Clinical impact of the flattening filter free irradiation in fixed-field IMRT and VMAT for stage I-II nasal natural killer/T-cell lymphoma

Xianfeng Liu, Fu Jin, Huanli Luo, Xin Zhang, Mingfang Guo, Xiujuan Zhao, Furong Wu and Qishuai Guo

*Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital, Chongqing, China; †Department of Radiation Oncology, Chongqing University Cancer Hospital, Chongqing, China; ‡Department of Gynecologic Oncology, Chongqing University Cancer Hospital, Chongqing, China

ABSTRACT

The study aimed to investigate clinical impact of the flattening filter free (FFF) irradiation in fixed-field intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) for patients with stage I–II nasal natural killer/T-cell lymphoma (NNKTCL). Four different plans, fixed-field IMRT, and VMAT plans with and without flattening filter (FF) (IMRT FF, IMRT FFF, VMAT FF, and VMAT FFF) were created for each of selected patients. Target quality, organs at risk (OARs) sparing, and tumor control probability (TCP) were compared between IMRT and VMAT with and without FF. The values of $D_{2.0\%}$, $V_{50\%}$, and conformal index were 0.03 Gy ($P = 0.028$), 0.03% ($P = 0.048$), and 0.002 ($P = 0.002$) lower with IMRT FFF than with IMRT FF, and the values of $D_{2.0\%}$, $D_{mean}$, and homogeneity index were 0.14 Gy ($P = 0.018$), 0.1 Gy ($P = 0.007$), and 0.002 ($P = 0.008$) higher with VMAT FFF than with VMAT FF. The TCP was higher with FFF beam than flattening beam in IMRT and VMAT. The results show that FFF irradiation achieved slightly worse target quality than FF irradiation in IMRT and VMAT for stage I–II NNKTCL. FFF beam was advantageous to increase the TCP in IMRT and VMAT.

1. Introduction

Nasal natural killer/T-cell lymphoma (NNKTCL) is a regional tumor, which has a low incidence in Western countries but is relatively common in Mexico, South America, and Eastern Asia (Liu et al., 2017; Yong Yang et al., 2017). Radiotherapy (RT) is the main therapy for stage I–II NNKTCL and has shown its advantage in overall survival benefit for patients with NNKTCL (Au et al., 2009; Huang et al., 2008). Fixed-field intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT), which are standard external beam RT techniques, have emerged as the first-line therapies to treat NNKTCL due to significant benefits in target quality and organs at risk (OARs) sparing compared with three-dimensional conformal RT (Liu et al., 2017).

In recent years, flattening filter free (FFF) irradiation has been adopted on standard linear accelerators (LAs) with large field sizes. Without a flattening filter (FF) in the beam path, FFF irradiation offers an opportunity to lower the out-of-field dose and delivers radiation doses with high dose rate and high efficiency (Dobler et al., 2017; Georg et al., 2011; Kragl et al., 2011). FFF irradiation reduces delivery times in stereotactic treatments and lowers the second primary cancer risk in peripheral organs, which has been confirmed by many researches (Dobler et al., 2017; Lu et al., 2015; Murray et al., 2015; Scorsetti et al., 2014; Swamy et al., 2015).

Striving for excellent plan quality and higher tumor control probability (TCP), adopting a reasonable RT plan will be significant for NNKTCL. To the best of our knowledge, the plan characteristics and TCP of fixed-field IMRT and VMAT with FFF irradiation for treating NNKTCL have not yet been studied. To assess the clinical impact of FFF irradiation, in this study we compared the plan quality and TCP between fixed-field IMRT and VMAT with and without FF for patients with stage I–II NNKTCL.

2. Methods

2.1. Patients and materials

Twenty-four cases with NNKTCL recently treated at our institution were randomly selected. Of them, 22 cases were in Stage I and two cases were in Stage II. None of the cases had distant metastasis or had received prior RT. The ethics committee of Chongqing University Cancer Hospital had approved this study, and each patient had signed informed consent. All of the computed tomography (CT) scans were obtained utilizing a Philips Big Bore CT scanner (Philips, The Netherlands) with 3 mm slice thickness. Patients were positioned in the supine position.

Delineation of the target volumes and adjacent OARs was performed on the Eclipse treatment planning system.
2.2. RT plans

For each of the 24 cases, four different RT plans (IMRT FF, fixed-field IMRT with FF; IMRT FFF, fixed-field IMRT with FFF; VMAT FF, VMAT with FF; VMAT FFF, and VMAT with FFF) were created on the Eclipse TPS. Dose optimization and calculation were performed using 6 MV photon beams generated by a Varian Edge device for all 96 RT plans. The Dose–Volume Optimizer algorithm was used for IMRT FF and IMRT FFF dose optimizations, the Progressive Resolution Optimizer was used for VMAT FF and VMAT FFF dose optimizations, and the anisotropic analytical algorithm was used for final-dose calculations for all plans (Bragg et al., 2008; Mingzhan et al., 2013). A bolus with a thickness of 0.5 mm was added to all the fields of the 96 plans for dose optimization and calculation. The boundaries of the bolus were described in previous studies (Liu et al., 2019, 2017).

2.2.1. IMRT FF plans

All the IMRT FF plans contained eight coplanar fields, with gantry angles of 255°, 290°, 325°, 0°, 0°, 35°, 70°, and 105°, and the rotation angles of the collimator and the couch for all the fields were set to 0°. To maximize protection of the lenses and eyes, the position of the jaw in the two fields with gantry angles of 0° was adjusted and fixed before dose optimization, as described previously (Liu et al., 2019). Dynamic sliding-window IMRT delivery, a flattened beam, and a fixed dose rate (DR) of 300 monitor units (MUs)/min were adopted to deliver radiation.

2.2.2. IMRT FFF plans

Except for adopting the FFF beam, without an FF in the beam path, the settings for IMRT FFF plans were the same as for IMRT FF plans.

2.2.3. VMAT FF plans

All the VMAT FF plans contained two coplanar arcs, with a gantry rotation angle of 255° to 105° clockwise and 105° to 255° counterclockwise. The rotation angles of the collimators were 30° and 330°, and the rotation angle of the couch was 0°. All the VMAT FF plans were optimized and calculated with a flattened beam and a maximum DR of 600 MUs/min.

2.2.4. VMAT FFF plans

Except for utilizing the FFF beam, the settings for VMAT FFF plans were the same as for VMAT FF plans.

The prescribed dose was set as 50 Gy in 25 fractions for the PTV of all plans. The prescribed 100% isodose should cover at least 95% of the PTV, and the percentage of the PTV receiving a radiation dose greater than 107% of the prescription dose should be less than 2%. Dose constraints for OARs were reset with minor adjustments in accordance with the Radiation Therapy Oncology Group 0615 Protocol. The detailed adjusted-dose constraints for all of the OARs are described in detail. The maximum dose (D_{max}) of lenses and spinal cord were not greater than 15 Gy and 45 Gy, respectively, and the D_{max} of optic nerves, optic chiasm, eyes, and brainstem was not greater than 50 Gy. The mean dose (D_{mean}) of parotid glands was less than 26 Gy.

2.3. Treatment plan evaluation

To achieve consistency in plan evaluation, all of the plans were normalized to the prescribed isodose covering 95% of the PTV, and the data derived from dose–volume histograms (DVHs) of the 96 plans were collected and analyzed. Figure 1 shows representative DVHs for the four different RT plans. The plan evaluation concentrated on target quality and OARs sparing.

PTV: The minimum dose (D_{min}), D_{max}, and D_{mean} of the PTV were analyzed. D_{min} and D_{max} of the PTV were defined as the dose received by 98% and 2% (D_{98%} and D_{2%}) of the PTV, respectively. The percentage of the PTV covered by 95% of the prescribed dose (V_{95%}) and the cold spot volume, defined as the percentage of the PTV covered by less than 93% of the prescribed dose, were also analyzed. The cold spot volume of the PTV should be less than 1%. The conformity index (CI) and the homogeneity index (HI) of the PTV were also assessed. The Paddick conformity index was utilized to evaluate the CI, which was defined as CI = TV_{PTV} / (TV \times PIV), where TV_{PTV} represents the PTV volume receiving 95% of the prescribed dose, TV is the PTV volume, and PIV is the body volume covered by 95% of the prescription dose. The closer the value of the CI is to 1, the better the irradiation conformity of the PTV. The HI was calculated with HI = (D_{98%} - D_{95%})/D_{mean}, where D_{5%} and D_{95%} represent the minimum dose delivered to 5% and 95% of the PTV, respectively. The closer the value of the HI is to 0, the better the irradiation uniformity of the target volume.

OARs: The dosimetric comparative analysis was conducted for D_{max} and D_{mean} of the contoured OARs (lenses, eyes, optic chiasm, optic nerves, brainstem, parotid glands, and spinal cord).
2.4. TCP calculation

Niemierko (Gay & Niemierko, 2007) proposed a phenomenological model to define the equivalent uniform dose (EUD) for tumors using the following equation:

\[
EUD = \sum_i \left( v_i D_i^a \right)^{1/a}
\]

where \( v_i \) is the \( i \)th partial volume receiving a dose of \( D_i \) in Gy and \( a \) is a unitless model parameter which describes the dose–volume effect. The paired data were derived from the differential DVH of an RT plan. For tumors, the concept of EUD represents a biologically uniform dose, which leads to the same cell death in the tumor as the actual non-uniform dose distribution.

Niemierko (Gay & Niemierko, 2007; Liu et al., 2020) also introduced an EUD-based TCP mathematical model, where the TCP is calculated using the following formula:

\[
TCP = \frac{1}{1 + \left( \frac{TCD_{50}}{TCD_{50}} \right)^{4.950}}
\]

where \( TCD_{50} \) represents the dose to kill 50% of the tumor cells when the tumor is homogeneously irradiated and the unitless parameter \( r_{50} \) describes the slope of the dose–response curve. The values of \( TCD_{50} \), \( r_{50} \), and \( a \) used to calculate the TCP in this study were 14.65, 0.41, and -13, respectively (Liu et al., 2020).

2.5. Statistical analysis

Statistical analysis was carried out using the paired Student t-test in SPSS (SPSS, Chicago, IL, USA). A \( P \) value less than 0.05 indicated that the difference was statistically significant.

3. Results

3.1. PTV coverage

All of the results with respect to the PTV are shown in Table 1. The values of \( D_{98\%} \), \( V_{95\%} \), and CI were 0.03 Gy (\( P = 0.028 \)), 0.03% (\( P = 0.048 \)), and 0.002 (\( P = 0.002 \)) lower with IMRT FFF than with IMRT FF, respectively, whereas the value of \( D_{mean} \) was 0.06 Gy (\( P = 0.002 \)) higher with IMRT FFF than with IMRT FF. The values of \( D_{2\%} \), \( D_{mean} \), and HI were 0.14 Gy (\( P = 0.018 \)), 0.1 Gy (\( P = 0.007 \)), and 0.002 (\( P = 0.008 \)) higher with VMAT FFF than with VMAT FF, respectively, whereas the CI was 0.003 (\( P = 0.008 \)) lower with VMAT FFF than with VMAT FF.
Table 1. Dosimetric and TCP results of PTV for the four different RT plans (means ± SEM).

| Parameters      | IMRT          | p-Value | VMAT         | p-Value |
|-----------------|---------------|---------|--------------|---------|
|                  | FF            | FFF     | FF VS. FFF   | FF      | FFF     | FF VS. FFF   |
| D_{mean} (Gy)   | 49.08 ± 0.05  | 49.05 ± 0.05 | 0.028     | 49.10 ± 0.06 | 49.12 ± 0.06 | 0.149  |
| D_{mean} (Gy)   | 52.42 ± 0.11  | 52.49 ± 0.10 | 0.266     | 52.63 ± 0.08 | 52.77 ± 0.09 | 0.018  |
| D_{mean} (Gy)   | 51.40 ± 0.07  | 51.46 ± 0.06 | 0.002     | 51.43 ± 0.05 | 51.53 ± 0.06 | 0.007  |
| V_{95%} (%)      | 99.59 ± 0.07  | 99.56 ± 0.06 | 0.048     | 99.59 ± 0.08 | 99.59 ± 0.08 | 0.632  |
| Cold spot volume (%) | 0.173 ± 0.040 | 0.179 ± 0.038 | 0.497   | 0.200 ± 0.052 | 0.202 ± 0.056 | 0.871  |
| CI              | 0.879 ± 0.005 | 0.877 ± 0.005 | 0.002     | 0.865 ± 0.005 | 0.862 ± 0.005 | 0.008  |
| HI              | 0.044 ± 0.002 | 0.046 ± 0.002 | 0.110    | 0.047 ± 0.001 | 0.049 ± 0.002 | 0.008  |
| TCP (%)         | 79.672 ± 0.164 | 79.704 ± 0.165 | 0.002     | 79.690 ± 0.155 | 79.736 ± 0.153 | 0.012  |

Table 2. Radiation doses of OARs for the four different RT plans (means ± SEM).

| Parameters      | IMRT          | p-Value | VMAT         | p-Value |
|-----------------|---------------|---------|--------------|---------|
|                  | FF            | FFF     | FF VS. FFF   | FF      | FFF     | FF VS. FFF   |
| Optic chiasm    | D_{mean} (Gy) | 44.65 ± 1.35 | 44.44 ± 1.37 | 0.144     | 43.19 ± 1.57 | 43.60 ± 1.50 | 0.112  |
| Left optic nerve| D_{mean} (Gy) | 49.30 ± 0.81 | 49.40 ± 0.76 | 0.256     | 49.92 ± 0.73 | 49.79 ± 0.90 | 0.643  |
| Right optic nerve| D_{mean} (Gy) | 48.87 ± 0.76 | 48.87 ± 0.81 | 0.989     | 49.60 ± 0.55 | 49.55 ± 0.60 | 0.822  |
| Left eye        | D_{mean} (Gy) | 49.53 ± 0.97 | 49.55 ± 0.92 | 0.827     | 50.10 ± 0.96 | 50.49 ± 0.72 | 0.107  |
| Right eye       | D_{mean} (Gy) | 47.23 ± 1.07 | 47.14 ± 1.15 | 0.505     | 48.73 ± 0.76 | 49.01 ± 0.74 | 0.105  |
| Left lens       | D_{mean} (Gy) | 19.81 ± 0.76 | 19.99 ± 0.77 | 0.041     | 25.13 ± 0.77 | 25.57 ± 0.83 | 0.104  |
| Right lens      | D_{mean} (Gy) | 11.33 ± 0.31 | 11.36 ± 0.30 | 0.686     | 12.62 ± 0.30 | 12.87 ± 0.31 | 0.030  |
| Spinal cord     | D_{mean} (Gy) | 10.70 ± 0.35 | 10.79 ± 0.39 | 0.144     | 13.61 ± 0.42 | 13.79 ± 0.53 | 0.342  |
| Brainstem       | D_{mean} (Gy) | 15.81 ± 2.41 | 15.90 ± 2.41 | 0.314     | 12.11 ± 2.12 | 12.16 ± 2.18 | 0.836  |
| Left parotid    | D_{mean} (Gy) | 1.49 ± 0.28  | 1.53 ± 0.29  | 0.049     | 1.26 ± 0.24  | 1.30 ± 0.26  | 0.216  |
| Right parotid   | D_{mean} (Gy) | 32.04 ± 1.59 | 31.60 ± 1.71 | 0.024     | 27.40 ± 2.09 | 27.15 ± 2.14 | 0.485  |
| D_{mean} (Gy)   | 19.31 ± 0.82  | 18.39 ± 0.80 | 0.000     | 15.28 ± 0.88 | 14.85 ± 0.86 | 0.288  |
| D_{mean} (Gy)   | 23.73 ± 1.98  | 24.52 ± 2.00 | 0.102     | 24.70 ± 2.10 | 23.85 ± 2.25 | 0.144  |
| D_{mean} (Gy)   | 5.84 ± 1.12   | 5.92 ± 1.12  | 0.046     | 7.08 ± 1.08  | 7.27 ± 1.15  | 0.224  |
| D_{mean} (Gy)   | 22.75 ± 2.10  | 23.74 ± 2.14 | 0.007     | 22.28 ± 2.37 | 20.92 ± 2.31 | 0.014  |
| D_{mean} (Gy)   | 5.73 ± 1.26   | 5.74 ± 1.25  | 0.497     | 6.93 ± 1.33  | 6.81 ± 1.28  | 0.465  |

3.2. OARs

The values of D_{mean} of the optic chiasm, the left lens, and the brainstem were 0.72 Gy (P = 0.001), 0.08 Gy (P = 0.045), and 0.92 Gy (P = 0.000) lower with IMRT FFF than with IMRT FF, respectively, whereas the values of D_{mean} of the left and right optic nerves, the right eye, the spinal cord, and the left parotid were 0.37 Gy (P = 0.028), 0.37 Gy (P = 0.007), 0.18 Gy (P = 0.041), 0.04 Gy (P = 0.049), and 0.08 Gy (P = 0.046) higher with IMRT FFF than with IMRT FF, respectively. The value of D_{max} of the brainstem was 0.44 Gy (P = 0.024) lower with IMRT FFF than with IMRT FF, whereas the value of D_{max} of the right parotid was 0.89 Gy (P = 0.007) higher with IMRT FFF than with IMRT FF. Similarly, the values of D_{mean} of the left eye and the left lens and the value of D_{max} of the left lens were 2.19% (P = 0.026), 2.87% (P = 0.012), and 1.98% (P = 0.030) higher with VMAT FFF than with VMAT FF, respectively, whereas the value of D_{max} of the right parotid was 6.10% (P = 0.014) lower with VMAT FFF than with VMAT FF. The radiation doses of the OARs are shown in Table 2.

3.3. TCP calculation

The results with respect to the TCP are shown in Table 1. The TCP was 0.032% (P = 0.002) higher with IMRT FFF than with IMRT FF. The TCP was 0.046% (P = 0.012) higher with VMAT FFF than with VMAT FF.

4. Discussion

Research in relation to the assessment of fixed-field IMRT and VMAT with FFF irradiation for stage I–II NNKTCL is rare; therefore, the plan quality and TCP of
fixed-field IMRT and VMAT with and without FF for stage I–II NNKTCL need to be studied further. The aim of this study was to assess whether FFF irradiation is advantageous compared with flattened beam irradiation in fixed-field IMRT and VMAT with respect to plan quality and TCP, as well as further guide the optimization of RT plans for treating stage I–II NNKTCL.

The advantages of IMRT FF, which is characterized by good target-dose sculpturing and OARs sparing, have previously been demonstrated in the treatment of stage I–II NNKTCL; however, previous studies also confirmed that VMAT FF achieved better target coverage in steeper dose gradients and dose uniformity than IMRT FF (Liu et al., 2019; Maier et al., 2016). Some studies suggested that the plan quality of FF irradiation was comparable with flattened beam irradiation in stereotactic treatments for small target volumes (Hrbacek et al., 2014; Stieler et al., 2013). However, the literature concerning the effects of FFF irradiation on the plan quality reveals contradictory results. Some studies (Nicolini et al., 2012; Subramaniam et al., 2012) of larger target volumes showed that FFF irradiation achieved similar target coverage and significantly decreased the irradiation of OARs, whereas other studies (Mingzan et al., 2013; Spruijt et al., 2013; Zhuang et al., 2015) reported flattened beam irradiation was superior to FFF irradiation with respect to plan quality. Our present study indicates that FFF irradiation is inferior to flattened beam irradiation with respect to target quality, and we obtained approximately the same radiation doses to several OARs as flattened beam irradiation in IMRT and VMAT. FFF beam is softer and easier to deposit on the body surface than flattened beam, and it is more conducive to tumor irradiation of NNKTCL. However, the FFF beam requires more modulation to achieve a homogeneous dose in the target volume, which reduces the advantage of the FFF irradiation. This may be the reason why FFF beam is inferior to flattened beam in target quality in this study.

In planning IMRT or VMAT cases, the RT plan is generally designed and evaluated on the basis of physical objectives; however, the plan evaluation based on biological indicators is more relevant to the clinical efficacy (Liu et al., 2020). Utilizing DVHs data and reliable biological parameters, various radiobiological models, such as the Poisson model, the Niemierko model, and the Marsden model, have been developed to calculate the TCP and normal tissue complication probability to estimate the clinical efficacy of RT plans (Gay & Niemierko, 2007; Liu et al., 2020). However, the application of these models is limited by the inaccuracy of fitting biological parameters. In this study, the biological parameters for calculating the TCP in the Niemierko model were derived from stage I–II Hodgkin’s lymphoma. We showed that FFF beam irradiation led to an increase in TCP of the PTV in IMRT and VMAT of less than 0.1%. Of course, the accurate prediction of the TCP in this study depended on the accuracy of the model and related parameters, which need to be verified in future studies.

5. Conclusion

FFF irradiation reduced scatter, affecting target coverage, OARs sparing, and the TCP. In IMRT and VMAT for stage I–II NNKTCL, FFF irradiation could mildly deteriorate the target quality and increase the TCP. FFF irradiation offers new options for treating stage I–II NNKTCL.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| FFF          | flattening filter free |
| IMRT         | intensity-modulated radiotherapy |
| VMAT         | volumetric-modulated arc therapy |
| OARs         | organs at risk |
| TCP          | tumor control probability |
| RT           | radiotherapy |
| CT           | computed tomography |
| TPS          | treatment planning system |
| CTV          | clinical target volume |
| PTV          | planning target volume |
| DR           | dose rate |
| MUs          | monitor units |
| DVHs         | dose–volume histograms |
| CI           | conformal index |
| HI           | homogeneity index |
| EUD          | equivalent uniform dose |

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