Volumetric intensity-modulated arc therapy vs conventional intensity-modulated radiation therapy in nasopharyngeal carcinoma: a dosimetric study

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Dosimetric comparisons between RapidArc (RA) and conventional Intensity-Modulated Radiation Therapy (IMRT) techniques for nasopharyngeal carcinoma (NPC) were performed to address differences in dose coverage of the target, sparing of organs-at-risk (OARs), delivery of monitor units (MUs) and time, to assess whether the RA technique was more beneficial for treatment of NPC. Eight NPC patients (Stages I–IV), who had completed RA treatment, were selected for this study. Computed tomography data sets were re-planned using 7-fields fixed beam IMRT. Quantitative measurements of dose-endpoint values on the dose-volume histograms were carried out for evaluation of: (i) dose homogeneity ($D_{5\%}-D_{95\%}$); (ii) degree of conformity ($\text{CI}_{95\%}$); (iii) tumor control probability (TCP); (iv) doses to OARs; (v) normal tissue complication probability (NTCP); (vi) treatment time; and (vii) MUs. RA plans achieved better dose conformity and TCP in planning target volumes (PTVs). Target dose homogeneity was not as high as for IMRT plans. Doses to temporo-mandibular joints, clavicles, parotid glands and posterior neck, and their NTCPs were significantly lower in RA plans ($P < 0.05$). Mean doses to the brainstem and spinal cord were slightly lower in IMRT plans. RA plans allowed for a mean reduction in MUs by $78\%$ ($P = 0.006$), and a four-fold reduction in treatment delivery times, relative to IMRT plans. RA plans showed superior, or comparable, target coverage and dose conformity in PTVs, but at the expense of inferior dose homogeneity. RA plans also achieved significant improvements in dose reduction to OARs and healthy tissue sparing. A significant reduction in treatment delivery time for RA treatment technique was also noted.

Keywords: nasopharyngeal carcinoma; RapidArc; IMRT; dosimetry; planning

INTRODUCTION

Head-and-neck cancer (HNC) accounts for 6% of all malignancies, and almost half of the patients present with a locally advanced stage [1]. Among all types of HNC, nasopharyngeal carcinoma (NPC) is endemic in Southern China and parts of Southeast Asia. In the Hong Kong Chinese population, NPC has been in the top ten most common cancers in the past decade, according to the Hong Kong Cancer Registry. Head and neck squamous cell carcinoma displays a clear radiation dose-response relationship. This implies that both the probability of tumor control and the risk of radiation-induced normal tissue damage increase with radiation dose. Therefore, treatment of NPC with radiation therapy is curative for many patients with localized disease. However, treatment planning for NPC is challenging because of the complex anatomy, with bones, soft tissues and air cavities all in need of consideration. Organs at risk (OARs), like spinal cord, brain stem and salivary glands, are located very close to the target volume. In addition, the target volume is often an irregular concave shape.

Overview of IMRT

Over the last decade, Intensity-Modulated Radiation Therapy (IMRT) has been implemented for routine clinical use. IMRT combines several intensity-modulated beams to
provide improved dose homogeneity and highly conformal dose distributions [2], allowing for improved sparing of normal tissues for many tumor sites. A considerable amount of research has demonstrated the advantages of IMRT. Studies have concluded that IMRT allows more conformal dose coverage of the tumor, especially in situations where the tumor is in close proximity to critical normal tissues, thereby sparing the surrounding normal tissues [2–5]. They have also pointed out that a highly conformal dose distribution is essential to reduce the dose to normal tissues, thus late radiation-induced toxicities can be minimized. Besides, dose escalation becomes possible, which can potentially improve local tumor control. For each daily fraction, IMRT can give higher dose to the gross tumor volume, resulting in a more effective biological dose.

Overview of RA

More recently, there has been an increasing interest in using arc delivery of radiation for treatment of cancers. As introduced by Takahashi [6], the principle of simple conformal arc therapy is to spread the entrance dose shaped to the projected tumor outline over many angles. The rotational centre is in the tumor so that the high dose is focused on the projected tumor outline over many angles. The rotational centre is in the tumor so that the high dose is focused there with a steep fall-off outside the tumor. RapidArc (RA) consists of a single arc or multiple arcs modulated technique which was released for clinical use in April 2008 [6]. In RA, multileaf collimator (MLC) positions, dose rates and gantry speeds can be dynamically varied during the delivery of radiation over one arc, typically taking 70–90 seconds [6–8]. RA enables IMRT-like dose distributions to be delivered using a single rotation or multiple rotations of the gantry. RA aims to achieve several objectives at once: (i) improve OARs and healthy tissue sparing compared to other IMRT solutions; (ii) maintain or improve the same degree of target coverage; (iii) reduce significantly the treatment time (beam on time) per fraction [9].

Advantages of RA over IMRT

For HNC, treatment planning comparisons between RA and IMRT have shown that RA offers equivalent or superior target coverage and greatly improves sparing of OARs [8, 10]. Concerning the beam on time, Verbakel et al. [9] indicated that the delivery of a double-arc plan requires less than 3 minutes. This was in contrast to a typical IMRT sliding window delivery for seven fields, which required 8–12 minutes. The reduction in delivery time can lower the risk of intra-fraction movement. In addition, a shorter delivery time is more patient-friendly and enables an increase in patient throughput or implementation of more on-line imaging technologies. Moreover, a shorter fraction delivery time can prevent the chance of reducing local tumor control due to sub-lethal damage repair. The improved local tumor control is essential for long-term survival [7, 11].

Another important advantage is the efficient use of monitor units (MUs), as RA only requires 40% of the number of MUs compared with 7-fields sliding window IMRT plans [9]. Collimator transmission and scatter radiation from the linear accelerator contribute dose to healthy organs that are not in proximity to the target volume, and the dose can induce secondary malignancy. Since the amount of scattered radiation generated is a linear function of the number of MUs [12], the chance of having secondary tumors due to scattered doses can be reduced by using RA.

Justification for the study

Investigations have shown that arc-based solutions associated with intensity modulation are particularly promising in terms of physical dose calculations [8]. It is therefore of clinical interest to assess the application of new arc modulation techniques. RA has already been investigated for prostate, rectum, intracranial and cervix uteri cancers [6, 8, 13–15]. These clinical cases are relatively simple. So, further studies on more complex cases, like NPC, will be an ideal benchmark for assessment of the effectiveness of RA in a broader clinical perspective.

In the light of recent developments and the potential advantages of RA, this study aimed to compare RA technique with IMRT technique, and to examine the potential clinical application of RA for NPC patients. Among the HNC patients, NPCs were selected because the treatment planning techniques are more demanding than for other HNCs, due to large and irregular planning target volumes (PTVs) and the large number of adjacent sensitive structures [9]. Moreover, extensive studies on treatment planning and dosimetric comparison of RA technique with conventional IMRT technique for NPC have seldom been reported.

Aim and objectives

This study aimed to perform a dosimetric comparison between conventional IMRT techniques and RA techniques in order to assess whether the latter is more beneficial for treatment of NPC. The study sought to compare dose homogeneity, degree of conformity and tumor control probability (TCP) in order to assess the degree of target coverage. For assessing OARs and normal tissue sparing, the doses to OARs and their normal tissue complication probability (NTCP) were compared. The number of MUs and treatment delivery times were also compared for RA plans and IMRT plans. It was hypothesized that treatment planning by RA technique would improve dose homogeneity and degree of conformity in the PTVs, deliver less dose to OARs, require less treatment time and fewer MUs.
MATERIALS AND METHODS

Patient selection
A total of eight NPC patients were selected by convenience sampling. Since different staging of NPC has its own characteristics, which may affect the treatment planning outcomes, two patients for each stage of Stages I–IV (American Joint Committee on Cancer, 6th edition), were selected. Patient demographics are shown in Table 1.

All patients had completed treatments by RA at Prince of Wales Hospital, Hong Kong (PWH). Their Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans were retrieved and used as anatomic references for planning. They were re-planned using the IMRT planning system (Varian Eclipse, version 8.6) at PWH. The same images and contours were used for both IMRT and RA treatment planning. Prior to data collection, ethics approval was granted by the Department Research Committee, Department of Health Technology and Informatics, at the Hong Kong Polytechnic University, and support was gained from the Medical Physics Unit of the Department of Clinical Oncology, PWH.

Delineation of target volumes and critical structures
In the Eclipse Treatment Planning System, CT and MRI image fusions were retrieved. The critical structures and target volumes were delineated by the oncologists and physicists on the axial slices of the fused CT and MRI images.

According to ICRU reports 50 and 62 [16–17], the gross tumor volume (GTV) was defined as the gross extent of the tumor shown by CT/MRI fusion images, and included the primary tumor as well as all gross regional lymph nodes. The clinical target volume (CTV) was defined as the GTV plus a 1-cm margin for potential microscopic extension, together with the regional lymphatics. The PTV was generated by the CTV plus a 5-mm margin to account for uncertainty in delivery.

The main OARs were the brainstem, spinal cord, optic nerves, optic chiasm, lens, parotid glands, cochlea, auditory nerve (VIII), laryngo-pharynx, mandible and temporo-mandibular joints (TMJs). Critical organs, such as brainstem and spinal cord, plus 3-mm margins were used to generate the Planning Organ-at-Risk Volume (PRV).

Treatment planning system
All IMRT plans and RA plans were optimized on the Varian Treatment Planning System, (Varian Medical Systems, USA), Eclipse version 8.6.15, using the 6 MV photon beam of Varian Linear accelerators. The optimization software allows users to adjust all the optimization criteria (dose constraints and priorities) interactively during optimization in order to achieve an optimal treatment plan.

IMRT planning technique
IMRT plans were generated with seven coplanar fields with gantry angles of 0°, 50°, 90°, 150°, 200°, 250° and 300° using an isocentric technique. The fluence of each modulated field was optimized by inverse planning software. The fluence for each radiation beam was generated by sliding window technique based on 120 MLCs of 0.5 and 1 cm leaf-width at the iso-center. Volumetric doses were calculated using the Anisotropic Analytical Algorithm (AAA, version 8.6) with a dose calculation grid of 2.5 mm [6, 10, 15].

RA planning technique
Treated RA plans were extracted from the patient server for comparison. RA plans were generated using two complementary coplanar arcs of 350° (one counter-clockwise from 175° to 185°, one clockwise from 185° to 175°). Two arcs

| Gender | Age | Volumes of each PTV (cm³) |
|--------|-----|--------------------------|
|        | PTV54 | PTV56 | PTV62 | PTV70 | PTV74 |
| Stage I |        |       |       |       |       |
| P1 M    | 64    | –     | 151.3 | 610.1 | 435.4 | 154.2 |
| P2 M    | 84    | 200.7 | –     | –     | –     | –     |
| Stage II|        |       |       |       |       |       |
| P3 F    | 64    | –     | 148.5 | 491.9 | 405.8 | 163.8 |
| P4 M    | 78    | 204.6 | 10.9  | 372.2 | 107.9 | 68.9  |
| Stage III|       |       |       |       |       |       |
| P5 F    | 38    | –     | 123.4 | 504.7 | 316.3 | 213.5 |
| P6 F    | 44    | 18.9  | 203.6 | 439.1 | 154.3 | 76.7  |
| Stage IV|        |       |       |       |       |       |
| P7 F    | 71    | –     | 274.3 | 491.7 | 371.4 | 224.8 |
| P8 M    | 73    | –     | 464.8 | 584  | 297  | 196.1 |

PTV74, PTV70, PTV62, PTV56 and PTV54 = Planning Target Volumes (PTV) being prescribed with 74 Gy, 70 Gy, 62 Gy, 56 Gy and 54 Gy, respectively.
were used to achieve dose distributions with a higher PTV dose homogeneity and lower OARs involvement \([9-10, 18]\). In order to minimize the contribution of tongue and groove effect during the arc rotation, and to benefit from leaf trajectories which were non-coplanar with respect to the patient’s axis, the collimator rotation for RA remained at a value different from zero \([8, 15, 17]\). For this study, the collimator rotation was set to 20° from 0° in either direction. The field size of the collimator was set manually before optimization to include the whole tumor in 3D. The modulated intensity of dose was delivered with continuous variation of the gantry speed, dose rate and MLC positions during the beam on time.

The optimization was based on the Progressive Resolution Optimization (PRO) algorithm. The iterative inverse planning process aimed to simultaneously optimize the instantaneous MLC positions, the dose rates and the gantry rotation speeds to achieve the desired dose distributions \([8]\), beginning with coarse gantry sampling. As the optimization progressed, the arc resolution was gradually improved. The purpose was to reduce the optimization time by using small control points first and progressively enhancing the number of control points to achieve precise dose distributions \([8, 19]\). After optimization, the dose was calculated using AAA, version 8.6 with a dose calculation grid of 2.5 mm.

### Planning objectives

The dose constraints of IMRT plans and RA plans used for optimization were defined based on the acceptance criteria specified by the oncologist. Both RA plans and IMRT plans utilized simultaneous integrated boost (SIB) approaches with targets of GTV74, GTV70, PTV62, PTV56 and PTV54 being prescribed with 74 Gy, 70 Gy, 62 Gy, 56 Gy and 54 Gy, respectively. Each plan was normalized to an isodose level such that the coverage of multiple targets could meet the acceptance criteria.

According to the Radiation Therapy Oncology Group (RTOG) \([20]\), the planning objectives for targets were:

1. (i) more than 95% of the target volume received the prescription dose;
2. (ii) less than 20% of the target volume received more than 110% of the prescription dose;
3. (iii) less than 1% of the target volume received less than 93% of the prescription dose; and
4. (iv) less than 5% of the target volume received more than 80 Gy.

The acceptance criteria for OARs used as the guidelines in defining planning objectives are shown in Table 2. For

### Table 2. Acceptance criteria for Organs-At-Risk (OARs)

| OARs                                | Specification                                      | Reference  |
|-------------------------------------|----------------------------------------------------|------------|
| Brainstem                           | \(D_{\text{max}} < 54 \text{ Gy}\)                 | RTOG       |
| PRV of brainstem                    | 1\% vol < 60 Gy (preferable: 54 Gy vol <5\%)       | RTOG       |
| Spinal cord                         | \(D_{\text{max}} < 45 \text{ Gy}\)                 | RTOG       |
| PRV of spinal cord                  | 1\% vol < 50Gy (preferable: 45 Gy vol <3\%)         | RTOG       |
| Chiasm                              | \(D_{\text{max}} < 54 \text{ Gy}\)                 | PWH        |
| Lt and Rt optic nerve               | \(D_{\text{max}} < 54 \text{ Gy}\)                 | PWH        |
| Lt and Rt eyeball                   | \(D_{\text{max}} < 54 \text{ Gy (RTOG < 50 Gy)}\)  | PWH        |
| Lt and Rt lens                      | \(D_{\text{max}} < 10 \text{ Gy (RTOG < 25 Gy)}\)  | PWH        |
| Lt and Rt temporal lobe (TML)       | \(D_{\text{mean}} < 26 \text{ Gy or } <4 \text{ cm}^3 \text{ vol < } 60 \text{ Gy}\) | PWH        |
| Lt and Rt parotid gland             | \(D_{\text{mean}} < 26 \text{ Gy or } 50\% \text{ vol < } 30 \text{ Gy}\) | RTOG       |
| Combined parotid glands             | \(> 20 \text{ cm}^3 \text{ vol received < } 20 \text{ Gy}\) | RTOG       |
| Lt and Rt VIIIn and cochlea         | \(<5\% \text{ vol } > 55 \text{ Gy or } D_{\text{mean}} < 50 \text{ Gy}\) | RTOG       |
| Lt and Rt brachial plexus           | \(D_{\text{max}} < 66 \text{ Gy}\)                 | RTOG       |
| Laryngo-phyrynx                     | \(D_{\text{mean}} < 45 \text{ Gy}\)                 | RTOG       |
| Lt and Rt TMJ                       | \(D_{\text{max}} < 70 \text{ Gy or } <1 \text{ cm}^3 \text{ vol < } 75 \text{ Gy}\) | RTOG       |
| Oral cavity/trachea–oesophagus      | \(D_{\text{mean}} < 40 \text{ Gy}\)                 | RTOG       |
| Unspecified tissues outside target: | \(<5\% \text{ vol } > 70 \text{ Gy or } <1\%/1\text{cm}^3 \text{ vol < } 70 \text{ Gy}\) | RTOG       |

\(D_{\text{max}} = \text{Maximum Dose, } D_{\text{mean}} = \text{Mean dose, PRV = Planning Organ-at-Risk Volume, VIIIn = Auditory nerve, TMJs = temporo-mandibular joints, RTOG = Radiation Therapy Oncology Group, PWH = Prince of Wales Hospital.}
brainstem and spinal cord, 3-mm margins were generated to become the PRVs of brainstem and spinal cord. For parotid glands, mean dose was kept below 26 Gy. If a large volume of the parotid glands received a higher mean dose, measurable saliva would not be produced and the gland would not recover [4]. If this was not achievable, 50% of the volume receiving < 30 Gy was an alternate acceptance criteria.

Besides the dose and dose-volume parameters in the dose constraints, the priority setting of different targets and structures are also an important parameter to achieve an optimal plan. For instance, high priorities should be given to critical structures and target volumes to ensure the dose limits of these critical structures are not exceeded and the dose coverage of the targets is adequate.

Evaluation of the plans

The targets (PTVs)
The dose homogeneity was expressed in terms of the $D_{5\%} - D_{95\%}$ difference (difference between the dose received by 5% and 95% volume of the PTV) [9, 10, 15]. The dose homogeneity was calculated for each PTV. The degree of conformity of the plans was measured with a Conformity Index, $CI_{95\%}$. This was defined as the ratio between the patient volume receiving at least 95% of the prescribed dose and the volume of the PTV [9, 10]. The $CI_{95\%}$ of each PTV was found and analyzed. The TCP of each PTV was also assessed. The BIOPLAN (BIOlogical evaluation of PLANS) software package was used for the biological evaluation of treatment plans. In BIOPLAN, TCP was computed based on the Poisson model [21] with the assumptions: $\alpha = 0.4 \text{ Gy}^{-1}$, $\sigma = 0.09 \text{ Gy}^{-1}$, $\alpha/\beta = 10 \text{ Gy}$, and homogeneous clonogenic cell density $= 10^5 \text{ cell cm}^{-3}$.

The OARs
For OARs, the analysis included the mean dose for parotid glands, auditory nerve (VIIIth), cochlea, laryngo-pharynx and trachea-oesophagus. The maximum doses to one percentage volume (D1%) of spinal cord, brainstem, optic chiasm, clavicles, mandibles, posterior brain tissues, posterior neck muscles, temporal lobe (TML) and TMJs were analyzed [9, 15]. The $CI_{95\%}$ of each OAR was also assessed. In BIOPLAN, the NTCP was calculated using the Lyman-Kutcher-Burman model [21].

Treatment time and number of MUs
The estimated treatment delivery time was defined as the time recorded between beam-on for the first field and beam-off for the last field. For sliding window IMRT, it was the number of MUs divided by the dose rate per field, plus a parameter ‘delta’ which took into account the time that the gantry rotates between successive fields, the time for mode up, data transfer of the MLC delivery files, error in the estimated rotation time, and operator reaction time.

For RA, the treatment delivery time was recorded as the time between beam-on for the first arc and beam-off for the second arc [18]. PWH had carried out similar measurements in 2009, so the results were taken as a reference for this study. The number of MUs used between IMRT plans and RA plans with double arcs were recorded and compared.

Statistical analysis
The confidence interval was set at 95% and the level of significance at $\alpha = 0.05$ with a statistical power of 80%. Thus, the threshold for statistical significance was $P < 0.05$. One-tailed Wilcoxon Signed Rank Tests were used for statistical analysis using the Statistical Package of Social Sciences (SPSS) software, version 15.0.

Intraclass Correlation Coefficient
Since the planning of IMRT was divided among the research team, there might be variations in the planning outcomes. In order to assess the inter-rater reliability, the Intraclass Correlation Coefficient (ICC) was calculated using Model 2 for a single rating score. Before testing the inter-rater reliability, each member in the group (three in total) was required to generate an IMRT plan for the same patient. Data covering the seven areas of evaluation were collected for the three IMRT plans. Then, the data were used to calculate the ICC using SPSS software.

RESULTS

The targets (PTVs)
Target coverage, dose homogeneity and conformity
The coverage of PTVs of RA plans and IMRT plans were evaluated by comparing the target volumes receiving 95% of the prescribed dose ($V_{95\%}$), dose homogeneity and conformity index. For both RA plans and IMRT plans, > 99% of the target volumes received 95% of the prescribed dose (Table 3). Dose homogeneity of RA plans and IMRT plans for each PTV are shown in Table 3. For PTV56, IMRT plans achieved better homogeneity ($P = 0.05$) than RA plans. Similarly, IMRT plans provided slightly improved dose homogeneity for PTV62 and PTV70, but their differences were not statistically significant. Figure 1 shows the DVHs of PTV56, PTV62, PTV70 and PTV74 of a Stage IV patient. The dose homogeneity of RA plan was slightly inferior to the IMRT plan but the difference was not statistically significant.

RA plans and IMRT plans were comparable in terms of $CI_{95\%}$, with no statistical differences (Table 4). However, all PTVs had smaller values of $CI_{95\%}$ for RA plans, suggesting that RA plans achieved higher conformity in the PTVs. The relative decrease in $CI_{95\%}$ of RA plans was in a range of 3.33–14.96%.
The TCP of the PTVs are shown in Table 4. In general, RA plans resulted in higher TCP for all PTVs. There was significant difference in TCP for PTV56 ($P = 0.006$) and PTV74 ($P = 0.02$).

The OARs

The OARs are doses to OARs. Critical structures being analyzed were brainstem, spinal cord and optic chiasm (Table 5). Figure 2 shows the comparison of the DVHs of multiple targets (PTV54, PTV56, PTV62, PTV70 & PTV74) between RA plans and IMRT plans.

| V$_{95\%}$ (%) | Dose homogeneity (D$_{5\%} - D_{95\%}$) |
|----------------|----------------------------------------|
| RA Plans       | IMRT Plans                             | RA Plans       | IMRT Plans | P-value |
| PTV54          | 99.66                                  | 99.83         | 5.95 ± 1.37 | 7.44 ± 3.28 | 0.143   |
| PTV56          | 99.8                                   | 99.91         | 5.12 ± 0.92 | 4.00 ± 1.54 | 0.05*   |
| PTV62          | 99.77                                  | 99.91         | 9.26 ± 1.62 | 8.65 ± 1.23 | 0.20    |
| PTV70          | 99.73                                  | 99.9          | 7.11 ± 1.20 | 6.94 ± 0.99 | 0.43    |
| PTV74          | 99.75                                  | 99.91         | 4.43 ± 0.83 | 4.87 ± 1.05 | 0.43    |

*Significant at $P < 0.05$. PTV74, PTV70, PTV62, PTV56 and PTV54 = Planning Target Volumes (PTV) being prescribed with 74 Gy, 70 Gy, 62 Gy, 56 Gy and 54 Gy, respectively. D$_{5\%} - D_{95\%}$ = difference between the dose received by the 5% and 95% volume of the PTV.

Fig. 1. Comparison of DVHs of targets (PTV 56, PTV 62, PTV 70 and PTV 74) between RA plan and IMRT plan of a stage IV patient.
brainstem and spinal cord between the RA plan and the IMRT plan for a Stage IV patient. There was no significant difference in dose maximum (Dmax) delivered to the spinal cord and brainstem, though the mean Dmax was lower in IMRT plans. The NTCP of the spinal cord was higher in the RA plan and was slightly significant. For the NTCP of the brainstem, the difference was not significant, though the RA plan was higher than the IMRT plan.

**Group II: bony structures.** The mean maximum doses delivered to the TMJs and clavicles were analyzed and are shown in Table 5. The doses to the Lt TMJ and clavicle were significantly lower in the RA plans than in the IMRT plans ($P = 0.02$ and $P = 0.04$, respectively). The mandible was contoured in one of the patients only. The Dmax received by the mandible was higher in IMRT plans than in RA plans.

**Group III: soft tissues and muscles.** When comparing the RA plans and the IMRT plans for posterior brain tissues, lower posterior neck (post neck 1) and upper posterior neck (post neck 2), significant reductions were

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**Table 4.** Comparison of Conformity Index (CI95%) and Tumor Control Probability (TCP) of targets (PTV56, PTV62, PTV70 and PTV74) between RA plans and IMRT plans

| Conformity Index (CI95%) | TCP (%) |
|--------------------------|---------|
| RA Plans | IMRT Plans | P-value | Relative decrease | RA Plans | IMRT Plans | P-value |
| PTV56 | 3.98 ± 1.33 | 4.68 ± 1.84 | 0.09 | 14.96% | 86.1 ± 7.62 | 84.29 ± 8.19 | 0.01* |
| PTV62 | 1.72 ± 0.13 | 1.85 ± 0.33 | 0.09 | 7.03% | 89.24 ± 3.83 | 88.38 ± 5.56 | 0.36 |
| PTV70 | 2.03 ± 0.51 | 2.10 ± 0.70 | 0.16 | 3.33% | 96.34 ± 1.12 | 96.33 ± 1.02 | 0.34 |
| PTV74 | 3.13 ± 0.54 | 3.34 ± 0.59 | 0.06 | 6.29% | 98.73 ± 0.39 | 98.58 ± 0.43 | 0.02* |

*Significant at $P < 0.05$. †Relative decrease = (RA Plans – IMRT Plans)/IMRT Plans × 100%. CI95% = ratio between the patient volume receiving at least 95% of the prescribed dose and the volume of the PTV.

**Table 5.** Comparison of doses to OARs and the corresponding Normal Tissue Complication Probability (NTCP) between RA plans and IMRT plans

| Dose to OARs (Gy) | NTCP (%) |
|-------------------|----------|
| RA Plans | IMRT Plans | P-value | RA Plans | IMRT Plans | P-value |
| Spinal cord (D1%) | 44.27 ± 2.57 | 43.43 ± 2.16 | 0.08 | 0.85 ± 0.20 | 0.51 ± 0.38 | 0.04* |
| Brainstem (D1%) | 54.09 ± 1.60 | 53.45 ± 3.59 | 0.31 | 0.30 ± 0.20 | 0.18 ± 0.24 | 0.10 |
| Chiasm (D1%) | 39.84 ± 18.52 | 46.17 ± 20.97 | 0.10 | 2.98 ± 4.23 | 6.76 ± 10.51 | 0.05 |
| Lt temporo-mandibular joint (D1%) | 63.40 ± 7.79 | 66.28 ± 5.39 | 0.02* | 1.99 ± 3.07 | 3.88 ± 5.55 | 0.01* |
| Clavicle (D1%) | 60.62 ± 0.99 | 62.47 ± 1.91 | 0.04* | 15.62 ± 14.75 | 15.78 ± 14.00 | 0.17 |
| Mandible (D1%) | 78.16 | 81.45 | N/A | 0.36 ± 0.39 | 0.66 ± 0.57 | 0.03* |
| Post brain (D1%) | 69.65 ± 2.51 | 73.78 ± 3.02 | 0.02* | 0.30 ± 0.20 | 0.18 ± 0.24 | 0.10 |
| Post neck 1 (D1%) | 63.91 ± 3.32 | 70.11 ± 7.24 | 0.05* | 0.30 ± 0.20 | 0.18 ± 0.24 | 0.10 |
| Post neck 2 (D1%) | 70.14 ± 2.22 | 78.21 ± 4.40 | 0.009* | 1.50 ± 0.95 | 7.16 ± 5.30 | 0.01* |
| Laryngo-pharynx (Dmean) | 51.22 ± 3.42 | 43.69 ± 5.54 | 0.01* | 1.43 ± 4.03 | 2.65 ± 7.50 | 0.33 |
| Trachea-oesophagus (Dmean) | 45.76 ± 2.67 | 47.30 ± 4.45 | 0.11 | 3.78 ± 3.41 | 6.78 ± 5.45 | 0.03* |
| Lt temporal lobe (D1%) | 70.00 ± 3.43 | 71.33 ± 3.12 | 0.02* | 4.18 ± 6.80 | 6.64 ± 12.06 | 0.06 |
| Lt cochlea (Dmean) | 52.39 ± 7.47 | 47.47 ± 8.91 | 0.01* | N/A | N/A | N/A |
| Lt auditory nerve (Dmean) | 52.55 ± 8.98 | 46.59 ± 10.56 | 0.05* | N/A | N/A | N/A |
| Combined parotid gland (vol < 20 Gy)† | 10.21 ± 7.53 | 1.87 ± 2.30 | 0.01* | N/A | N/A | N/A |

*Significant at $P < 0.05$. †Volume of combined parotid glands receiving < 20 Gy (cm³).
observed in the mean Dmax of RA plans \((P = 0.02, 0.05\) and \(0.009\), respectively) as reflected in the DVHs of these structures, shown in Fig. 3. On the other hand, the laryngo-pharynx received a significantly higher dose mean (Dmean) in the RA plans \((P = 0.01)\).

Group IV: others. There was a statistically significant difference in dose received by the Lt TML, Lt cochlea and Lt VIII n. Regarding the parotid glands, there was no significant change in the Dmean. However, when analyzed by the volume of combined parotid glands receiving < 20 Gy, there was a significant increase in the volume for RA plans \((P = 0.01)\), as shown in Table 5.

NTCP

The NTCPs of the brainstem \((P = 0.1)\) and spinal cord \((P = 0.04)\) were higher in the RA plans. There were significant reductions in NTCP in RA plans for the posterior brain \((P = 0.03)\), lower posterior neck (posterior neck 1) \((P = 0.04)\), upper posterior neck (posterior neck 2) \((P = 0.01)\), trachea-oesophagus \((P = 0.03)\) and Lt TMJ \((P = 0.01)\).

MU and treatment delivery times

The average MUs for RA plans and IMRT plans were 499 and 2268, respectively. The MUs were significantly reduced by 78% in the RA plans \((P = 0.006)\). Results of treatment times indicated that for RA, two arcs could be delivered within 3 minutes. For a 7-fields IMRT plan, the overall delivery time was 11.8 minutes.

ICC

Inter-rater reliability was tested by ICC Model 2. The result was 0.991, indicating that there was good reliability between raters for clinical measurement.

DISCUSSION

This study presents a comparison of volumetric intensity-modulated arc therapy (Varian-RapidArc) with fixed beam IMRT (Varian-Eclipse) for the treatment of NPC patients. Clinically acceptable plans were achieved with both RA plans and IMRT plans.

Dose homogeneity

Except for PTV56, there was no significant difference in target dose homogeneity between the RA plans and IMRT
plans. This finding was similar to that observed by Bertelsen et al. [22], who conducted a dosimetric comparison between Volumetric Modulated Arc Therapy (VMAT) and IMRT for 25 patients with oropharyngeal or hypopharyngeal carcinoma. Their results showed that there was no significant difference in the dose homogeneity for each PTV. Similar dose homogeneity between RA plans and IMRT plans has also been reported for prostate cancer and NPC [13, 23].

In this study, though the difference was not significant, IMRT plans achieved better homogeneity for PTV56, PTV62 and PTV70 while RA plans achieved better homogeneity for PTV54 and PTV74. The phenomenon of different PTVs having different degrees of dose homogeneity, when comparing RA plans and IMRT plans, has previously been observed [24]. Their study compared VMAT plans with IMRT plans for ten patients with oropharynx or nasopharynx carcinoma. They found that the dose inhomogeneity was higher for high-dose PTV (PTV70) in IMRT plans. However, the dose homogeneity was better in IMRT plans for intermediate-dose (PTV63) and low-dose PTVs (PTV56). A similar phenomenon was also reported in the study by Cheung et al. [23]. This phenomenon is due to problems with suboptimal dose distribution within the superficial volume of the PTVs in RA plans. It is believed that the RA optimization algorithm is likely to increase the dose in the build-up regions by creating intensity peaks, which could lead to undesirable hot spots elsewhere [23]. Therefore, as the price to pay for better target conformity, the homogeneity for some PTVs is inevitably reduced.

The results were in contrast to those observed in other studies involving HNC cases, where RA plans using two arcs achieved better dose homogeneity when compared with IMRT plans [9, 10]. The dose prescribed to PTVs in the current study differed from previous studies for HNC cases. The prescription scheme for the current study consisted of SIB targets, with three dose levels in the nasopharynx as well as two separate dose levels for the nodal regions. On the contrary, previous studies for HNC cases only consisted of two dose levels. Since a greater number of dose levels increases the complexity of planning and dose delivery [23], the outcomes of the plans might indeed be different.

Conformity

The conformity of the dose to the PTVs was expressed by CI\text{95\%}. The CI\text{95\%} should be > 1, and an increase in CI\text{95\%} signifies a decrease in dose conformity. Though the dose

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**Fig. 3.** Comparison of DVHs of posterior brain tissues, post neck 1 and post neck 2 between RA plan and IMRT plan of a stage IV patient.
conformity (Cl95%) of all targets in RA plans was better than in IMRT plans, with smaller mean and standard deviations, the differences were not significant. When compared with IMRT plans, RA plans achieved a reduction from 3.33% to 14.96% in the mean value of Cl95% for all targets. This may relate to the lower dose homogeneity in RA plans. The results were in line with those reported for prostate, rectal and cervix uteri cancers [13–14, 25], which showed that RA plans resulted in at least comparable, and possibly superior, conformity compared with IMRT plans. Regarding HNC, Vanetti et al.’s study reported that RA plans and IMRT plans were equivalent in terms of Cl95% [10], while Bertelsen et al. indicated that Cl95% was improved by VMAT [22].

A possible reason for lower conformity in IMRT plans was that hot spots were found. Lee and Le [3] investigated new developments in radiation therapy for HNC, such as IMRT. They mentioned that, on top of the hot spots found, a greater target dose inhomogeneity was noted for IMRT because of the varying degrees of intensity in the pencil beams. In addition, throughout RA optimization, the gantry and MLC position sampling was progressively increased. The utilization of the full gantry range theoretically provided increased flexibility in generating highly conformal treatment plans [19]. Moreover, RA plans reduced hot spots inside the target volume [14]. These factors might explain why RA plans did slightly better in terms of conformity.

**Doses to OARs**

**Group I: critical structures**

As per Johnston et al. [24], there was no significant difference in the mean Dmax received by the brainstem and spinal cord between RA plans and IMRT plans. However, both brainstem and spinal cord received lower mean Dmax in IMRT plans. This concurs with results reported by Tang et al. [26].

The results contrasted with expectations. This might be due to the fact that IMRT plans used a limited number of beams, which allowed a biased beam arrangement such that minimal dose was delivered to the centrally-located structures like the brainstem and spinal cord [26]. On the contrary, RA provided a full rotational arc configuration, and centrally-located structures might be exposed to radiation throughout the arc. The limited number of beams in IMRT plans may be useful in some cases, but the optimal beam angles can be missed, which may prevent the plan from producing the optimal dose distributions [26]. In the current study, the improved dose to brainstem and spinal cord might be at the expense of slightly lower dose conformity to the PTVs in IMRT plans.

**Group II: bony structures**

The bony structures included in the investigation were the TMJs, clavicles and mandible. Since the mandible was contoured in one patient, only one result was available. As shown in Table 5, the Dmax received by the bony structures was lower in RA plans. However, the results for Lt TMJ and clavicles were of statistical significance.

Vanetti et al. [10] found that RA allowed some reduction of Dmax and Dmean to the mandible, but bony structures were rarely investigated in RA studies. Therefore, it is difficult to compare the results and to draw any conclusions. One explanation for the results is that hot spots in IMRT plans over the bony regions were higher than in RA plans. Besides, lower dose conformity in IMRT plans also contributed some doses to the bony structures near the targets.

The results have important clinical implications because hot spots could result in unwarranted complications like osteoradionecrosis. Radiation-induced trismus was a common late complication experienced by NPC patients. Fang et al. conducted a study to assess the health-related quality of life for 182 NPC patients [27]. Of the NPC survivors, 30% had severe trismus, which was related to total radiation dose, fractionation and treatment technique [28–29]. Different studies have shown that up to 50% of patients with radiotherapy to the TMJs and the masseter muscles had limitations in mouth opening [30]. The loss of function and range of mandibular motion appeared to be related to damage to and fibrosis in the muscles of mastication, as well as necrosis of bone and soft tissues [31].

Limited mouth opening was associated with problems with eating and drinking and might result in major effects on nutrition, weight loss and oral hygiene [32–33]. There was a proven relationship between trismus in HNC patients and quality of life deficits [34], which could result in social exclusion and depression [35]. Therefore, new treatment techniques are essential to lower the doses to TMJs and mandible.

**Group III: soft tissues**

The soft tissues that received significantly lower Dmax in RA plans were the posterior brain, lower posterior neck (post neck 1) and upper posterior neck (post neck 2). In most cases, the Dmax and Dmean received by these structures were higher in IMRT plans, demonstrated in their DVHs, as shown in Fig. 3.

Reduction in dose to posterior brain and posterior neck is essential to minimize late toxicities, such as brain and neck fibrosis. Post-irradiation fibrosis of the neck is one of the most common late effects of radiation therapy for patients with malignancies of the head and neck. In one previous study, among the 182 NPC survivors, 22% had severe neck stiffness [27]. Another study assessing the quality of life of 192 NPC survivors indicated that 38% of the participants experienced a little neck stiffness [36]. Symptoms related to neck fibrosis include the presence of discomfort in the neck and the experience of restriction in turning the head during activities of daily living [37].
Nowadays, adjuvant chemotherapy is indicated for NPC patients to prolong survival and to reduce the incidence of distant metastases [38]. In this study, patients with Stages II–IV disease received concurrent chemotherapy. However, it was found that moderate to severe soft tissue fibrosis, with neck stiffness and limitation in neck movement, were more commonly observed among patients with adjuvant chemotherapy than those without adjuvant chemotherapy [39]. Increase in incidence of radiation-induced soft tissue fibrosis was likely to be related to bleomycin.

Unexpectedly, the laryngo-pharynx received a significantly lower Dmean in IMRT plans. PTV62 usually extends to both sides of the neck, with the laryngo-pharynx located centrally. It was found that the dose homogeneity of PTV62 was higher in IMRT plans. This suggested that the dose fall-off in PTV62 was sharper for IMRT plans than for RapidArc. As the laryngo-pharynx was located between PTV62, sharper dose fall-off in PTV ensured a lower dose to the laryngo-pharynx.

Lowering the dose to the larynx and pharyngeal constrictor muscles could reduce difficulties with swallowing [40–43]. It is known that sparing of the constrictors, with mean doses below 60 Gy, is highly correlated with improved swallowing, laryngeal elevation and epiglottic inversion [10]. However, care must be taken not to compromise target coverage. Since PTV62 is usually in close proximity to the laryngo-pharynx, over-protection of the laryngo-pharynx may lead to clinically unacceptable inhomogeneity and inadequate target coverage.

**Group IV: others**
The cochlea and VIIIIn were comprised of small volumes, and their involvement in PTV was case-dependent. One possible reason for achieving lower mean doses in the Lt Cochlea and Lt VIIIIn was that smaller volumes were more sensitive to changes during optimization, especially in IMRT planning.

The involvement of the parotid glands was also case-dependent. The volume of unaffected parotid glands and their proximity to PTVs largely influenced the ability to spare them [2]. However, it is noteworthy that the RA technique preserved a significantly larger volume of the combined parotid glands at a dose < 20 Gy. This suggests that RA has the potential to spare organs at very low dose levels.

In radiotherapy for HNC, the major salivary glands frequently receive a high radiation dose. This results in a reduction of salivary output and in turn causes xerostomia, which has been cited by patients as a major cause of decreased quality of life in the areas of nutrition, dentition, communication and emotional well-being [3, 44–45].

Data on dose response in the parotid glands has revealed that the mean dose to the glands was related to their residual salivary output [4]. It has been shown that one year after radiotherapy, parotid glands receiving a moderate dose (i.e., a mean dose of 17–26 Gy) recovered, on average, to the pretreatment salivary production levels [46]. Regardless of the dose threshold, it is now apparent that spared glands not only partly retain salivary output, but the output increases over time through at least two years after radiotherapy [46]. Therefore, it is essential to spare as much volume of the parotid glands as possible.

**TCP and NTCP**
In view of the fact that distributions of absorbed dose in the form of DVHs did not provide any information about the biological response of the tumour and OARs, it was recommended that TCP and NTCP were calculated for plan intercomparisons [21]. In this study, BIOPLAN was used to compute TCP and NTCP, based on the Poisson model and Lyman-Kutcher-Burman (LKB) model, respectively.

BIOPLAN has been conceived as PC-based, user-friendly software. It allows users to exploit the potential that DVH information may provide. BIOPLAN allows plan intercomparisons, particularly useful in situations like crossing over of two DVHs. It is also a very useful research tool to evaluate new treatment techniques according to predictions of the outcome, especially probability of radiation-induced effects [21].

In this study, it was found that RA plans resulted in better TCP than IMRT plans, although not all were statistically significant. The calculation of TCP took into account the radiosensitivity, tumor dose distribution, initial clonogenic cell density, average doubling time of tumor cells, the overall treatment time and the time at which proliferation begins after the start of the treatment [21]. Since RA plans achieved a slightly better target dose conformity, TCP was higher in RA plans.

The results of NTCP for OARs are consistent with doses to OARs. As IMRT technique delivered lower Dmean and Dmax to the brainstem and spinal cord, the NTCP was lower in IMRT plans. On the contrary, since the RA technique spared posterior brain, upper and lower posterior neck, trachea-oesophagus and Lt TMJ, their NTCP results were lower in RA plans.

**Number of MUs**
RA plans allowed for a mean reduction in the number of MUs by 78%, relative to 7-fields sliding window IMRT plans. Two main reasons account for the significant reduction of MUs. Firstly, the sliding window method is used to generate the intensity map. MLCs will travel from left to right and vary the speed and relative opening between two pairs of leaves. Most of the time, the field size is small in order to have sufficiently high modulation power to deliver a high dose gradient. Hence, more MUs should be delivered with small field sizes. Secondly, when MLCs travel from left to right and past the target, the target is shielded by the MLCs and target dose is contributed to by the
transmission dose of MLCs. Therefore, the delivery of a specified dose to the isocenter from a modulated field using IMRT technique would require more MUs [47]. In the RapidArc technique, MLCs do not travel from one side to the other. Most of the time MLCs maintain a wide open field size when the gantry rotates. Therefore, comparatively fewer MUs are delivered to achieve the same target coverage.

Furthermore, part of the IMRT field was open at any given time and hence radiation leakage through MLCs was greater than that of the leakage from the head of the linear accelerator. Since the leakage from the head was limited to 0.1% of the dose rate at the isocenter, while that from an MLC was in the order of 1–3% [47], greater interleaf scatter dose and leakage radiation from MLCs aroused concern.

The increased number of MUs and leakage radiation in IMRT plans leads to an increase in the number of radiation-induced secondary malignancies [1, 9, 13, 47]. One study has reported a linear relationship between cancer and dose [47], suggesting that secondary cancer is mostly induced by low dose radiation.

One of the advantages of RA techniques found in this study was the possibility of significantly reducing the treatment delivery time per fraction. An RA plan with double arcs normally required ≤ 3 minutes delivery time, while a 7-fields IMRT plan took approximately 12 minutes. Given the larger number of MUs and multiple field arrangement, the delivery time for IMRT was significantly higher since it included dead time such as that needed to reposition the gantry and to reprogram the linear accelerator after every field [23, 48].

Due to longer beam delivery times, intra-fraction patient motion is more likely to occur. In order to realize the benefits of the IMRT technique, it is essential to have great precision in patient setup and immobilization [49], as it is important for organ sparing [2]. However, longer treatment delivery times increase the chance of patient displacement during IMRT treatment [9, 22, 49].

In addition to the reduction of the risk of intra-fraction movement, a shorter delivery time could have a clinical impact on patients in terms of comfort on the couch and an increase of patient throughput. It could also allow more time for implementation of on-line imaging technologies [6, 10, 13]. Daily use of accurate and precise image-guidance techniques results in the best possible patient positioning over the course of treatment [50]. However, each technique is associated with cost in terms of machine time, patient imaging dose, or both. Targets in the head-and-neck region are assumed to be rigidly attached to bony anatomy. It is believed that the main source of uncertainty in positioning these patients is the set-up error [50]. Zeidan et al. [50] demonstrated the necessity of daily imaging, because imaging on every other treatment day resulted in 11% of all treatments being subjected to set-up errors of ≥ 5 mm in 3D for HNC patients.

In the head-and-neck region, although organ movement is minimal, progressive deformation of the patient’s soft tissue structures during the course of treatment has been reported [51]. Critical organs may receive a 10% increase in the prescribed dose owing to anatomic variations caused by set-up accuracy, organ deformation, tumor shrinkage or weight loss [52]. One example of an image-guidance technique is cone-beam computed tomography (CBCT). Den et al. [53] have shown that image-guidance radiotherapy using CBCT for HNC was effective, reducing the CTV to PTV margins by 50%. Margin reduction facilitated dose escalation and improved normal tissue toxicity.

**CONCLUSION**

This study demonstrated that, in the treatment planning of NPC, RA plans gave at least similar, and possibly superior, target coverage and dose conformity when compared with IMRT plans, with the exception of reduced dose homogeneity in PTVs. RA also demonstrated a significant improvement in dose reduction to bony structures (e.g. TMJs, clavicles and mandible) and soft tissues (e.g. posterior brain, back of the neck and parotid glands). The RA technique allows for large reductions in the number of MUs and treatment delivery times. Since the RA technique is equally effective in producing clinically acceptable plans, but has the advantage of sparing OARs and normal tissues, the RA technique may be more beneficial for NPC treatments than IMRT.

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**CONFLICT OF INTEREST**

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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