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FULL PAPER

Reirradiation of nasopharyngeal carcinoma focusing on volumetric modulated arcs with flattening filter-free beams

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Objective: The goal of this study was to assess the role of flattening filter-free (FFF) beams in volumetric modulated arc radiotherapy for patients with recurrent nasopharyngeal carcinoma (rNPC).

Methods: 13 patients with rNPC were replanned for FFF RapidArc® (RA-FFF) and conventional RapidArc (RA) (Varian Medical Systems, Palo Alto, CA). Quantitative evaluation was performed for the planning target volume (PTV) and organs at risk (OARs). Phantom dose verifications, treatment delivery time and monitor units (MUs) were also assessed.

Results: Each technique delivered similar doses to the PTV. RA-FFF had a better sparing effect on the brain stem and normal tissue when compared with RA, whereas RA provided lower mean doses to the skin. No significant difference between the two techniques could be established for other OAR parameters. Both techniques showed

equally good gamma scores in dosimetric verification. RA-FFF required more MUs than RA, whereas the delivery time for RA-FFF was slightly shorter than for RA.

Conclusion: Both treatment plans met the planning objectives. Dose measurements also showed good agreement with computed doses. In addition to slightly faster delivery times, RA-FFF produced better sparing of brain stem and normal tissue with uncompromised target coverage compared with RA.

Advances in knowledge: FFF beams have recently been assembled for clinical use. Our findings show RA-FFF is useful in the salvage treatment of rNPC owing to better brain stem and normal tissue sparing with uncompromised target coverage compared with RA. This may be beneficial in the case of tumour invasion close to the brain stem.

Nasopharyngeal carcinoma (NPC) is highly prevalent in the southeastern part of China. Radiotherapy remains the mainstay treatment for NPC owing to the radiosensitivity of the disease. Although patient outcomes have improved over recent years, local recurrences are not uncommon, with recurrence rates of 19–25% at 5 years after completion of combined therapy.¹ However, treatment of patients with recurrent NPC (rNPC) remains a challenge owing to the emergence of radioresistant clones, decreased local blood supply in the nasopharyngeal structures and proximity of critical structures. Proper salvage radiation therapy can achieve local control and improve survival, but such therapy often increases therapy-related complications owing to high doses of radiation delivered to normal tissues.

Initial experience has shown that reirradiation using intensity-modulated radiation therapy (IMRT) results in encouraging local control and provides satisfactory clinical outcome for patients with early restage diseases.² However, reirradiation causes accumulation of normal tissue injury, resulting in an increase in treatment-related

morbidity and mortality and a decrease in the quality of life of patients.

The application of sophisticated techniques is required to minimize the risk of toxicity and adequately deliver curative doses. RapidArc® has recently gained popularity as a treatment for many tumours. This is a relatively new volumetric modulated arc therapy (VMAT) technique based on simultaneous optimization of multileaf collimator shapes, dose rate and gantry rotation speed.³ Numerous studies have shown that RapidArc provides comparable target coverage with a general improvement in sparing organs at risk (OARs), reduced beam-on time and lower numbers of monitor units (MUs) than other IMRT approaches.^{4,5}

Recently, there has been an increasing interest in the clinical use of flattening filter-free (FFF) beams. In particular, with FFF beams, the dose rate can be increased up to 1400 MU min⁻¹ for the 6-MV beam. Removal of the flattening filter also reduces the out-of-field dose by reducing both head scatter and residual electron contamination. This

leads to a possible faster treatment with reduced out-of-field dose exposure.^{6,7}

In order to enhance efficacy and reduce side effects, we investigated the feasibility of reirradiation of rNPC focusing on volumetric modulated arcs with FFF beams. Navarria *et al*⁸ found that VMAT with FFF beams offers a safe delivery of high doses per fraction in a short treatment time and results in an earlier radiological response than conventional beams. However, it cannot be assumed that the dosimetric characteristics of reirradiation in rNPC will be in agreement with lung studies owing to the complex anatomic situation of rNPC. Hence, it is important to demonstrate whether these advantages could be extended to the reirradiation of patients with rNPC.

METHODS AND MATERIALS

Patient selection

This study was approved by the ethics committee of Shantou University Medical College Tumor Hospital. From 2011 to 2013, 13 patients with rNPC, confirmed by histology, were enrolled in this study, and included 10 males and 3 females with a median age of 58 years (range, 47–76 years). Eight patients were diagnosed with undifferentiated NPC, whereas five had differentiated, non-keratinizing, rNPC. Each patient had previously received one cycle of irradiation, with a total dosage ranging between 70 and 72 Gy. According to the American Joint Committee on Cancer/International Union Against Cancer 2007 stage classification, two patients were in restage I, four patients in restage II, four patients in restage III and three patients in restage IV.

Delineation of target volumes and organs at risk

All target volumes and OARs were delineated slice by slice on CT images. Tumour volumes were defined by the CT/MRI studies in accordance with the International Commission on Radiation Units and Measurements Report 83. The recurrent gross tumour volume (rGTV) of the nasopharynx and lymph nodes were determined according to diagnostic CT/MRI and physical examination. The recurrent clinical target volume (rCTV) was defined as the rGTV plus a 0.5- to 1-cm margin. Planning target volume (PTV) for rCTV was generated automatically after delineation of tumour targets according to the immobilization and localization uncertainties. The median PTV volume was 86 cm³ (range, 20–219 cm³). OARs surrounding the PTV included the brain stem, optic chiasm, optic nerves, lens, spinal cord, parotid glands, oral cavity and larynx. Normal tissue was defined as the body volume subtracted by all the PTVs and OARs, and the skin was defined as the ring generated by the 5-mm intermargin of the body.

Treatment plan management

Two treatment plans were replanned for each patient on the CT imaging, to be either RA with FFF beams (RA-FFF) or RA with conventional flattened beams. All RA plans were optimized on the Eclipse™ (Varian® Medical Systems, Palo Alto, CA) treatment planning system, using 6-MV beams or 6-MV FFF beams from a TrueBeam™ (Varian® Medical Systems) linear accelerator. Considering the different situations of target volumes and surrounding complex OARs, one to three arcs were adopted for both RA plans with the collimator rotation set at 30°. The maximal dose rate was set to 600 MU min⁻¹ for RA and 1400 MU min⁻¹ for RA-FFF.

The accelerator was calibrated to deliver 0.01 Gy MU⁻¹ to water at a depth of maximal dose for a 10 × 10-cm² field at a source-to-surface distance of 100 cm following the American Association of Physicists in Medicine Task Group 51 report.⁹ Optimization methods and parameters were the same between different techniques. The progressive resolution optimizer algorithm v. 10.0.28 (Varian Medical Systems) was used for RA optimization. For all patients, the dose-volume constraints were defined to match the planning objectives, and the normal tissue objective automatic tool was activated to minimize the dose spread outside the PTVs. Volumetric doses were calculated using the anisotropic analytical algorithm v. 10.0.28 (Varian Medical Systems) with a dose calculation grid of 2 mm.

Each plan was generated with the prescribed dose covering 95% of the PTV. The dose prescription was varied according to the general condition of the patient, the distance of the tumour from the OARs and the interval time from the end of the first course of radiotherapy until recurrence. For these 13 patients, the median total reirradiation dose was 62 Gy (range, 36–70 Gy) delivered in a 2.00–2.40 Gy daily fraction dose. Because of different situations for the recurrent patients, dose constraints for the PTV and OARs were also varied for different patients. The threshold of doses to critical adjacent structures in the reirradiation was limited as low as possible without compromising target coverage. In order to make a fair comparison, both RA-FFF and RA plans were optimized with the same dose constraints for the same patient, although dose constraints for different patients were varied. To compare various fractionation schemes, the 2 Gy-per-fraction equivalent dose was calculated using the equation:

$$D_{2\text{Gy}} = \frac{D \times \left(1 + \frac{(D/n)}{(\alpha/\beta)}\right)}{\left(1 + \frac{2}{(\alpha/\beta)}\right)}$$

where $D_{2\text{Gy}}$ is the 2 Gy-per-fraction equivalent dose to the specific tissue type α/β ; D is the total physical dose delivered to the tissue; n is the total number of fractions; and the quotient α/β is the parameter to determine the shape of the cell survival curve in the linear quadratic model. In this study, we used $\alpha/\beta = 10$ for tumour and $\alpha/\beta = 3$ for normal tissues.^{10,11}

Quantitative evaluation of the plans was performed using the dose-volume histograms (DVHs). For PTVs, $D_{98\%}$ and $D_{2\%}$ (dose received by 98% and 2% of the volume), mean dose, conformity index (CI) and homogeneity index (HI) were compared. CI was calculated using the equation:

$$\text{CI} = \left(\frac{\text{PTV}_{\text{ref}}}{V_{\text{PTV}}}\right) \times \left(\frac{\text{PTV}_{\text{ref}}}{V_{\text{ref}}}\right)$$

where PTV_{ref} represents the volume receiving the prescribed dose in the target volume, V_{PTV} stands for the volume of the PTV and V_{ref} is the volume that received the prescribed dose. The HI was evaluated as the difference between $D_{2\%}$ and $D_{98\%}$ divided by the mean dose.^{12,13} For OARs, $D_{2\%}$ was applied to evaluate doses to the brain stem, spinal cord, optic chiasm, optic nerves and lens, and the mean dose was applied to evaluate

doses to the parotid glands, larynx, oral cavity, normal tissue and skin. Treatment delivery time (including machine preparation) and MUs of the two techniques were also compared. The RA fields were connected to each other as doable with TrueBeam.

Dose verification

Dose verifications for RA plans were analysed with the cylindrical Delta⁴ phantom (ScandiDos, Uppsala, Sweden), a cylindrical phantom for patient-specific quality assurance. Absorbed dose was measured in two orthogonal detector arrays. The spacing between the detectors was 5 mm in the centre ($8 \times 8 \text{ cm}^2$) and 10 mm outside ($20 \times 20 \text{ cm}^2$). The measured dose planes were compared with the ones computed with a criterion of 3% and 3 mm. A detector point was considered to pass if the calculated gamma index (GI) was <1 . Points with $<5\%$ of the maximum dose were not taken into account. Acceptance criteria were specified to be met if 95% of the evaluated points did not exceed one.

Statistical analysis

A non-parametric Wilcoxon test was used to compare the difference between the two techniques. A p -value of <0.05 was considered to be statistically significant. Analysis was performed using SPSS® v. 16.0 software (IBM, Chicago, IL). Data are presented as medians with interquartile ranges.

RESULTS

Each plan was normalized to a prescribed dose covering 95% of the PTV. Both techniques delivered similar doses to the PTV. No significant difference among the different techniques could be established in the PTV parameters. Table 1 lists the statistical data of the PTVs for all studied cases. The dose distributions and DVHs for both plans are shown for one patient in Figures 1 and 2, respectively.

RA-FFF gave a better sparing effect on the brain stem ($p = 0.002$) and normal tissue ($p = 0.039$) when compared with RA, whereas RA provided for lower mean doses to the skin ($p = 0.033$). There was no significant difference in the doses delivered to other OARs between the two techniques (Table 2).

Table 3 lists the GI, delivery time and MUs, as grouped by plan type. Patient-specific dose verifications were performed for 13 plans in the 2 different techniques. Both techniques showed equally good gamma scores. Using 3%/3 mm criteria, 98.16 (97.85, 98.54) and 98.15 (97.65, 98.54) of points passed with a GI of <1 for RA-FFF and RA, respectively. All plans had

a GI $>95\%$. RA-FFF required more MUs than RA [RA-FFF: 472 (420, 584) MUs, RA: 436 (395, 557) MUs], whereas the delivery time per fraction for RA-FFF [118 (108, 134) s] was slightly shorter than for RA [131 (116, 148) s].

DISCUSSION

Local failure after primary radiotherapy has been a crucial clinical challenge owing to damage accumulated from previous exposure to high doses of radiation. The high cumulative radiation dose to adjacent organs, inefficiency of radiation and the risk of inducing another malignancy are the major concerns for reirradiation. IMRT has been proven to be a valuable treatment strategy for rNPC.² However, IMRT requires more fields and MUs, which prolongs delivery time, resulting in increased swallowing movement and position shift during treatment.

FFF beams have several potential advantages, such as increased dose rate, reduced collimator scatter, head leakage and out-of-field doses to the patient. This may allow faster treatment with reduced out-of-field dose exposure.^{6,7} Because of the potential advantage in protecting the normal tissue surrounding tumours, which is of the utmost concern, we evaluated RA with FFF beams for the treatment of patients with rNPC. The RA advantage in decreasing the MUs and treatment time compared with IMRT plans is well known. Our previous studies also demonstrated the feasibility and dosimetric advantage for using RA in the treatments of NPC to reduce treatment time, compared with IMRT.¹⁴ In this study, we decided not to work with IMRT techniques for which the VMAT advantage in the treatment of NPC compared with IMRT plans is well documented.

Our findings in this study show that the use of FFF beams is useful in the salvage treatment of rNPC owing to better brain stem and normal tissue sparing with uncompromised target coverage compared with conventional flattened beams, which agrees with our hypothesis. These results are in contrast to those observed in our previous studies for advanced NPC.¹⁴ One important reason to explain the improving dosimetric outcome is that relatively small field sizes and simple target volumes were applied in this study. Lechner et al¹⁵ also found that the advantageous characteristics of FFF beams could be better exploited for smaller targets.

Because of the forward peaked profile of FFF beams, the requirement for more MUs was always found in the RA-FFF plans than in the RA plans, which still represents a major limitation in

Table 1. Comparison of planning target volume (PTV) doses between flattening filter-free RapidArc® (RA-FFF) and conventional RapidArc (RA)

PTV	RA-FFF (Gy)	RA (Gy)	p -value
$D_{98\%}$ (Gy)	59.46 (52.35, 64.26)	59.46 (56.95, 63.79)	0.754
$D_{2\%}$ (Gy)	69.56 (66.74, 71.58)	70.66 (66.93, 71.87)	0.650
D_{mean} (Gy)	67.91 (61.16, 69.44)	68.75 (61.07, 69.96)	0.249
Conformity index	0.852 (0.784, 0.887)	0.874 (0.843, 0.887)	0.093
Homogeneity index	0.084 (0.058, 0.129)	0.092 (0.058, 0.131)	0.701

$D_{2\%}$, dose received by 2% of the volume; $D_{98\%}$, dose received by 98% of the volume; D_{mean} , dose received. All doses are 2 Gy-per-fraction equivalent doses.

Figure 1. The dose distributions for flattening filter-free RapidArc® (RA-FFF) and conventional RapidArc (RA). Both techniques delivered adequate dose coverage for the planning target volume. However, higher dose splashing to the brain stem and spinal cord was noticed in RA.

the application of FFF beams. Several studies have addressed this issue within the context of treatment planning in order to take into account the MUs. According to a prior study with FFF beams on radiation doses in brain metastases, increased MUs were observed with FFF treatment plans, but depended on the plan complexity and degree of modulation.¹⁶ Another recent study investigated the potential capabilities in achieving flat dose profiles from FFF beams, which would be highly beneficial for treatments that

require large fields, and showed these beams to combine dosimetric advantages of conventional flattened beams and FFF beams, potentially offering more efficient treatment with less scatter, less radiation leakage and fewer MUs required to deliver the dose.¹⁷

Regardless of the greater MUs in the RA-FFF plans, the treatment delivery times for RA-FFF are slightly faster than for RA, which may also be beneficial in the case of stereotactic radiotherapy for patients

Figure 2. Dose-volume histograms for flattening filter-free RapidArc® (RA-FFF) and conventional RapidArc (RA). Although both techniques provided good target coverage, the dose to the brain stem and spinal cord was lower in RA-FFF.

with rNPC. The dose rate for the FFF beams can be substantially higher than for conventional beams (1400 vs 600 MU min^{-1}), which is also observed in our RA-FFF plans. In hypofractionated treatment for liver tumours, Mancosu et al¹⁸ found RA with FFF beams to be feasible with short beam-on time. In our cases, there are no substantial changes in the delivery times. The reason may be limitations in the gantry rotation speed, but it may also be partly owing to the limitation of leaf speed (maximum speed, 2.0 cm s^{-1}).

Use of intensity-modulated radiosurgery with FFF beams in brain metastases is similar to ours in some respects.¹⁶ However, the treatment of rNPC is more difficult owing to its special anatomical site, compared with many other types of head and neck cancer. The more radioresistant clones of rNPC may necessitate larger fractional dosing. Larger dose per fraction,

however, may lead to serious sequelae, including nasopharyngeal mucosal infection and/or inflammation, necrosis, massive haemorrhage and even death.

There are several practical limitations to this study, and our analysis is intended only as an initial examination of the dosimetric impact of FFF beams and analysis on rNPC cases. We note that the cases for comparing two treatment techniques may not be sufficient. Follow-up studies in assessment of treatment outcomes would be helpful to better evaluate these techniques. These more elaborate scenarios should be evaluated in future clinical studies, augmented by more data from multicentre clinical trials. Multicentre clinical trials also should be conducted to examine the impact of the response outcome of FFF beams in future research in order to speed accrual, and to ensure generalizability of study results.

Table 2. Comparison of organ-at-risk (OAR) doses between flattening filter-free RapidArc® (RA-FFF) and conventional RapidArc (RA)

OARs	RA-FFF (Gy)	RA (Gy)	<i>p</i> -value
Brain stem, $D_{2\%}$	13.29 (12.58, 17.52)	15.26 (13.29, 18.68)	0.002
Optic chiasma, $D_{2\%}$	1.41 (1.23, 24.24)	1.41 (1.24, 23.65)	0.422
Optic nerve (right), $D_{2\%}$	2.04 (1.05, 30.98)	2.11 (1.11, 31.27)	0.173
Optic nerve (left), $D_{2\%}$	2.58 (1.01, 47.14)	1.40 (0.72, 45.56)	0.650
Lens (right), $D_{2\%}$	0.89 (0.70, 2.19)	0.92 (0.70, 2.35)	0.071
Lens (left), $D_{2\%}$	0.83 (0.48, 5.58)	0.88 (0.50, 5.77)	0.099
Spinal cord, $D_{2\%}$	11.00 (5.03, 12.83)	10.14 (4.86, 12.83)	0.182
Parotid gland (right), D_{mean}	7.37 (4.22, 13.44)	7.92 (3.97, 12.92)	0.583
Parotid gland (left), D_{mean}	12.37 (5.33, 16.61)	12.55 (5.13, 16.72)	0.311
Oral cavity, D_{mean}	11.88 (4.58, 17.12)	11.29 (4.41, 17.95)	0.101
Larynx, D_{mean}	0.62 (0.44, 1.03)	0.65 (0.45, 1.28)	0.861
Normal tissue, D_{mean}	3.32 (2.54, 3.76)	3.35 (2.58, 3.94)	0.039
Skin, D_{mean}	1.72 (1.36, 2.27)	1.69 (1.32, 2.29)	0.033

$D_{2\%}$, dose received by 2% of the volume; D_{mean} , mean dose received. All doses are 2 Gy-per-fraction equivalent doses.

Table 3. Comparison of gamma index (GI), delivery time and monitor units (MUs) between flattening filter-free RapidArc® (RA-FFF) and conventional RapidArc (RA)

Parameters	RA-FFF	RA	p-value
GI (%)	98.16 (97.85, 98.54)	98.15 (97.65, 98.54)	0.861
Time (s)	118 (108, 134)	131 (116, 148)	0.002
MUs	472 (420, 584)	436 (395, 557)	0.011

CONCLUSIONS

In conclusion, both treatment plans met the planning objectives. The dose measurements also show good agreement with computed doses. Besides the advantage of slightly faster delivery times, RA-FFF gives superior results over RA in terms of brain stem and normal tissue sparing with uncompromised target coverage, and this may be beneficial in the case of tumour invasion close to the brain stem. Our results suggest that volumetric modulated arcs with FFF beams is a possible and potentially curative approach for rNPC and may play an important role in the treatment of rNPC in the near future. Further investigations, focusing on optimizing radiation dose and

establishing effective treatment strategies, are required to evaluate their clinical outcomes.

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