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Original Article

Comparison of Field-in-Field Radiotherapy with Conformal Radiotherapy for Unilateral Cervical Malignant Lymphoma

Mako Yamashita[a,b], Norihisa Katayama[b*], Takahiro Waki[b], Kuniaki Katsui[b], Kengo Himei[c], Mitsuhiro Takemoto[d], and Susumu Kanazawa[b]

[a]Department of Radiology, Nippon Kokan Fukuyama Hospital, Fukuyama, Hiroshima 721–0927, Japan, [b]Department of Radiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, [c]Department of Radiology, Japanese Red Cross Okayama Hospital, Okayama 700–8607 Japan, and [d]Department of Radiology, Japanese Red Cross Society Himeji Hospital, Himeji, Hyogo 670–8540 Japan

This study compared field-in-field (FIF) radiotherapy with conformal radiotherapy with physical wedges for the treatment of unilateral cervical malignant lymphoma. Two treatment plans, the FIF technique and conformal RT, were generated for each of 32 patients with unilateral cervical malignant lymphoma. To compare the 2 treatment plans, dose-volume histograms of the planning target volume (PTV), the thyroid, submandibular gland, carotid artery, mucosa, spinal cord, and surrounding normal tissue, and monitor unit (MU) were analyzed. The FIF technique showed significant reduction in the mean dose of thyroid, submandibular gland, carotid artery and mucosa, the maximum dose of the spinal cord and PTV, and the volume receiving > 107% of the prescribed dose of surrounding normal tissue ($p < 0.001$). In addition, there were gains in the homogeneity index of the PTV for FIF. Furthermore, the total MU was also lower for the FIF technique than for the wedge technique ($p < 0.001$). Compared with the wedge technique, the FIF technique improved the dose homogeneity of the PTV, reduced the dose to normal structures, and was associated with fewer MUs in the treatment of patients with cervical malignant lymphoma.

Key words: field-in-field technique, wedge, lymphoma, monitor units, dose-volume histogram

Radiotherapy remains a key component of combined modality therapy for patients with malignant lymphoma [1]. In regard to the optimal treatment volume for radiotherapy (RT) of localized malignant lymphoma, involved-field RT (IFRT) is usual [1–5]. The frequency of cervical lymph node involvement is high in cases of primary lesions of Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL) [6–10].

Engert *et al.* reported that, among lymphoma patients treated with high-dose radiation, the rates of radiation toxicity were higher in patients with early-stage Hodgkin's lymphoma. The most common acute toxicities were dysphagia and mucositis [5].

To limit the adverse events of RT, the treatment aim has been to focus the prescribed dose on the target as much as possible and to avoid exposure to the surrounding organs and normal tissues. By reducing the volume of normal tissues exposed to intermediate- to high-dose irradiation, intensity-modulated radiation therapy (IMRT) has the potential to substantially improve dose distribution. However, IMRT is rarely

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*Corresponding author. Phone: +81–86–235–7313; Fax: +81–86–235–7316
E-mail: norihisa@md.okayama-u.ac.jp (N. Katayama)

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employed for the treatment of patients with malignant lymphoma [8], and the parallel-opposed pair technique is generally used in cervical radiation therapy.

The field-in-field (FIF) technique is generally regarded as a manual, forward intensity-modulated therapy. Prabhakar *et al.* [11] reported some advantages of using the FIF technique over the wedge technique, which uses a physical, wedge-shaped filter to provide gradation of radiation beams. First, the FIF technique reduces dose scattering in the patient. Second, the total monitor unit (MU) usage is considerably reduced. Third, the total time required for treating a patient can be reduced. Fourth, some hot spots may persist even after the use of the wedge technique because of extreme tissue homogeneity and counter irregularities; these can be avoided with the FIF technique. In general, the higher number of MUs with the wedge technique, associated with increased dose scattering, can, along with leaf radiation leakage, increase the risk of secondary cancers [12, 13].

Many studies have compared field-in-field (FIF) RT with conformal RT using the wedge technique in breast cancer [14-16], but, to the best of our knowledge, a study comparing the effectiveness of these modalities in unilateral cervical lymphoma has not yet been reported.

The wedge technique, which is associated with a longer treatment time, is not typically used in RT for bilateral cervical lymphoma. However, the wedge technique can be used in RT for unilateral cervical lymphoma. We therefore considered that the advantages of RT using the FIF technique may be more pronounced for unilateral cervical lymphoma than for bilateral cervical lymphoma. Thus, we limited our study to patients with unilateral cervical lymphoma only.

The current study was conducted to evaluate the clinical benefit of the FIF technique compared with conformal RT using the physical wedge technique for the treatment of unilateral cervical lymphoma.

Patients and Methods

Between April 2002 and August 2012, 40 patients with cervical malignant lymphoma underwent RT at Okayama University Hospital. Of the 40 patients, 32 patients met the following criteria and were thus eligible for this study: (1) Pre-chemotherapy CT images were available; (2) There were no extranodal lesions; and (3) The cervical lymphoma was unilateral.

Patient characteristics are shown in Table 1. This study complied with the Declaration of Helsinki 1989 recommendations and was approved by the ethics committee of the Okayama University.

All patients were scanned in the supine position with their arms at their sides using immobilization devices usually consisting of thermoplastic masks. Data from planning computed tomography (CT) scans taken at 2- or 5-mm intervals were transferred to the radiation treatment planning system (XiO 4.62; Computerized Medical System, Inc., St Louis, MO, USA). Two treatment plans against unilateral cervical malignant lymphoma were generated for the study for each patient: for the FIF technique and for conformal RT. A total dose of 30 Gy in 15 daily fractions of 2 Gy was planned.

Treatment was simulated using 4 MV X-rays with a dose rate of 400 MU/min, using an ONCOR Impression Plus linear accelerator (Siemens Medical Systems, Erlangen, Germany) equipped with 80 pairs of double-focused multi-leaf collimators (MLCs) with a leaf slice thickness of 5 mm. At least 2 open beams consisting of 2 anterior-posterior (AP) parallel-opposed fields (gantry angles, 0°-180°) shaped with MLCs on a beam's-eye-view (BEV) were used.

The weight point was set so that the dose gradient was low, and the planning target volume (PTV) of V95 was similar for both plans. The target field was designated according to the guidelines of the Cancer and Leukemia Group B study for Hodgkin's lymphoma [17] (Table 2). The isocenter was placed at the same point for both plans. The clinical target volume (CTV) included ipsilateral neck node levels I-VI, the parotid area, and the volume of pre-chemotherapy involved lymph nodes plus a 5-mm margin based on anatomical bases reviewed by Lengelé B *et al.* [18]. The PTV included the CTV plus a 3-mm margin. Target volumes and organs at risk were delineated by the same radiologist (M.Y.) and checked by a senior radiologist (N. K.).

For conformal RT, the MLCs in the AP and posterior-anterior (PA) fields were shaped to the noted field in the BEV and the collimator was set to 0° or 180°. A conventional hard wedge was applied at 15°.

For the FIF technique, a step-by-step iterative process inherent to forward planning was used. The

Table 1 Patient characteristics

	Age	Gender	Lesion Level	Histologic type	Lesion volume (cc)
1	71	F	IV	Follicular	7.03
2	48	M	IIA	Diffuse large B cell	9.91
3	30	F	VB	Diffuse large B cell	2.68
4	59	M	IIA	Diffuse large B cell	2.68
5	55	M	IIA	Diffuse large B cell	3.77
6	60	M	IIA	Diffuse large B cell	2.65
7	64	F	IB	Diffuse large B cell	5.40
8	80	F	IIB	Diffuse large B cell	0.79
9	57	F	IIA, IIB	Diffuse large B cell	9.70
10	60	M	IB	Diffuse large B cell	4.39
11	58	M	IB	Follicular	2.47
12	62	M	III, IV	Diffuse large B cell	14.92
13	57	M	IIA, III	Follicular	3.53
14	73	F	IB	MALT	3.65
15	45	F	IV	Diffuse large B cell	3.03
16	60	F	IIB, III, IV	Diffuse large B cell	41.82
17	73	M	IIB, III, IV	B-cell lymphoblastic	11.80
18	73	M	IB, IIA	Diffuse large B cell	4.79
19	51	M	IIA, III	Follicular	18.20
20	69	M	IIA	Follicular	2.71
21	57	M	IIA	Diffuse large B cell	1.83
22	46	F	IIA, III	Follicular	11.59
23	49	M	IIA	Diffuse large B cell	0.78
24	82	M	IIA, IIB, III, IV	Diffuse large B cell	46.45
25	15	F	IV, VB	Nodular sclerosis	26.72
26	19	M	IV	Nodular sclerosis	3.56
27	44	M	IIA	Diffuse large B cell	6.84
28	47	M	IIB	Follicular	11.22
29	64	F	IA, IB, IIA	Low grade B cell	73.86
30	23	F	IV	Nodular sclerosis	0.97
31	27	F	IV	Diffuse large B cell	9.84
32	57	F	IIA	Diffuse large B cell	2.27

MALT, mucosa-associated lymphoid tissue.

Table 2 The involved field borders of unilateral cervical/supraclavicular region in the guidelines for Cancer and Leukemia Group B studies in Hodgkin's lymphoma

Involvement at any cervical level with or without involvement of the supraclavicular (SCL) nodes	
Arm position	Akimbo or at sides
Upper border	2 cm above the lower tip of the mastoid process and mid-point through the chin
Lower border	2 cm below the bottom of the clavicle
Lateral border	To include the medial 2/3 of the clavicle
Medial border	At the contralateral transverse processes

starting point was the conventional AP-PA plan with subsequent manual addition of 2 or 4 MLC-shaped subfields with the same AP-PA isocenter and gantry position. Optimization was obtained by weighting the open pairs and avoiding hot spots ($>107\%$ of the dose prescription). Only segments with more than 5 MUs were used. An example of one of the FIF technique portals that consists of one main AP field (Fig. 1A) and 2 subfields (Fig. 1B and C) is depicted in Fig. 1.

Plan evaluation. To evaluate and compare treatment plans, dose-volume histograms (DVHs) were assessed quantitatively for each plan and patient.

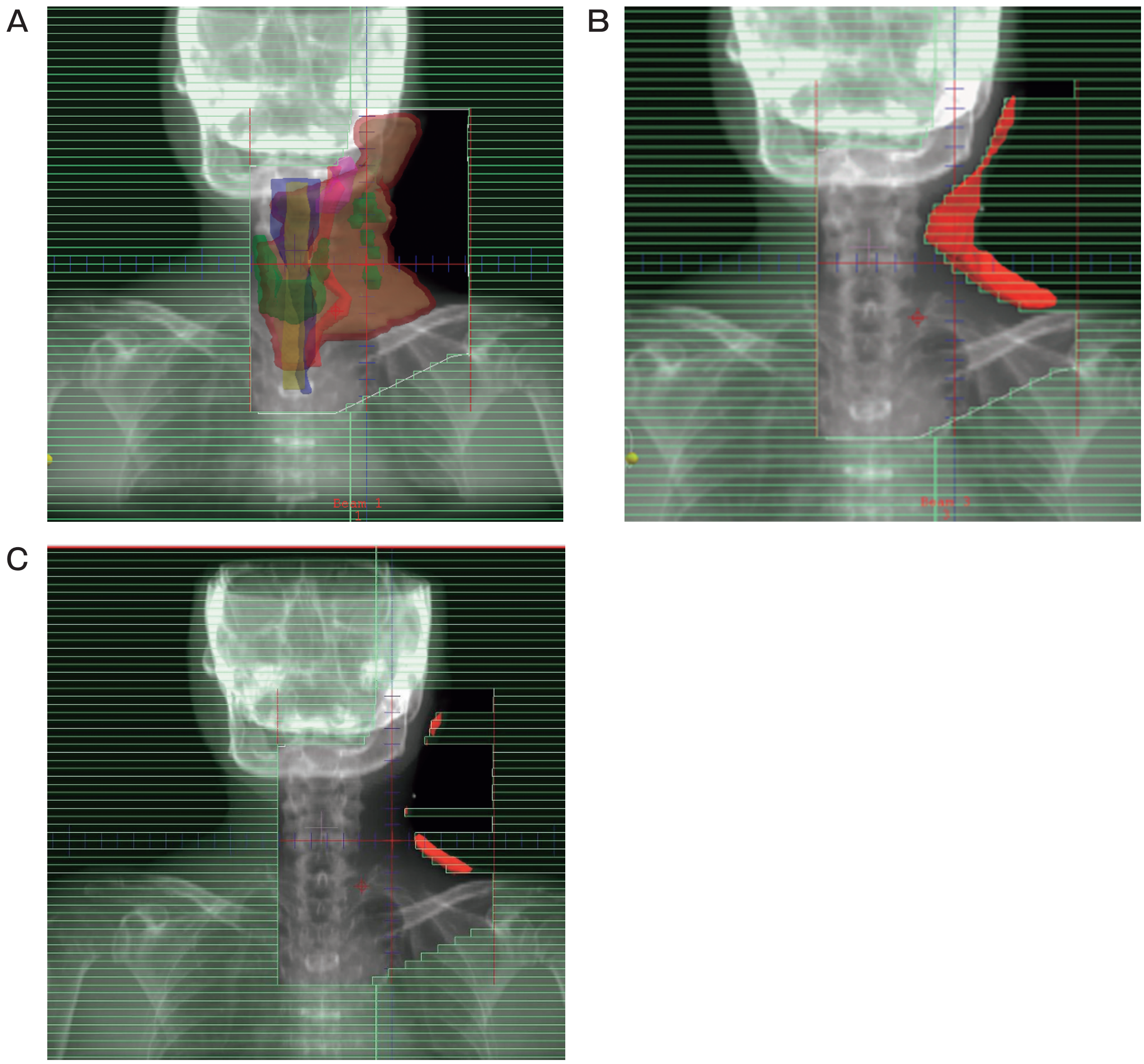

Fig. 1 Example of the FIF technique portals: A, main anterior-posterior (AP) field; B, subfield 1; C, subfield 2. The hot spots (> 107% of the dose prescription) are shown in red color. These subfields were designed to avoid the hot spots.

DVHs were computed using the following parameters:

(i) The percentage of the volume of the PTV that receives at least 95% of the prescribed dose (PTV V95)

(ii) The percentage of the volume of the PTV that receives > 107% of the prescribed dose (PTV V107)

(iii) The maximum dose to the PTV (PTV Dmax)

(iv) The volume of surrounding normal tissues that receives > 107% of the prescribed dose (surrounding normal tissue V107)

(v) The percentage of the volume of PTV that receives a dose of between 95% and 107% of the prescribed dose (PTV homogeneity index (HI))

(vi) The mean doses to the thyroid (thyroid Dmean)
The mean doses to the submandibular gland (submandibular gland Dmean)
The mean doses to the carotid artery (carotid artery Dmean)
The mean doses to the mucosa (mucosa Dmean)

(vii) The maximum dose to the spinal cord (spinal cord Dmax)

Statistical analyses. Data processing and statistical analyses were carried out using SPSS 19.0 (SPSS, Chicago, IL, USA). Analyses were

Table 3 Comparison of DVH parameters and MU between the FIF technique and wedge technique

		FIF	Wedge	*P* value
PTV	V95 (%)	85.81 ± 9.10	85.95 ± 8.41	0.758
	V107 (%)	1.06 ± 2.76	10.55 ± 11.07	<0.001
	Dmax (Gy)	32.43 ± 0.74	33.11 ± 0.78	<0.001
	HI (%)	84.87 ± 9.37	76.50 ± 10.76	<0.001
Thyroid	Dmean (Gy)	28.80 ± 1.57	30.52 ± 4.42	<0.001
SG	Dmean (Gy)	28.88 ± 1.55	29.38 ± 1.54	<0.001
CA	Dmean (Gy)	29.26 ± 1.77	29.68 ± 1.80	<0.001
Spinal cord	Dmax (Gy)	30.83 ± 0.93	31.70 ± 1.24	<0.001
Mucosa	Dmean (Gy)	31.56 ± 0.90	32.67 ± 2.41	<0.001
SNT	V > V107 (ml)	3.79 ± 6.10	41.52 ± 55.99	<0.001
MU		223.91 ± 20.45	343.56 ± 12.73	<0.001

SG, submandibular gland; CA, carotid artery; SNT, surrounding normal tissues; FIF, field-in-field technique; Wedge, wedge technique; PTV, planning target volume. (mean ± standard deviation)

performed using the Wilcoxon signed rank test to determine whether there was a significant difference in any of the parameters examined. Differences with p value < 0.05 were considered statistically significant.

Results

Results of the analyses are presented in Table 3. Briefly, the PTV V95 was similar for both techniques. The Dmean of the thyroid, submandibular gland, carotid artery, and were all significantly lower with the FIF technique ($p < 0.001$), as was the Dmax for the spinal cord ($p < 0.001$).

In addition, the FIF technique was significantly better than the wedge technique ($p < 0.001$) in decreasing PTV V107. Finally, there was a significant difference in the mean total MUs between the FIF and wedge techniques ($p < 0.001$) equivalents to a mean of 17.9 sec of machine treatment on average, assuming a dose rate of 400 MU/min.

Discussion

Patients with malignant lymphoma are usually treated with a combination of chemotherapy and IFRT. Investigators at the MD Anderson Cancer Center reviewed 469 patients with diffuse large B-cell lymphoma treated between 2001 and 2007 with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP, 6–8 cycles) with or without radiotherapy (RT). Of these patients, 40% had stage I or II disease and 60% had stage III or IV disease. Overall, 30% received consolidation involved-field RT (IFRT) at a dose of 30–39 Gy after a complete response (CR) to chemotherapy. Local control was achieved in 100% of patients, with all relapses outside the RT field [2, 3]. Clinical trials have demonstrated that IFRT shows an efficacy equivalent to those of extended-field or subtotal-lymphoid irradiation in the context of combined modality therapy programs, and IFRT has been adopted as the standard for combined modality therapy [4, 5, 19]. However, the optimal treatment volume or field size for RT of localized NHL is somewhat controversial because of the lack of definitive phase III trials. Many of the conclusions regarding appropriate field size are extrapolated from information regarding patterns of failure. In view of this, treatment of the original volume plus the adjacent nodal areas has largely been abandoned, suggesting that IFRT is an appropriate treatment for patients with NHL [4, 5, 19]. Two-thirds of NHL lesions are nodal at presentation and one-third are extranodal, whereas in Hodgkin's lymphoma, extranodal lesions are rare. Hodgkin's lymphoma mostly originates in the lymph nodes, and > 80% of the patients present with cervical lymph node involvement. Likewise, in NHL, the neck is the most frequent sites of nodal involvement (70% of the cases), followed by the groin (60%), and axilla (50%) [9, 10]. Therefore we evaluated the FIF technique compared with conformal RT for the treatment of cervical lymphoma.

The data demonstrate the clear advantages of using the FIF radiotherapy technique as opposed to the conformal RT using wedge technique for treating patients with unilateral malignant cervical lymphoma. The Dmean for all areas was significantly reduced and the PTV 107 was significantly lower for FIF, thereby minimizing patient exposure to radiation and reducing the likelihood of off-target radiation damage to other organs. In addition, the FIF technique significantly improved PTV homogeneity and decreased the total MUs. The reduction in MUs speeds up the treatment time and improve throughput on linac, which is obviously advantageous for the patient.

In a retrospective study involving 910 patients, Elerding *et al.* showed a trend towards an increased incidence of stroke after neck irradiation in patients with HD, NHL, or head and neck carcinoma [20]. In addition, asymptomatic carotid arterial disease occurs frequently in young patients after neck radiation therapy for Hodgkin's lymphoma [21]. And, even though the arterial region was different, Darby *et al.* reported a linear relationship between the rate of major coronary events and heart exposure, with a 7.4% increase in the rate per Gy [22]. These findings suggest that the improved dose distribution with the FIF technique could also reduce the risk of carotid arterial diseases associated with RT.

The main disadvantage of the FIF technique is the long planning time however, we recommend this technique because of the many advantages explained above.

Our study limitation is the difference between interobserver and intraobserver. Some errors may have been introduced in our method of contouring. But we consider that such errors would be trivial because we defined the target volume delineation and the radiation techniques in detail.

In conclusion, the FIF technique improved dose homogeneity of the PTV in the management of unilateral cervical malignant lymphoma and reduced the dose to normal structures and the total MUs, compared with the conventional wedge technique.

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