ORGINAL ARTICLE

Volumetric modulated arc therapy versus step-and-shoot intensity modulated radiation therapy in the treatment of large nerve perineural spread to the skull base: a comparative dosimetric planning study

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Abstract

Introduction: Cutaneous squamous cell carcinoma with large nerve perineural (LNPN) infiltration of the base of skull is a radiotherapeutic challenge given the complex target volumes to nearby organs at risk (OAR). A comparative planning study was undertaken to evaluate dosimetric differences between volumetric modulated arc therapy (VMAT) versus intensity modulated radiation therapy (IMRT) in the treatment of LNPN. **Methods:** Five consecutive patients previously treated with IMRT for LNPN were selected. VMAT plans were generated for each case using the same planning target volumes (PTV), dose prescriptions and OAR constraints as IMRT. Comparative parameters used to assess target volume coverage, conformity and homogeneity included V95 of the PTV (volume encompassed by the 95% isodose), conformity index (CI) and homogeneity index (HI). In addition, OAR maximum point doses, V20, V30, non-target tissue (NTT) point max doses, NTT volume above reference dose, monitor units (MU) were compared. **Results:** IMRT and VMAT plans generated were comparable for CI ($P = 0.12$) and HI ($P = 0.89$). VMAT plans achieved better V95 ($P = < 0.001$) and reduced V20 and V30 by 652 cubic centimetres (cc) (28.5%) and 425.7 cc (29.1%), respectively. VMAT increased MU delivered by 18% without a corresponding increase in NTT dose. **Conclusion:** Compared with IMRT plans for LNPN, VMAT achieved comparable HI and CI.

Introduction

Australia has the highest incidence of non-melanoma skin cancer in the world.[1] In up to 6% of head and neck cases, malignant cells infiltrate the space surrounding neuronal axons.[2] While smaller nerve involvement is usually asymptomatic, retrograde perineural infiltration involving larger cranial nerves may result in sensorimotor deficits in the distribution of affected nerve(s). Large nerve perineural (LNPN) infiltration involving the base of skull most commonly involves the trigeminal and facial cranial nerves and is associated with a poor prognosis and decreased survival.[3,4]

The classification of LNPN involving the base of skull is outlined in Table 1.[5] Disease confined to Zone 1 is usually managed with surgery alone. In cases involving Zone 2, surgical resection to the skull base is recommended and post-operative radiotherapy (RT) is required to optimise local control. Zone 3 disease is rarely operable and definitive or high-dose palliative RT should be considered.

The design of clinically safe and deliverable RT plans for LNPN is technically challenging because complex

Table 1. Large cranial nerve zonal classification.

Zone 1	Zone 2	Zone 3
V1 (ophthalmic nerve) to the superior orbital fissure	V1, V2, V3: from Zone 1 to the Gasserian ganglion cistern	All nerves: proximal to the ganglion, into the cisterns, or into the brain stem
V2 (infraorbital nerve) to the external aperture of the foramen rotundum	VII from Zone 1 up to the lateral end of the internal auditory canal, in the geniculate ganglion and the labyrinthine segment	
V3 (mandibular nerve) to the external aperture of the foramen ovale		
VII (facial nerve) to the external aperture of the stylomastoid foramen		

target volumes lie in close proximity to multiple organs at risk (OAR) including the brain stem, optic chiasm, optic nerves, globes and retinae, all with strict dose constraints. Until recently, all patients with LNPN treated at our centre with definitive or high-dose palliative RT received step-and-shoot intensity modulated radiation therapy (IMRT). Following the implementation of volumetric modulated arc therapy (VMAT), it was hypothesised there would be no clinically relevant dosimetric detriment to using this potentially faster delivery method. Therefore, the purpose of this planning study was to compare the dosimetric performance of VMAT with IMRT in the treatment of LNPN utilising the technologies available at our centre during the transition from IMRT to VMAT.

Methods

Patient selection and ethics

Institutional research ethics board approval was obtained to retrospectively identify consecutive patients who had previously undergone treatment for LNPN with IMRT in our department. No patient contact was made and all five patients that were identified had completed their treatment at the time of comparison. Patient demographics, diagnoses and cranial nerves involved are outlined in Table 2.

Simulation and planning objectives

All patients were simulated in a supine position with thermoplastic shell immobilisation (CIVCO, Kalona, IA). Computed tomography (CT) scans using 2 mm slices were acquired from the skull vertex to hyoid. All target volumes were delineated by one radiation oncologist (M.F.) according to the International Commission on Radiation Units (ICRU) reporting specifications.[6] OAR were contoured uniformly according to consensus guidelines.[7] Dose prescriptions with descriptors, planning target volumes (PTV) and dose fractionations are outlined in Table 2.

In all cases, sites of microscopic residual disease received 63–66 Gy in 30–33 fractions. All sites of resected disease received 60 Gy in 30–33 fractions and areas

Table 2. Patient demographic data, diagnoses, nerve(s) affected, dose prescriptions and organ at risk (OAR).

Patient	Diagnosis	Age	Surgery	Zone	Planning target volume (PTV) dose prescriptions in Gray (fractions)	PTV Volume (cm³)
1	Recurrent cutaneous squamous cell carcinoma right orbit	56	Yes	2	PTV 54 (30)	321.6
					PTV 56 (30)	191.7
					PTV 60 (30)	80.5
					PTV 63 (30)	29
2	Recurrent cutaneous squamous cell carcinoma right cheek	46	Yes	2	PTV 60 (30)	386.6
					PTV 63 (30)	8.7
3	Recurrent cutaneous squamous cell carcinoma right inferior pinna to infratemporal fossa	74	Yes	2	PTV 60 (30)	244.1
4	Cutaneous squamous cell carcinoma left cheek, nasolabial fold	69	No	3	PTV 60 (33)	403.2
					PTV 66 (33)	96.4
5	Recurrent cutaneous squamous cell carcinoma right ear, pre-auricular region	63	Yes	2	PTV 56 (30)	702.7
					PTV 60 (30)	211.6
					PTV 63 (30)	52.3

Table 3. Homogeneity index (HI), conformity index (CI), V95 (95% coverage of planning target volume with the 95% isodose).

	IMRT	VMAT	
Metric	Mean (SD); median (range)	Mean (SD); median (range)	*P*-value
HI	0.14 (0.04); 0.14 (0.09–0.20)	0.15 (0.04); 0.15 (0.10–0.20)	0.89
CI	0.49 (0.22); 0.50 (0.03–0.76)	0.53 (0.28); 0.54 (0.03–0.80)	0.12
V95 (per cent)	95.16 (4.45); 97.02 (85.2–99.2)	96.22 (2.31); 95.93 (92.09–99.98)	<0.001

P-values calculated using Bland Altman, Pitmans test of difference in variance.

considered at high risk received 54–56 Gy in 30–33 fractions. Daily dose per fraction ranged from 1.8 to 2.2 Gy and was delivered using 6 megavoltage photons.

IMRT planning

All IMRT plans were generated using the Eclipse Treatment Planning System (TPS) (v8.6; Varian Medical Systems, Palo Alto, CA, USA). Beam and collimator angles were chosen at the discretion of the radiation therapist and utilised five to seven coplanar static step-and-shoot fields.

Optimisation parameters were set according to departmental protocol and used physical/dose–volume-based objectives. OAR and non-target tissue (NTT) dose constraint objectives were used to reduce OAR maximum doses and hot spots outside the PTV respectively. Inhomogeneity corrections were applied and dose–volume histogram (DVH) data were generated. Final calculations were made using Eclipse AAA algorithm version 8.6 on an Elekta Synergy beam model using 1 centimetre (cm) multileaf collimators (MLC).

VMAT planning

Using the same CT data set, five VMAT plans were generated by two radiation therapists (RT) (R.F. and T.B.) with no changes to PTV or prescription parameters. Data sets were exported to the Monaco TPS v3.0 (Elekta, Stockholm, Sweden) for VMAT planning. Arc arrangements, maximum number of segments and the minimum dose rate are all modifiable variables in Monaco Treatment Planning System (TPS). The Elekta Axesse beam data model consisting of 4 mm MLC was used. To reduce planner bias, the two RT were blinded to existing IMRT dosimetry.

In Monaco TPS, biological cost functions were assigned to all target volumes while physical constraints were applied to OAR in an attempt to maximise V95 while meeting OAR dose constraints. Single full ($-180°$ to $180°$) or a combination of single and multiple partial ($-180°$ to $0°$) gantry arcs were used. Collimator angles were 45°, 315° or a combination of both to minimise any tongue and groove effect. The number of segments per arc ranged from 100 to 150 with a minimum dose rate set at 120 MU/min.

Comparative metrics

Quality of target volume coverage was assessed using homogeneity index (HI) and conformity index (CI).

HI was defined as per ICRU83:[6]

$$HI = (D2 - D98)/D50$$

incorporating the near-maximum dose (D2), near-minimum dose (D98) and median dose (D50) to the target volume.

CI was defined as per ICRU83:[6]

$$CI = (TV95)^2/TV \times V95$$

incorporating the total volume of PTV covered by the 95% isodose (TV95), total volume of the PTV (TV) and total volume covered by the 95% isodose (V95).

Surrogate parameters were used to estimate integral dose: NTT, volume receiving 20 Gy (V20) and volume receiving 30 Gy (V30). MU calculations were made to estimate treatment delivery time.

Statistical analysis

Statistical analysis was performed using Stata 12 software (Statacorp LP; College Station, TX). The Bland Altman test method was used to measure agreement with CI, HI and V95. The Wilcoxon signed-rank test for matched pairs was used to calculate the two-sided *P*-value for NTT cc, NTT max, V20, V30 and MU. A value of $P < 0.01$ (where the Bonferroni adjustment was made for a low sample size) was defined as having statistical significance.

Results

PTV dose and coverage

All VMAT plans were clinically acceptable, resulting in similar PTV coverage compared with IMRT. The V95 was

Table 4. Organ at risk mean max doses and relative reductions expressed as percentages for all cases.

	IMRT (Gy)	VMAT (Gy)	Relative reduction (%)
Thecal sac (entire spinal canal)	33.2	28.2	15.2
Thecal sac planning organ at risk volume (3 mm anisotropic expansion on thecal sac)	37.9	30.9	18.3
Ipsilateral optic nerve	51.9	52.1	−1.0
Contralateral optic nerve	39.4	35.6	10.0
Optic chiasm	47.1	50.1	−6.4
Right lens	9.4	9.3	0.4
Left lens	6.9	7.3	−7.0
Brainstem	59.4	58.1	2.2

statistically different between VMAT and IMRT ($P < 0.001$). VMAT V95 was on average $96.22 \pm 2.31\%$ and V95 IMRT was on average $95.16 \pm 4.45\%$ (Table 3). HI were similar for both VMAT (0.15 ± 0.04) and IMRT (0.14 ± 0.04). There was a trend towards improved CI with VMAT (0.53) compared with IMRT (0.49).

OAR doses

Both modalities produced clinically acceptable OAR doses. OAR used for the purposes of comparison are listed in Table 4.

VMAT reduced the maximum dose to the thecal sac and thecal sac PRV by 18.3% and 15.2% respectively. VMAT increased the ipsilateral optic nerve maximum dose by 1% and reduced the contralateral optic nerve maximum dose by 10%. Brainstem doses improved marginally with a relative reduction using VMAT of 2.2%. Dose to the optic chiasm was higher with VMAT (50.1 Gy) than IMRT (47.1 Gy).

NTT, integral dose and MU

NTT was reduced using VMAT when compared to IMRT. The VMAT V20 and V30 ranged from 1285 cc to 1704.8 cc and 787.6 cc to 1107.8 cc respectively (Table 5). The IMRT V20 and V30 ranged from 1526.37 cc to

2539.18 cc and 952.27 cc to 1652.09 cc respectively. Compared with IMRT, VMAT reduced the V20 and V30 by 28.5% and 29.1% respectively. Furthermore, VMAT reduced the maximum dose in the NTT by 1.12 Gy and reduced the NTT volume receiving above the reference dose by 4.7 cc. VMAT increased the MU required per plan compared with IMRT. MU required per plan for VMAT ranged from 500 to 755 MU and 472 to 618 MU for IMRT. This was an 18% increase using VMAT.

Discussion

At the Princess Alexandra Hospital, definitive or adjuvant RT is used to improve local control and delay symptomatic progression in patients with LNPN. To the best of our knowledge, this is the first planning study evaluating the performance of IMRT and VMAT in the treatment of LNPN involving the base of skull. Many patients with LNPN can expect long disease-free intervals; hence planning studies are needed to optimise management of these complex cases. This planning study was designed to compare IMRT to VMAT in an attempt to transition patients with LNPN to VMAT without comprising dosimetric outcomes.

In this study, both IMRT and VMAT delivered clinically acceptable plans. In the analysis, VMAT was superior in optimal target volume coverage (V95). However, there was no statistically significant difference in CI or HI. This similarity may be due to the fact that the same endpoints are required for clinically acceptable plans.

Optimising PTV coverage and meeting OAR dose constraints are critical plan objectives. Following ICRU guidelines, irrespective of the inverse planning method used, values incorporated into the HI (D2, D50 and D98) would be expected to show no significant difference between IMRT and VMAT. Conversely, CI relates to how well the 95% isodose conforms to the shape of the PTV. Even with similar CI values, in our analysis VMAT plans were able to lower the maximum dose and volume (cc) of the reference dose outside the PTV. In our small cohort, we found VMAT resulted in better control of dose placement according to optimisation plan objectives.

Table 5. Non-target tissue (NTT), integral dose (ID), V20, V30, monitor units (MU).

	IMRT (median; range)	VMAT (median; range)	*P* value*
NTT max (Gray)	67.7 (66.3–70.9)	66.6 (63.2–69.8)	0.04
NTT cubic centimetres (reference dose)	8.0 (1.7–25.3)	3.3 (0.008–11.3)	0.04
V20 cubic centimetres	2190.1 (1526.4–2539.2)	1537.3 (1285–1704.8)	0.04
V30 cubic centimetres	1397.4 (952.3–1652.1)	971.7 (787.6–1107.8)	0.04
Monitor units	491.6 (322–618)	592.1 (449.6–755.5)	0.14

**P*-values calculated using Wilcoxin signed-rank test. A Bonferroni adjustment was used ($\alpha = 0.01$).
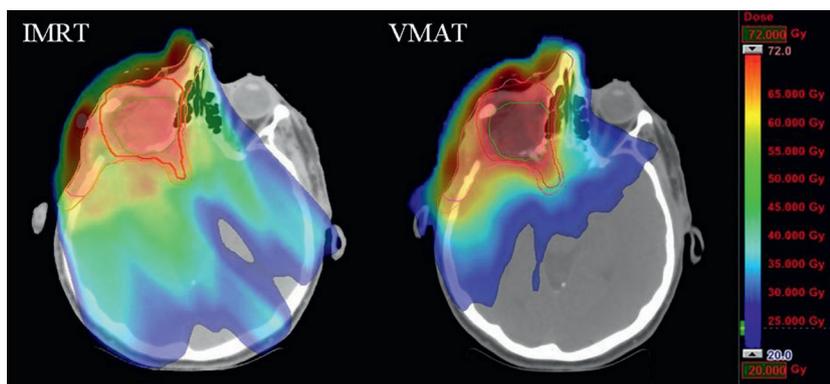
Figure 1. Differences in isodose distribution between intensity modulated radiation therapy (IMRT) in the Eclipse treatment planning system and volumetric modulate arc therapy (VMAT) in the Monaco treatment planning system. Green volume represents high risk tumour volume. The red volume represents clinical target volume. Notice the significant reduction in low dose wash with VMAT.

It is postulated this may be due to VMAT technology or the biological optimisation process used in the TPS.

IMRT plans use physical- or dose–volume based planning objectives that drive the DVH at points specified by the planner. For example, for a lacrimal gland to receive 20 Gy to less than 50% of its volume, the planning algorithm will only use this DVH parameter to achieve this objective, regardless of how high or low the dose bathing. Conversely, biological cost functions used in our VMAT plans "drove" the entire DVH by the use of equivalent uniform dose (EUD), that is, the non-uniform dose distribution that if given uniformly, would result in the same cell death rate.[8] This works twofold. Not all voxels in the PTV can always receive the specified 95% of the reference dose. This is due to a variety of reasons like being too close to skin, nearby OAR, or air cavities. To account for this the TPS calculates what dose every voxel in the PTV requires which would result in the same cell death rate as if every voxel received the prescribed dose. In turn, the TPS does not penalise for hot spots within the target volume. However, due to specified maximum dose limitations, a maximum dose constraint still has to be applied to target volumes. For OAR, the cell death rate encountered at a specific point on the DVH is assumed to occur at other dose–volume intervals. The biologic cost function therefore "drives" the entire DVH curve to ensure OAR do not receive the specific dose–volume restraint, or other dose–volume values, that will result in similar OAR toxicities. Theoretically, biological optimisation for any intensity modulated planning technique should improve target coverage and reduce doses to OAR, particularly for parallel structures.[9] In an effort to improve target coverage, arc arrangements were a major factor in plan design. In theory, a single arc would be expected to deliver the ideal dose distribution, assuming no

constraint is put on the number of segments, leaf travel, dose rate or gantry speed. However, published reports suggest that for complex target volumes with more than one dose level, IMRT is superior to single arc VMAT.[10] In our cohort, all cases had complex target volumes across one to four dose levels. In our experience, cases with more than one dose level, single arc VMAT was insufficient to achieve plan objectives, necessitating the use of two partial/full arcs.

Gantry angles in fixed field step-and-shoot IMRT can be controlled to avoid beam entry and/or exit through OAR. VMAT requires continuous delivery through an arc, thus would not be expected to significant reduce dose to OAR. Interestingly, our results show statistically significant sparing of multiple OAR with VMAT compared with IMRT (Table 4), supported by other published results of the head and neck region.[11] Furthermore, surrogate markers to estimate integral dose were more likely to show a reduction with VMAT and a significant reduction in low dose wash can be seen in Figure 1.

MU comparisons can be used to estimate aspects of plan quality such as reducing MU, resulting in less dose being delivered. This reduction in unwanted dose should theoretically reduce scatter and further improve treatment efficiency. VMAT plans had an increase in MU when compared with IMRT. However, this is unlikely to have significant clinical implications as low-dose wash dose outside of the target was reduced.

Potential limitations of this study include the use of different TPS and small sample size. An effort was made to account for small sample size by the use of the Bonferroni adjustment. Although both TPS generated clinically acceptable plans, they differed in the optimisation process. IMRT plans were calculated using AAA pencil algorithm, while VMAT plans were generated

with Monte Carlo. Therefore, our data specifically address dosimetric differences between the two TPS used in this comparison. As a result, we caution the reader about extrapolating our conclusions across other platforms given the potential for differences in outcomes.

The only available beam model at the time of IMRT planning was Elekta Synergy comprising 1 cm leaves. At the time of VMAT planning, an Elekta Axesse beam model with 4 mm leaves was available. We are uncertain of the implications arising from changes in leaf width in our cohort. Some studies report changes in leaf width had no effect on VMAT dosimetry, while others suggest an advantage with 4 mm over 1 cm leaves.[12,13]

Conclusion

In the treatment of LNPN, both IMRT and VMAT achieve comparable target volume coverage, conformity and homogeneity. It remains unknown to what extent biologic cost functions impact on dosimetry in the treatment of LNPN. VMAT plans achieved better V95 ($P \leq 0.001$) and reduced V20 and V30 by 652 cc (28.5%) and 425.7 cc (29.1%) respectively. VMAT increased MU delivered by 18% without a corresponding increase in NTT dose. This study has demonstrated that for patients diagnosed with LNPN, a transition from IMRT to VMAT utilising the technologies applied herein results in comparable dosimetric outcomes.

Conflict of Interest

None declared.

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