward. Recurrence from the centre indicates biologic  
336 radiotherapy resistance, and increased radiation doses or intensified  
337 chemotherapy should be considered. However, recurrence from the  
338 margins implies an error in the radiotherapy process. Improvement  
339 in the accuracy of contouring and dose administration should be  
340 considered. Thus, the accurate classification of recurrence is  
341 important to improve radiotherapy outcomes. We believe that a  
342 more accurate DIR-based recurrence assessment is important, as  
343 recommended by Mohamed et al.  
344 Our results using DIR strongly suggest that recurrence occurs within  
345 high-dose regions. Since SIB-IMRT uses two CTs and two  
346 treatment plans, dose accumulation is usually difficult to evaluate,  
347 but DIR allowed us to analyse the DVH of recurrent tumours. Since  
348 all locoregional failures were within the high-dose region, more  
349 aggressive therapy for the GTV may be necessary. Network analysis

350 [22] for locally advanced HNC showed that hyperfractionated  
351 radiotherapy with concomitant chemotherapy had the highest OS  
352 rate, and this approach may be worth exploring in hypopharyngeal  
353 cancer.

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

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

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

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

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

394 Previous studies [25-29] have reported that SQB-IMRT is equivalent  
395 to SIB-IMRT in terms of treatment outcomes for patients with HNC.  
396 A few prospective randomized trials [27-29] have been conducted,  
397 and comparable treatment outcomes were reported. We believe that  
398 the findings in our study are consistent with these results and  
399 provide evidence to support that the clinical outcomes of SQB and  
400 SIB-IMRT are comparable, even in patients with hypopharyngeal  
401 cancer. There is one report indicating the benefit of SQB-IMRT in  
402 terms of dose reduction to the parotid gland for distant tumours  
403 [30]. This may indicate the potential benefit of SQB-IMRT, but it  
404 should be verified in a prospective study specifically exploring this  
405 aspect. In recent years, the benefits of SIB over SQB with respect  
406 to OS have been reported [31]. Although the methodology was  
407 retrospective and not described in detail, the study was noteworthy,  
408 as it potentially indicated the usefulness of SIB. In fact, SIB-IMRT  
409 has been adopted worldwide with the theoretical strengths of  
410 greater conformality and higher intratumour doses. The contour  
411 guidelines and institution and trial protocols almost exclusively use  
412 SIB.

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

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

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

437

## 438 **Conclusion**

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

443

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589

590 **Appendices**

591

592 **Appendix 1.** Details on the patients included in this study

593

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**Inclusion criteria**

- (1) Patients with histologically diagnosed squamous cell carcinoma
- (2) Stage I to IVb according to the 7<sup>th</sup>-8<sup>th</sup> edition of the UICC TNM classification
- (3) Definitive SQB-IMRT with a total dose of 66 Gy or higher

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**Exclusion criteria**

- (1) Patients who underwent surgery at the primary site before RT
- (2) SIB-IMRT
- (3) Conventional 3D conformal radiation therapy

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**Staging system**

- The 7<sup>th</sup> edition of the UICC TNM classification (between 2013 and 2017)
- The 8<sup>th</sup> edition of the UICC TNM classification (from 2018)

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**Workup before radiation therapy**

- Laryngoscopy
- Biopsy of the primary site
- CT
- With/without magnetic resonance imaging (MRI)
- With/without <sup>18</sup>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.

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594 Abbreviations: 3D= 3-dimensional, CT= computed tomography,

595 HNC=head and neck cancer, IMRT=intensity-modulated

596 radiotherapy, RT=radiation therapy, SQB=sequential boost,

597 UICC=Union for International Cancer Control

598

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**CT scans**

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

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**Radiation treatment planning system**

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

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**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 <sub>95</sub>	= 70 Gy	
	D <sub>98</sub>	> 65.1 Gy	> 63 Gy
	D <sub>15</sub>	< 77 Gy	< 80.5 Gy
	D <sub>max</sub>	< 84 Gy	< 87.5 Gy
Brainstem + 3 mm	D <sub>max</sub>	< 60 Gy	< 64 Gy
	D <sub>1cc</sub>		< 60 Gy
Spinal cord + 3 mm	D <sub>max</sub>	< 50 Gy	< 54 Gy
	D <sub>1cc</sub>		< 50 Gy
Brain	D <sub>max</sub>	< 70 Gy	< 74 Gy
	D <sub>1cc</sub>		< 70 Gy
Parotid gland	D <sub>mean</sub>	< 26 Gy	< 30 Gy
Submandibular gland	D <sub>mean</sub>		< 39 Gy
Oral cavity	D <sub>mean</sub>		< 45Gy
Larynx	D <sub>mean</sub>	As low as possible	
PCM	D <sub>mean</sub>	As low as possible	
Thyroid gland	D <sub>mean</sub>	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**

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- 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
- 

601

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

607

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

<b>Type</b>	<b>Description</b>
<b>A, Central high dose</b>	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>B, Peripheral high dose</b>	The centroid of $V_{rec}$ was in a high-dose TV, but D95% of $V_{rec}$ was <95% of the dose to this TV
<b>C, Central elective dose</b>	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
<b>D, Peripheral elective dose</b>	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
<b>E, Extraneous dose</b>	The centroid of $V_{rec}$ was outside all TVs

611

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

613



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

616

617 In the DIR workflow for dose accumulation using the first and  
618 second plans, six anatomical structures were identified—the  
619 brainstem, right and left parotid glands, mandible, oral cavity, and  
620 spinal cord—to assess the accuracy across the entire irradiated field.

621 In the DIR workflow for the analysis of  $V_{rec}$  using Recurrence\_CT  
622 and a 2nd pCT (with the accumulated dose), three anatomic  
623 structures were identified—the hyoid bone, cricoid cartilage, and  
624 cervical spinal cord—for accuracy around the recurrent tumour.

625 With reference to TGA 132 [3], we basically set the tolerances for  
626 quantitative evaluation as 3 mm or less for MDA and 0.8 or greater  
627 for DSC on the average of each structure. Finally, a qualitative  
628 evaluation was performed by two radiation oncologists, and the  
629 accuracy levels were categorized [3] as follows:

630 0: Whole scan aligned

631 1: Locally aligned

632 2: Useable with risk of deformation

633 3: Useable for diagnosis only

634 4: Alignment not acceptable

635

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

637

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	

638

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

641

642 **Appendix 5. Chemotherapy**

643

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

644

645 \* All 18 patients also received concurrent chemotherapy.

646 \*\* Docetaxel 75 mg/m<sup>2</sup> on day 1, cisplatin 75 mg/m<sup>2</sup> on day 1, and  
 647 5-fluorouracil 750 mg/m<sup>2</sup> on days 1 through 5, administered every  
 648 3 weeks

649 \*\*\* 400 mg/m<sup>2</sup> initial dose, followed by 250 mg/m<sup>2</sup> weekly for 6  
 650 cycles

651

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

653

654 **Appendix 6.** Univariate and multivariate analyses of overall  
 655 survival and locoregional progression-free survival  
 656

		<b>Univariate analysis</b>		<b>Multivariate analysis</b>	
		hazard ratio (95% CI)	p value	hazard ratio (95% CI)	p value
<b>Overall survival</b>					
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
<b>Locoregional progression-free survival</b>					
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

657  
 658  
 659  
 660  
 661  
 662

\* Statistical significance of difference at p < .05

\*\* According to the UICC TNM classification, 7<sup>th</sup>-8<sup>th</sup> edition.

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

663 **Appendix 7. Adverse events of all 102 patients**

664

		<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Acute adverse events*</b>		N (%)	N (%)	N (%)
(number of at risk)				
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%)
<b>Late adverse events</b>				
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

665

666 \* Evaluated according to the Common Terminology Criteria for  
667 Adverse Events (CTCAE) version 4.0 criteria

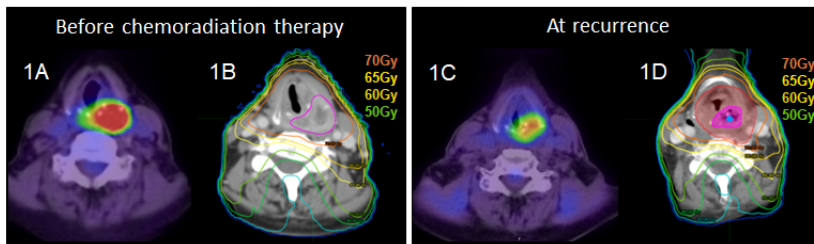
668

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

671

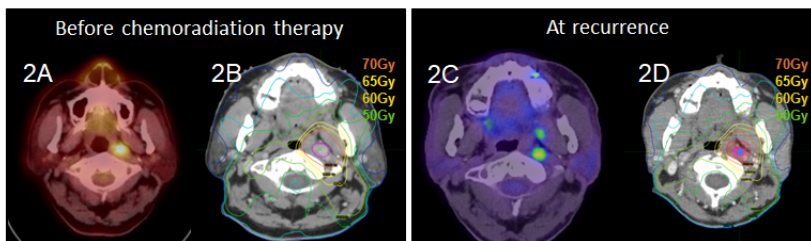
672 **Appendix 8. Recurrence patterns and dose distribution in**  
 673 **representative cases**

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



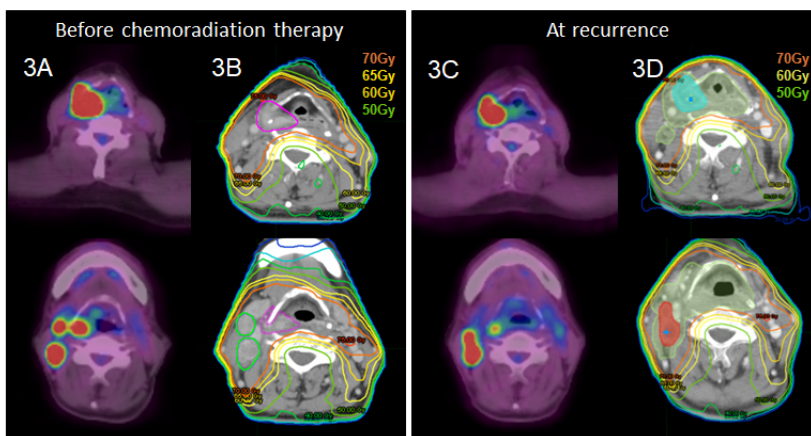
(1A) FDG-PET/CT of primary tumor before chemoradiation therapy  
 (1B) GTV-primary on planning CT (pink)  
 (1C) Recurrence of primary site on FDG-PET/CT  
 (1D) Recurrence of primary site (pink) on Recurrence\_CT and isodose line using DIR. Recurrence tumors was within high-dose region. Centroid (blue)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

676 **References (Appendix)**

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692

693 **Figure Legends**

694 Fig. 1. Schematic of the DIR workflow for analysing the dose to  
695 recurrent tumours.

696 Abbreviations: pCT = planning computed tomography, DIR =  
697 deformable image registration, fr = fractions

698

699 Fig. 2. Kaplan–Meier curves for (a) overall survival, (b) locoregional  
700 progression-free survival, (c) distant metastasis-free survival and  
701 (d) progression-free survival.

702 Abbreviations: OS = overall survival, LRPFS = locoregional  
703 progression-free survival, DMFS = distant metastasis-free survival,  
704 PFS = progression-free survival

705

706 Fig. 3. Patterns of failure.

707

708 Fig. 4. DVH analysis for the recurrent tumours of 32 locoregional  
709 recurrences.

710 Abbreviations: DVH = dose-volume histogram

711

712 **Tables**713 **Table 1.** Characteristics of all 102 patients

714

<b>Characteristic (N=102)</b>		<b>N (%)</b>
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	Pyramidal 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%)

715

716 \* According to the UICC TNM classification, 7-8<sup>th</sup> edition.

717 Abbreviations: KPS=Karnofsky performance status, ICT=induction

718 chemotherapy, CCRT=concurrent chemotherapy, IMRT=intensity-

719 modulated radiotherapy, VMAT=volumetric modulated arc therapy,



720 MRI=magnetic resonance imaging, FDG-PET/CT=<sup>18</sup>F-  
721 fluorodeoxyglucose positron emission tomography/computed  
722 tomography  
723

724 **Table 2.** Dosimetric analysis for recurrent tumours in 32 patients

725

<b>Recurrent tumour (N=32)</b>	<b>Median</b>	<b>(Range)</b>
Volume	4.7 cm <sup>3</sup>	(0.3-60.5 cm <sup>3</sup> )
D <sub>max</sub>	73.8 Gy	(72.3-76.5 Gy)
D <sub>min</sub>	71.0 Gy	(50.8-72.6 Gy)
D <sub>mean</sub>	72.5 Gy	(71.6-74.1 Gy)
V <sub>66.5 Gy</sub>	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%)	

726

727 Abbreviations: D<sub>max</sub>=maximum dose, D<sub>min</sub>=minimum dose,

728 D<sub>mean</sub>=mean dose, V<sub>66.5 Gy</sub>=the volume receiving more than 66.5 Gy

729

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)

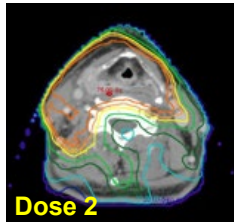
734

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

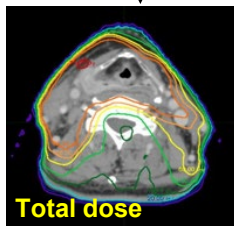
1<sup>st</sup> plan on 1<sup>st</sup> pCT



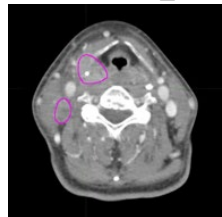
2<sup>nd</sup> plan on 2<sup>nd</sup> pCT



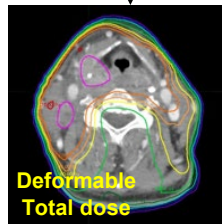
DIR: Dose1 was deformed to match 2<sup>nd</sup> pCT

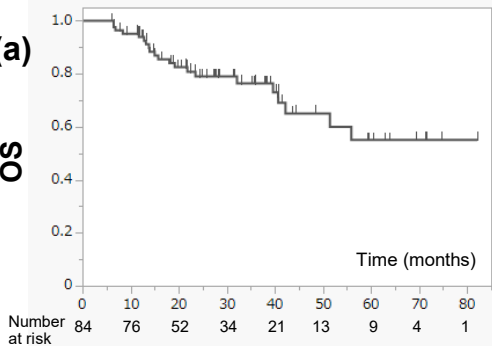
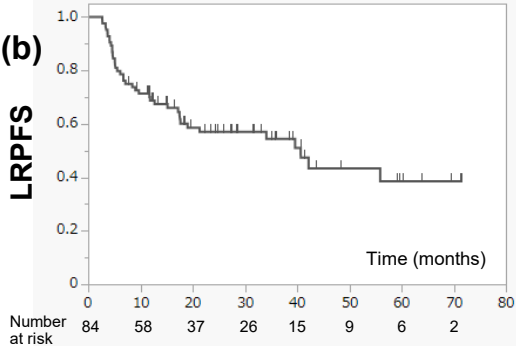
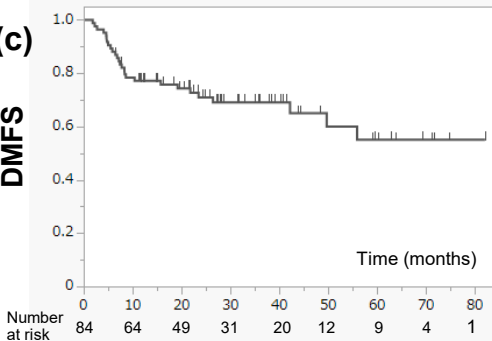


Recurrence\_CT



DIR: Total Dose was deformed to match Recurrence\_CT



**(a)****OS****(b)****LRPFS****(c)****DMFS****(d)****PFS**