Comparison of Failure Patterns Between Conventional and Intensity-modulated Radiotherapy for Stage III and IV Head and Neck Squamous Cell Carcinoma

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Abstract. *Background: We compared the patterns of failure between 3-dimensional radiotherapy (3D-RT) and intensity-modulated radiotherapy (IMRT) for head and neck squamous cell carcinoma (HNSCC). Patients and Methods: We reviewed the medical records of 49 patients with stage III-IV HNSCC treated with concurrent chemoradiotherapy. The treatment outcome, patterns of failure, and toxicities were compared between 3D-RT and IMRT. Results: There were 13 locoregional recurrences as initial failure sites. Eight recurrences were local, three were regional, and two were both local and regional. The recurrence pattern did not differ between the 3D-RT- and IMRT-treated groups, while toxicities were reduced in the IMRT-treated group. All recurrences were within the high-risk planning target volume except for one case in IMRT. Conclusion: IMRT did not increase the risk of locoregional recurrence neither did it change the pattern of failure in patients with stage III-IV locally advanced HNSCC, although it did reduce toxicities.*

The standard treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) is concurrent chemoradiotherapy (CCRT), which presents the advantage of organ preservation compared to surgery (1-5). However, CCRT results in long-term adverse sequelae, such as xerostomia, dysphagia, and soft tissue fibrosis (1, 5). With the advancement in radiation therapy techniques, from conventional 2-dimensional (2D) to 3D-conformal (3D-RT), and intensity-modulated radiotherapy (IMRT), it has become possible to spare critical organ structures from the high-dose radiation field, and preserve them functionally, as well as anatomically (6-9).

However, since IMRT provides highly conformal doses with steep dose gradients, there is also an increased risk of missing the target (10-13). Several factors such as the target delineation method, the width of margin, and the method of image guidance can contribute to this missing of target (14). There is also a concern regarding the fraction sizes in IMRT (15). In IMRT, usually a fraction size smaller than conventional 1.8 or 2.0 Gy is used for the low-risk area and a higher fraction size is used for the high-risk area when simultaneous integrated boost (SIB) technique is employed (15, 16). Combination of missing the target and low fraction size may alter the failure pattern in locoregional control or may increase the concern regarding a higher rate of regional recurrence.

At our Institution, patients with locally advanced HNSCC have been treated with the IMRT technique since March 2011. In the present study, we compared the treatment outcome and patterns of failure between 3D-RT and IMRT in patients with stage III-IV HNSCC who were treated with weekly low-dose cisplatin-based CCRT.

Patients and Methods

Study population. We performed a retrospective study by analyzing the medical records, RT treatment plans, and diagnostic images of patients with stage III and IV HNSCC. For this study, we only selected patients

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who satisfied the following criteria: i) pathologically proven squamous cell carcinoma of the head and neck, ii) staged as III or IVA-B according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging (17), iii) treated with curative intent CCRT, iv) received the entire planned RT, and v) Eastern Cooperative Oncology Group performance status 0 to 1. We excluded patients with i) histology other than SCC, ii) nasopharyngeal or salivary gland carcinoma, iii) whose treatment was interrupted, iv) who received induction chemotherapy, and v) received previous RT in the head and neck area. From 2005 to 2014, 49 patients with locally advanced HNSCC were treated with definitive CCRT at Gyeongsang National University Hospital, and satisfied the selection criteria.

Radiation therapy techniques. All patients were treated in the supine position with a thermoplastic mask. Planning computed tomographic (CT) scans were performed with 2.5 mm slices. Before the introduction of IMRT in March 2011, all patients were treated with the 3D-RT technique. Bilateral opposing fields for the upper neck, and anterior single field or anteroposterior opposing fields for the lower neck were used up to a dose of 45-50.4 Gy. Then the field was reduced to cover the primary site and the involved nodal areas, up to a dose of median 72 Gy (range=70.2-72.0 Gy). The fraction size was 1.8 Gy for all patients. Although IMRT was used as a boost in three patients, we included these patients in the 3D-RT group, since the majority of the RT course was 3D-RT, and the fraction size and total dose were the same as those for 3D-RT.

For patients treated with IMRT, the SIB technique was used. We defined the high-risk planning target volume (PTV1) as the primary and nodal gross tumor volume (GTV) with a 3 mm volumetric margin, and a median dose of 70.4 Gy (range=68.2-70.4 Gy) was prescribed with a median fraction size of 2.2 Gy (range=2.1-2.2 Gy). The intermediate-risk PTV (PTV2) was defined as the clinical target volume (CTV) encompassing the whole involved nodal area with a 3 mm margin, and a median dose of 66 Gy (range=63.9-66.0 Gy) was delivered (fraction size=2.0 to 2.1 Gy). The low-risk PTV (PTV3) was defined as the uninvolved lymph nodal area, and a median dose of 54 Gy (range=52.3-54.0 Gy) was delivered (fraction size=1.6 to 1.7 Gy).

Locoregional recurrence analysis. Radiological imaging studies and medical records of physical examination were used to identify the site of recurrence. If the recurrence site was the primary tumor site, the recurrence was regarded as local, and if the site was a lymph node, then the recurrence was regarded as regional. Persistent disease was also regarded as recurrence. The radiological images were also compared to the radiation treatment plans to assess the doses delivered to the recurrence site. If the recurrence site was within the 70 Gy or higher dose line in 3D-RT or within the PTV1 or PTV2 in IMRT, then the recurrence was regarded as occurring 'within the high-risk PTV'. If the recurred site was within the 50 Gy dose line in 3D-RT or within the PTV3 in IMRT, then the recurrence site was regarded as being 'within the low-risk PTV', and if it was not included within the radiation field or outside the PTV3, then the recurrence was regarded as 'outside the field'. In cases in which the recurrence was diagnosed only by biopsy of the primary tumor site, the recurrence was also regarded as 'within the high-risk PTV'. To analyze the prognostic factors affecting the locoregional control, the largest diameter on CT images and the peak-standardized uptake value (pSUV) in positron-emission tomography (PET)-CT were recorded for the primary tumor and largest lymph node, respectively.

Table I. *Patient and tumor characteristics (n=49).*

Characteristic, no. (%)	Total (n=49)	3D-RT (n=22)	IMRT (n=27)	*p*-Value
Age, year				0.698
<65	26 (53.1%)	11 (50.0%)	15 (55.6%)	
≥65	23 (46.9%)	11 (50.0%)	12 (44.4%)	
Tumor site				0.328
Oropharynx	22 (44.9%)	11 (50.0%)	11 (40.7%)	
Hypopharynx	21 (42.9%)	10 (45.5%)	11 (40.7%)	
Larynx	6 (12.2%)	1 (4.5%)	5 (18.5%)	
Clinical T-stage				0.990
T1-2	20 (40.8%)	9 (40.9%)	11 (40.7%)	
T3-4	29 (59.2%)	13 (59.1%)	16 (59.3%)	
Clinical N-stage				0.650
N0-1	14 (28.6%)	7 (31.8%)	7 (25.9%)	
N2	35 (71.4%)	15 (68.2%)	20 (75.9%)	
AJCC stage				>0.999
III	6 (12.2%)	3 (13.6%)	3 (11.1%)	
IV	43 (87.8%)	19 (86.4%)	24 (88.9%)	
Histological grade				0.713
Well to moderate	38 (82.6%)	16 (80.0%)	22 (84.6%)	
Poorly or undifferentiated	8 (17.4%)	4 (20.0%)	4 (15.4%)	
ECOG PS				0.104
0	13 (26.5%)	8 (36.4%)	5 (18.5%)	
1	36 (73.5%)	14 (63.6%)	22 (81.5%)	
Chemotherapy regimen				0.001
Cisplatin alone	38 (77.6%)	10 (45.5%)	26 (96.3%)	
Combined regimen	11 (22.4%)	12 (54.5%)	1 (3.7%)	

3D-RT: 3-Dimensional conventional radiotherapy; IMRT: intensity-modulated radiotherapy; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

Statistical analysis. The study was designed to compare the clinical outcome and patterns of failure between 3D-RT- and IMRT-treated patients. Chi-square or Fisher's exact test was used to compare the baseline characteristics between the two groups, and to determine the associations between categorical variables and recurrence patterns. Survival and recurrence outcomes were calculated from the date of last radiotherapy. Local control rate, regional control rate, locoregional control rate, progression-free survival, and overall survival were analyzed by the Kaplan–Meier method. Multivariate analyses using a logistic regression model was performed to define the prognostic factors for recurrences. To compare the recurrence and survival results, log-rank test and Cox proportional hazards model were used. Toxic effects of treatment were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (18). Grade 2 or higher toxicities were recorded, and were defined as acute or late if they occurred within 3 months or after 3 months following the treatment, respectively. All statistical analyses were performed with SPSS version 21.0 (Chicago, IL, USA), and *p*-values of less than 0.05 (two-sided) were considered statistically significant.

Table II. *Pattern of failures*.

Pattern	Total (n=49)	3D-RT (n=22)	IMRT (n=27)	*p*-Value
Isolated LR	8 (16.3%)	5 (22.7%)	3 (11.1%)	0.440
Isolated RR	3 (6.1%)	2 (9.1%)	1 (3.7%)	0.581
LR + RR	2 (4.1%)	1 (4.5%)	1 (3.7%)	>0.999
Within high-risk PTV	12 (24.5%)	8 (36.4%)	4 (14.8%)	0.462
Outside high-risk PTV	1 (2.0%)	0 (0.0%)	1 (3.7%)	

3D-RT: 3-Dimensional conventional radiotherapy; IMRT: intensity-modulated radiotherapy; LR: local recurrence; RR: regional recurrence; PTV: planning target volume.

Table III. *Univariate and multivariate analyses of factors affecting locoregional control rate (LRCR), local control rate (LCR), and regional control rate (RCR).*

	Univariate log-rank test		Multivariate Cox regression model		
	2-year LRCR	*p*-Value	LRCR	LCR	RCR
			p-Value	*p*-Value	*p*-Value
Primary site		0.409	0.064	0.328	0.735
Oropharynx	76.5%				
Non-oropharynx	60.1%				
T-Stage		0.612	0.144	0.923	0.109
T1-2	76.0%				
T3-4	62.3%				
N-Stage		0.152	0.266	0.270	0.412
N0-1	79.5%				
N2	64.1%				
Primary tumor size		0.001	0.001	< 0.001	n/a
<3 cm	93.8%				
≥3 cm	40.5%				
Primary tumor pSUV		0.233	0.532	0.229	n/a
<10.0	74.5%				
≥10.0	59.2%				
Lymph node size		0.549	0.150	n/a	0.731
<2 cm	74.4%				
≥2 cm	65.6%				
Lymph node pSUV		0.166	0.067	n/a	0.801
<7.0	80.8%				
≥7.0	59.5%				
RT technique		0.425	0.974	0.239	0.901
3D-RT	51.9%				
IMRT	76.5%				
Chemotherapy regimen		0.866	0.956	0.744	0.546
Cisplatin alone	67.3%				
Combined regimen	71.4%				

pSUV: Peak-standardized uptake value in PET-CT; 3D-radiotherapy: 3-dimensional conventional radiotherapy; IMRT: intensity-modulated radiotherapy.

Results

Patient and treatment characteristics. Table I provides the summary of patient and tumor characteristics. All patients except for one were male, and the median age was 63 years (range=34-82 years). The most frequent types of cancer were oropharyngeal and hypopharyngeal (87.8%). The majority of patients (n=43, 87.8%) had stage IV disease.

The CCRT regimen was mainly weekly low-dose cisplatin. In 38 (77.6%) patients, weekly low-dose cisplatin was used solely, while in 11 (22.4%) patients, cisplatin was used in combination with other regimens (in nine patients with docetaxel, in one patient with cetuximab, and in one patient with fluorouracil). The planned chemotherapy was completed in 21 (42.9%) patients, while the dose or number of cycles was reduced in 28 (57.1%) patients because of poor performance status (13 patients), hematological toxicity (six patients), infection (six patients), or renal dysfunction (three patients).

The patient and treatment characteristics did not differ between the 3D-RT- and IMRT-treated groups, except that more combined-chemotherapy regimens were used in the 3D-RT group (p=0.001).

Treatment outcome. After a median follow-up of 14.4 months (range=0.4-93.5 months), thirteen (26.5%) patients experienced recurrence after CCRT. Eight (16.3%) patients had local recurrences only, three (6.1%) patients had regional recurrences only, and two (4.1%) patients had both local and regional recurrences as a component of first failure. There was no distant metastasis as a first failure site. However, two (4.1%) patients developed distant lung metastases sequentially after locoregional recurrences. The 2-year locoregional control rate, local control rate, and regional control rate were 68.3%, 73.4%, and 89.9%, respectively.
At the last follow-up, overall 15 (30.6%) patients had died. Eight (16.3%) patients died because of cancer progression. Two (4.1%) deaths were related to treatment toxicities: one death was due to renal failure and the other was due to abrupt pharyngeal bleeding 1 month after the end of RT. The other five (10.2%) deaths were due to concurrent disease. The 2-year progression-free survival and overall survivals were 55.8% and 65.2%, respectively.

Patterns of failure. The recurrence patterns of 3D-RT and IMRT are shown in Table II. Out of the 22 patients treated with 3D-RT, all recurrences were within the high-risk PTV. Out of the 27 patients treated with IMRT, all recurrences except for one were within the high-risk PTV. The single

Table IV. *Comparison of toxicities between radiotherapy modalities.*

	Total (n=49)	3D-RT (n=22)	IMRT (n=27)	*p*-Value
Acute toxicity (≥grade 2)				
Hematological	7 (14.3%)	3 (13.6%)	4 (14.8%)	1.000
Mucositis	27 (55.1%)	16 (72.7%)	11 (40.7%)	0.025
Dermatitis	11 (22.4%)	2 (9.1%)	9 (33.3%)	0.083
Late toxicity (≥grade 2)				
Xerostomia	21 (42.9%)	13 (59.1%)	8 (29.6%)	0.038
Dysphagia	10 (20.4%)	6 (27.3%)	4 (14.8%)	0.311
Neck fibrosis	7 (14.3%)	3 (13.7%)	4 (14.8%)	1.000

3D-RT: 3-Dimensional conventional radiotherapy; IMRT: intensity-modulated radiotherapy.

exception was the patient who had regional recurrence only. The patient had base of tongue cancer initially with multiple enlarged left level II and III lymph nodes (clinical stage T3N2b). The recurrence occurred in the right level IB lymph node within the low-risk PTV, and also in the left supraclavicular lymph node which was outside of the radiation field (Figure 1).

Prognostic factors affecting locoregional control. Table III shows the results of univariate and multivariate analyses of the prognostic factors affecting locoregional control. The primary tumor size was the most important prognostic factor for locoregional control. The 2-year locoregional control rate for primary tumors of less than 3 cm was 93.8% compared to 40.5% for primary tumors 3 cm or larger (p=0.001, Figure 2a). The primary tumor size was also significant in multivariate analysis for locoregional control rate and local control rate, but it was not significant for the regional control rate. The primary tumor site (oropharynx *versus* non-oropharynx) showed marginal significance for its effect on the locoregional control rate in multivariate analysis. The 2-year locoregional control rate was higher in the IMRT-treated group at 76.5%, compared to 51.9% in the 3D-RT-treated group. However, this difference was not statistically significant (p=0.866, Figure 2b), and it also did not affect the local and regional control rates in multivariate analysis. The CCRT regimen also had no effect on the locoregional control rate or on failure patterns.

Toxicities. Table IV shows the acute and late toxicity data for patients treated with 3D-RT and IMRT. For acute toxicities, grade 2 or higher mucositis occurred less frequently in patients treated with IMRT (72.7% *vs.* 40.7%, p=0.025), whereas hematological toxicity and dermatitis were similar for the two groups. For late toxicities, grade 2 or higher xerostomia occurred more frequently in the 3D-RT-treated patients than in those treated with IMRT with statistical significance (59.1% *vs.* 29.6%, p=0.038). However, dysphagia and neck fibrosis developed similarly in both groups. On the other hand, the recorded toxicities also did not differ by CCRT regimen.

Discussion

The advantages of using IMRT for patients with HNSCC have been reported by several studies, and therefore, IMRT is quickly replacing older treatment techniques. The most distinct advantage of IMRT over 2D- or 3D-RT is the reduction of side-effects, especially xerostomia. Marta *et al.* performed a meta-analysis by analyzing five prospective randomized phase III trials, and concluded that IMRT provides a significant benefit in grade 2-4 xerostomia with a hazard ratio of 0.76 compared to 3D-RT (9). Some studies also reported less severe acute toxicities, such as mucositis, dysphagia, and weight loss with IMRT, but this finding was not consistent among studies (7-10). In our study, reduced mucositis and xerostomia were observed in IMRT-treated patients with statistical significance.

These advantages of IMRT are due to the high dose-gradient characteristics of IMRT. However, this characteristic also raises concerns of diminished locoregional control because of the increased possibility of missing the target. Inappropriate contouring, anatomic changes during the RT course, inter- or intra-fractional movement, small width of the margin, and the method of image guidance are all important factors that could affect targeting accuracy. Cannon *et al.* reported three cases of treatment failures in or near the parotid glands (12). In two cases, there were PET-negative small nodules near the parotid glands on pre-treatment imaging, and they recurred after parotid-sparing IMRT. Eisbruch *et al.* also reported cases of failure near the skull bases in the early era of IMRT (13), and they contribute to the development of contouring guidelines for HNSCC (19).

However, despite these cases of failure and theoretical concern, several studies reported similar local control rates and survival (7-9). Gupta *et al.* performed a randomized phase III trial comparing 3D-RT and IMRT in patients with stage I-IV HNSCC (8). They reported a 3-year local control rate and overall survival of 88.2% and 80.5% with 3D-RT, and 70.6% and 68% with IMRT, respectively, with no statistically significant differences. The only meaningful difference was less xerostomia in the IMRT-treated group. The meta-analysis results by Marta *et al.* also showed similar locoregional control rates between 3D-RT and IMRT (9).

There also exist studies that analyzed the pattern of failures in IMRT-treated patients. Chao *et al.* analyzed 126 patients with stage I to IV HNSCC who received IMRT for definite or adjuvant purpose (11). IMRT was used only for

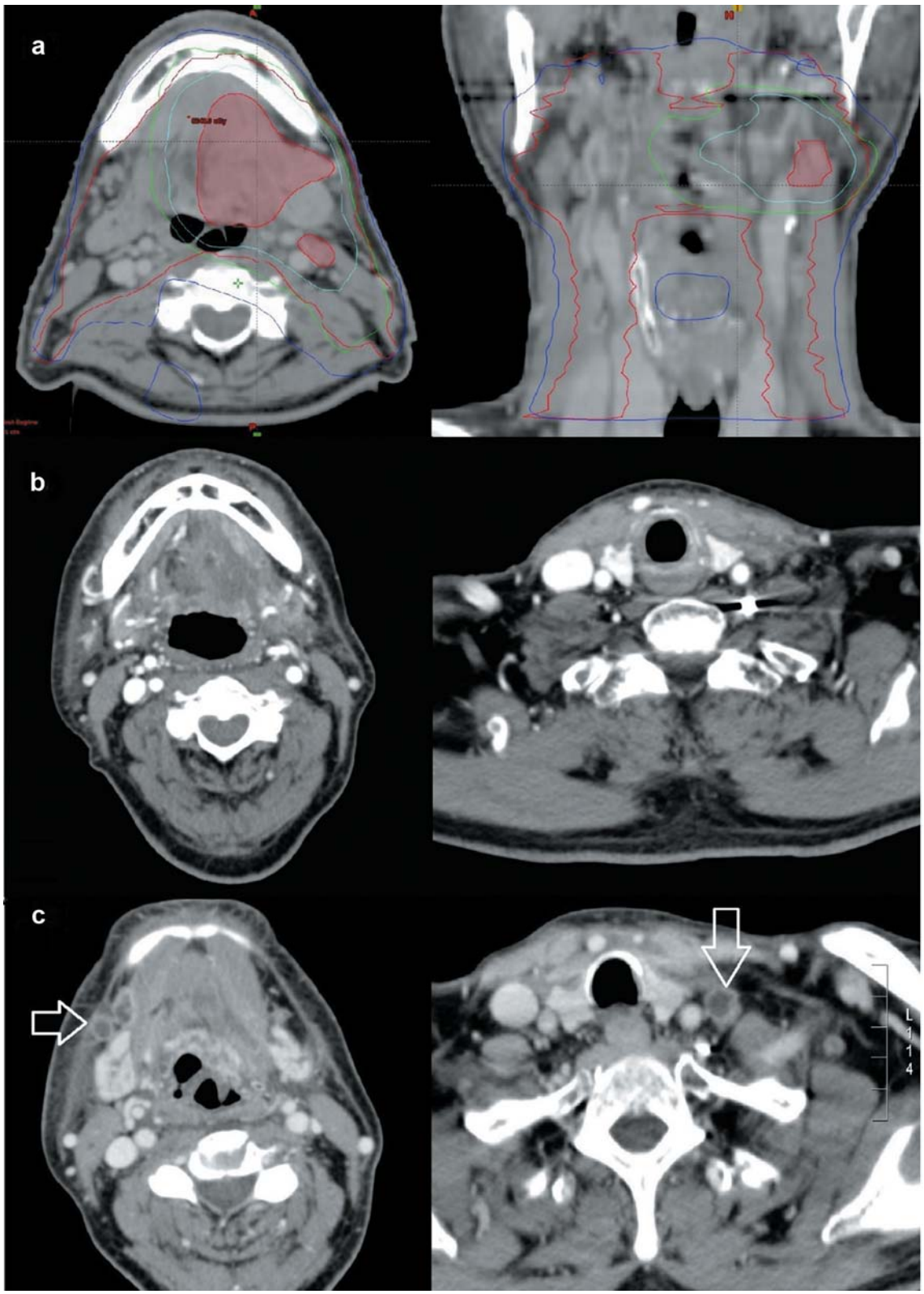

Figure 1. *The only case in which recurrence occurred outside the high-risk planning target volume. This patient had initial T3N2b base of tongue cancer, that was treated with concurrent chemoradiotherapy with intensity-modulated radiotherapy (a), and had complete response after concurrent chemoradiotherapy (b), but had recurrence 6 months later in level Ib and supraclavicular lymph nodes (c).*

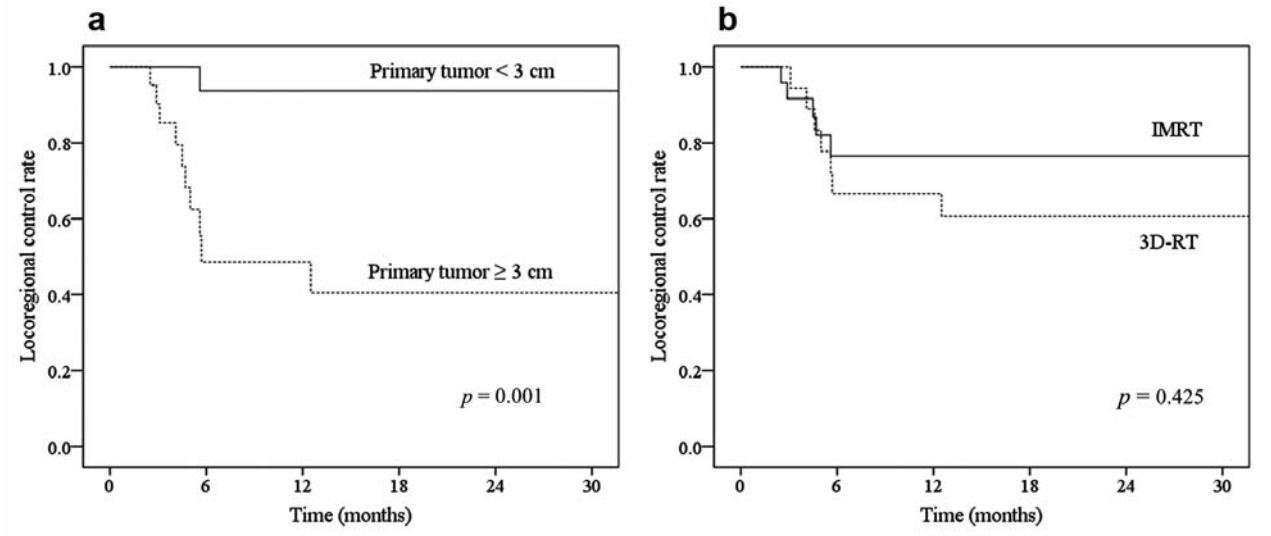

Figure 2. *The locoregional control rate by primary tumor size (a) and radiotherapy technique (b).*

Table V. *Studies that showed pattern of recurrences in head and neck cancer*

Study name or authors high-risk	Stage/no. of patients	LR failure	Local failure	Regional failure	Within high-risk	Outside
Non-IMRT trials						
GORTEC94-01 (2)	III-IV/109 (all OPX)	62 (56.9%)	40 (36.7%)	21 (19.3%)	n/a	n/a
RTOG 97-03 (4)	III-IV/241	33 (12.9%)	22 (9.1%)	11 (4.6%)	n/a	n/a
Nutting *et al*. (7)	I-IV/47	7 (14.9%)	n/a	n/a	7 (14.9%)	2 (4.3%)
Present study	III-IV/22	8 (36.4%)	6 (27.3%)	3 (13.7%)	8 (36.4%)	0 (0.0%)
IMRT trials						
Chao *et al*. (11)	I-IV/58	17 (10.8%)	5 (3.2%)	13 (8.2%)	13 (8.2%)	5 (3.2%)
Eisbruch *et al*. (13)	I-IV/133	21 (15.8%)	12 (9.0%)	15 (11.3%)	17 (12.8%)	4 (3.0%)
Dendekar *et al*. (15)	II-IV/114	18 (15.8%)	12 (10.5%)	10 (8.8%)	18 (14.8%)	0 (0%)
Garden *et al*. (22)	I-IV/776 (all OPX)	77 (9.9%)	51 (6.6%)	26 (3.4%)	65 (8.4%)	12 (1.5%)
Farrag *et al*. (23)	I-IV/63	13 (20.6%)	5 (7.9%)	9 (14.3%)	10 (15.9%)	3 (4.8%)
Nutting *et al*. (7)	I-IV/47	12 (25.5%)	n/a	n/a	11 (23.4%)	1 (2.1%)
Present study	III-IV/27	5 (18.5%)	4 (14.8%)	2 (7.4%)	5 (18.5%)	1 (3.7%)

IMRT: Intensity-modulated radiotherapy LR, locoregional; n/a, not assessed; OPX: oropharyngeal carcinoma

upper neck irradiation, and a conventional anteroposterior field was used for lower neck. They found 17 locoregional failures, and nine (53%) failures were within the high-risk CTV, one (6%) failure was marginal to high-risk CTV. Two failures were found inside or marginal to the intermediate-risk CTV, and five (28%) were found outside the IMRT field and in the lower neck. Dandekar *et al*. analyzed the pattern of relapse in 114 patients with stage II to IV HNSCC treated with tomotherapy, and found 12 local recurrences and 10 regional recurrences (15). All local and eight regional recurrences were entirely within or centered in the GTV, and the other two regional recurrences were located in the high-risk PTV, where 60 Gy of radiation was delivered. They reported that no recurrences occurred in the low-risk PTV where 54 Gy were delivered in 33 fractions.

Compared to the studies of patterns of failure (Table V), our study only included patients with stage III and IV HNSCC who had bulky disease and higher risk of recurrence. Therefore, the recurrence rate was slightly higher than that in other studies that included patients with all stages of HNSCC. However, the result showed that the recurrence pattern was similar to those in other studies. More

recurrences developed locally rather than regionally, and most recurrences were within the high-risk PTV where initially the GTV was present. Recurrences outside the high-risk PTV area occurred only in one (3.7%) patient. The most important prognostic factor for locoregional control was the primary tumor size. The regional control rate was neither affected by the lymph node size nor by the metabolic activity. The radiotherapy technique did not affect the locoregional control rate or survival.

It is well-known that differences in treatment strategy can alter the pattern of failure. In HNSCC, recent efforts to improve the locoregional control, such as concurrent use of chemotherapy, altered fractionation, and modern RT techniques, have also increased the proportion of distant failure as the primary recurrence site (20, 21). However, our data suggest that IMRT did not change the pattern of recurrences with respect to local *versus* regional recurrences in patients with stage III-IV HNSCC. Even though the baseline characteristics and treatment strategy were uniform between the 3D-RT and IMRT groups, some limitations exist in our study, such as its retrospective nature, small number of patients, short follow-up time, and difference in chemotherapy regimen between the two groups. Therefore, a longer-term follow-up study with a greater number of patients is warranted.

In conclusion, not only the risk of locoregional recurrences but also the pattern of failures were similar between IMRT and 3D-RT even in patients with stage III-IV HNSCC, although decreased toxicities were observed in IMRT. The most important factor for locoregional control was the primary tumor size rather than the radiotherapy technique.

Conflicts of Interest

The Authors have no potential conflicts of interest to declare.

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