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Three-Dimensional Conformal and Intensity Modulated Dynamic Radiotherapy in Juvenile Nasopharyngeal Angiofibroma

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Abstract

Objective: Juvenile Nasopharyngeal Angiofibroma (JNA) is a benign neoplasm with a high vascularity component, greater craniofacial involvement in adolescent patients, and aggressive local behaviour. In unresectable patients, radiotherapy is a therapeutic option for local control. Our aim in this study was to analyze the clinical benefit and local control provided by two modalities of radiotherapy: the Three-Dimensional Conformal (3DC) technique and volumetric modulated arc therapy (VMAT), applied to pediatric patients with JNA considered unresectable and non-recurrent. **Methods:** In retrospective study, the information was recorded from pediatric patients with a diagnosis of non-recurrent and unresectable JNA treated with radiotherapy at the Oncology Hospital of the National Medical Center SXXI of Mexico City, from March 2010 to March 2021. Radiotherapy management and its association with clinical outcomes of tumour control, and symptoms were assessed. In addition, an evaluation of acute and chronic toxicity was performed. **Results:** It was found that the median age was 14 years. 9 patients (37.5%) underwent 3DC and 15 (62.5%) VMAT. In terms of local control, and progression-free survival, we did not find significant difference between radiotherapy modalities ($p \leq 0.57$). Acute toxicity for both modalities presented statistical differences for radio epithelitis ($p = 0.03$). Only Grade I and II radiation-induced acute toxicity was observed. Regarding chronic toxicity, statistical significance was observed for craniofacial hypoplasia, in relation to its absence in the

VMAT group (p = 0.001). **Conclusion:** The VMAT presents improvements in dosimetry parameters that improve patient toxicity. In both techniques adequate tumour control was observed, however, the rarity of the disease is a limitation to establish the most appropriate therapeutic technique.

Keywords

Intensity-Modulated Radiotherapy, Nasopharyngeal Angiofibroma, Pediatric, Radiotherapy, Toxicity

1. Introduction

The Juvenile Nasopharyngeal Angiofibroma (JNA) is a benign tumour whose main origin is in the posterior part of the nasal cavity. It is a vascular lesion frequently derived from the internal maxillary and ascending pharyngeal artery; the growth of these lesions tends to erode bony structures at the base of the skull, with the capacity to extend towards the nose, paranasal sinuses, orbit and intracranial region [1]. It has an incidence of 0.05% - 0.5% and it is most frequently found in males between 10 and 25 years of age [2].

The therapeutic options for the most advanced lesions include craniofacial surgery with a high probability of residual rate and therefore progression or recurrence so that management with radiotherapy is an option in unresectable cases [3] [4]. A higher probability of recurrence (up to 40%) has been reported due to incomplete resection in voluminous tumours extending through bone structures. For the above-mentioned reasons, pre-operative embolization is convenient before surgery in bulky tumours, in addition to reducing the bleeding during surgery [2] [5].

We found 634 articles from 1948 to 2023 in the PubMed database with "Nasopharyngeal Angiofibroma" in its title. However, most publications emphasize the results of the surgical management, in fact, only 10.56% of the mentioned studies include the word "Radiotherapy" in their title/abstract and there are still only a few reports of new technologies such as intensity-modulated radiotherapy having a scarce record of its benefits in this orphan entity.

Advanced radiotherapy techniques have been validated worldwide, being intensity-modulated radiotherapy one of them, but due to the low prevalence of this pathology, it has been difficult to assess its global benefit in these patients, therefore, the main objective of this study was to assess and compare the clinical benefits of two radiotherapy modalities on patients diagnosed with unresectable and non-recurrent JNA, including volumetric modulated arc therapy (VMAT), and three-Dimensional Conformal (3DC) techniques, emphasizing on dosimetry, toxicity, local control and morbidity.

2. Material and Methods

The retrospective study was approved by the National Committee of Scientific Research with No. R-2018-3602-023. All the information reported followed the

national and international standards for the management of clinical files, as well as the official Mexican Norm NOM-012-SSA3-201218, which establishes the criteria for the execution of scientific projects for the health of human beings and with the Helsinki Declaration of 1975.

The inclusion criteria were patients under 18 years of age, with a diagnosis of unresectable and non-recurrent JNA confirmed with a histological report and having an imaging record before and after surgical management, as well as radiotherapy treatment with VMAT or 3DC techniques in the Oncology Hospital of the National Medical Center s. XXI.

Thirty-one patients were initially identified for this study, from those, seven individuals were removed for missing imaging records. The patients were evaluated after their referral from the Otorhinolaryngology and Pediatric Neurosurgery services, including clinical records and paraclinical data, patients were subsequently treated in the Pediatric Radiation Oncology service from March 2010 to March 2021.

To evaluate tumour control, the Magnetic Resonance Imaging (MRI) studies, and the clinical characteristics before radiotherapy treatment (considered as baseline) were analyzed, with the first control (9-week interval) and subsequent follow-ups (every 16 to 20 weeks). The evaluation of acute and chronic morbidity was carried out by obtaining information compiled by the clinical and radiological records based on the classification scales by RTOG, and SOMA-LENT.

The planning data were taken from the information present in the Varian System® in all cases based on the 3DC technique with lateral coplanar fields and inverse planning technique Intensity-modulated radiation therapy (IMRT) Volumetric Arc type.

The prescription dose was 36 - 54 Gy of 1.8 Gy per fraction, normalized to 100%, with 95% coverage (±7) of the Planning Target Volume (PTV). Therapeutic targets were assigned: Gross Treatment Volume (GTV) = residual tumour evidenced by functional resonance imaging (imaging study with evidence of residual tumour). Clinical Target Volume (CTV) = GTV + 1 cm and PTV = CTV + 3 - 5 mm. The inverse optimization planning targets were the organs at risk taking care of the cochlea with an average dose lower than 40 Gy, the hippocampus average dose lower than 20 Gy, as well as the optic pathway and optic chiasm at doses lower than 54 Gy.

The review of the dosimetry parameters in the treatment plans was carried out in the electronic file of the eclipse planning system, Varian®.

Statistical Analysis

The statistical analysis was performed with the GraphPad Prism® version 6.0 statistical package for descriptive statistics, carrying out a descriptive and inferential nonparametric statistical analysis between the different categorical variables with Fisher's exact test and adjusted X^2, as appropriate, and analysis of medians of dosimetry parameters and treatment modalities by the U-Mann

Whitney test, as well as their survival progression assessment with Kaplan Meier curves.

3. Results

The main characteristics of our patients include: 100% of our patients were males, with a median age of 14 years. Regarding the extension and size of the tumour, 15 patients (62.5%) were found with intracranial extension, with tumour diameters up to 88 mm^2. 15 (62.5%) patients were treated with the VMAT technique, and the rest with 3DC 9 patients (37.5%). There were 9 (37.5%) patients that underwent embolization before any surgical intervention. Histopathological confirmation was obtained in all 24 (100%) patients, of whom 16 individuals (66.6%) underwent subtotal resection, 1 person (4.2%) underwent total resection, and 7 (29.2%) were not candidates for surgical resection and only biopsies were obtained to confirm the diagnosis. (Table 1 describes the clinical characteristics of the patients.)

Table 1. Characteristics of pediatric patients and the multidisciplinary management

Radiotherapy modality		3D CRT	VMAT (IMRT)	TOTAL
n =		9 patients (37.5%)	15 patients (62.5%)	24 patients (100%)
Age (range)		9 - 17 years	12 - 17 years	9 - 17 years
Average		13.7	14.3	14.1
Tumour size		22 - 71 mm^2	21 - 88 mm^2	21 - 88 mm^2
Median		45 mm^2	49 mm^2	46.5 mm^2
Chandler*	CS III	4 (44.4%)	5 (33.3%)	9 (37.5%)
	CS IV	5 (55.5%)	10 (66.6%)	15 (62.5%)
Functional state (Initial)	Karnofsky > 90%	8 (88.8%)	14 (93.3%)	22 (91.66%)
	Karnofsky < 90%	1 (11.2%)	1 (6.7%)	2 (8.33%)
Symptoms (Initial)	Nasal Obstruction	9 (100%)	15 (100%)	24 (100%)
	Epistaxis	2 (22.2%)	10 (66.6%)	12 (50%)
Surgical Management	Subtotal Resection	5 (55.5%)	11 (73.3%)	16 (66.6%)
	Complete Resection	1 (11.2%)	0 (0%)	1 (4.2%)
	Non-surgical candidates	3 (33.3%)	4 (26.7%)	7 (29.2%)
Embolization	Given	3 (33.3%)	6 (40%)	9 (37.5%)
	Not Given	6 (66.7%)	9 (60%)	15 (62.5%)
Radiotherapy Dose	Less than 50 Gy	5 (55.5%)	2 (13.3%)	7 (29.16%)
	Equal to or greater than 50 Gy	4 (44.5%)	13 (86.7%)	17 (70.83%)

*Considering the Chandler stage of each group, a P-value = 0.58 was calculated by Fisher's exact test adjusted X^2. Abbreviations: 3D CRT: three-dimensional conformal radiation therapy, VMAT: Volumetric modulated arc therapy, IMRT: Intensity-modulated radiation therapy, CS: Clinical stage, Gy: Gray.

All treatments were performed in the radiotherapy department using the Varian System® in all cases based on the 3DC technique and in inverse planning technique with arc-type intensity-modulated dynamic technique. The prescription dose was a median of 50.4 Gy (36 - 54 Gy of 1.8 Gy per fraction).

The review of the dosimetry parameters in the treatment plans was calculated with the conformality, homogeneity, and integral dose indexes established by the R.T.O.G.; no statistical difference was found through the U-Mann-Whitney comparison between the dosimetry parameters of 3DC and VMAT (Table 2).

The initial clinical manifestations at diagnosis were epistaxis in 2 patients (8.3%) from the 3DC group and 10 (41.6%) from the VMAT group, also nasal obstruction was present in 9 (37.5%) patients from the 3DC group and 15 (62.5%) in the VMAT group. Post-treatment epistaxis was only found in 2 patients (8.3%) of the VMAT group ($p = 0.5$) but with a decrease to grade I. The nasal obstruction improvement demonstrates a statistical difference in both techniques 3DC group and the VMAT group ($p \leq 0.012$), also with a decrease to grade I after radiotherapy (See Table 3, Figure 1).

After treatment, just two patients had recurrence, one for the 3DC group and one for the VMAT group. It is important to mention that both patients were rescued with a second surgery; however, the patient treated with 3DC presented recurrence after the rescue surgery and was considered a candidate for re-irradiation and a third surgery.

Table 2. Dosimetric parameters.

Treatment technique	3D CRT	VMAT	p-value*
Conformity index	1.11	1.1	p = 0.7
Homogeneity index	1.12	1.1	p = 0.79
Integral dose	5290	5225.72	p = 0.47

*Comparison of the dosimetry parameters between different techniques calculated by the U-Mann Whitney test. Abbreviations: 3D CRT: three-dimensional conformal radiation therapy, VMAT: Volumetric modulated arc therapy.

Table 3. Efficacy of radiotherapy treatment in the control of epistaxis and nasal obstruction, evaluated at two months.

Technique	3D CRT (%)	VMAT (%)	P-value*
Epistaxis pre-treatment	2 (8.3%)	10 (41.6%)	p = 0.5
Epistaxis post-treatment	0 (0%)	2 (8.3)	
Nasal obstruction pre-treatment	9 (37.5%)	15 (62.5%)	p ≤ 0.012
Nasal obstruction post-treatment	0 (0%)	3 (12.5%)	

*Statistical differences between both techniques with Mantel-Haenszel adjusted X^2. Abbreviations: 3D CRT: three-dimensional conformal radiation therapy, VMAT: Volumetric modulated arc therapy.

Patients did not achieve median progression survival and both groups did not show statistical difference in progression free survival (Figure 2). The follow-up was 14 months (range 4 - 60 months), and they presented a local control of 8 (88.8%) and 14 (93.3%) for 3D vs VMAT respectively; there was no statistical significance found ($p \leq 0.57$) by Log-Rank Analysis (Mantel-Cox).

The presence of acute toxicity for both modalities was grade I, without the presence of infectious complications. Some differences found between modalities included radioepithelitis in 5 patients (20.83%) from the 3DC group and 6 (25%) from the VMAT group ($p = 0.03$). Regarding the presence of chronic toxicity, facial hypoplasia was present in 2 patients (8.3%) of the 3D group, contrasting to

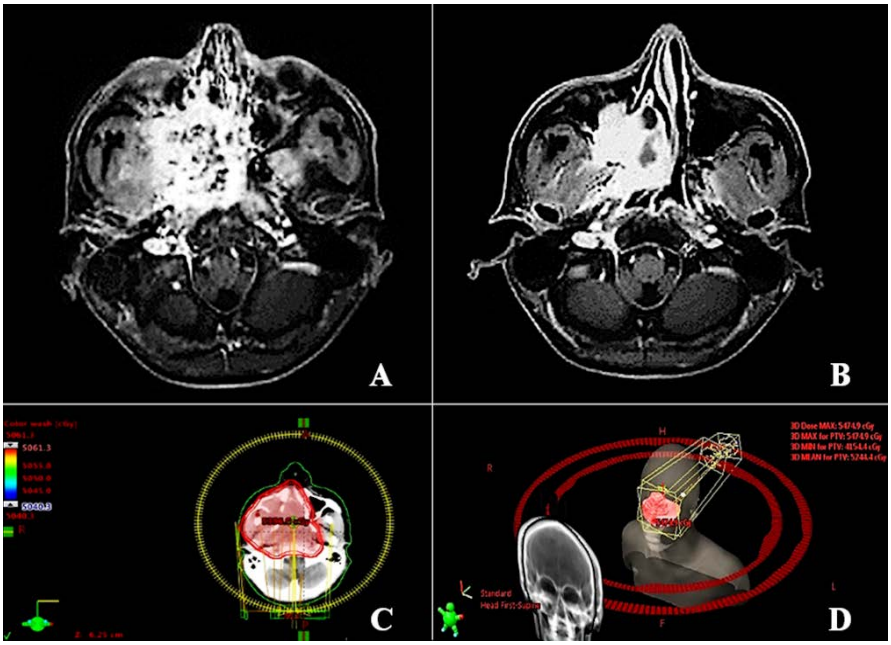

Figure 1. The patient was treated with VMAT. (A) MRI of the head before treatment. (B) MRI of the head follow-up 20 months after the end of radiotherapy. (C) and (D): Treatment with VMAT granted. Abbreviations: MRI: Magnetic Resonance Imaging, VMAT: Volumetric Modulated Arc Therapy.

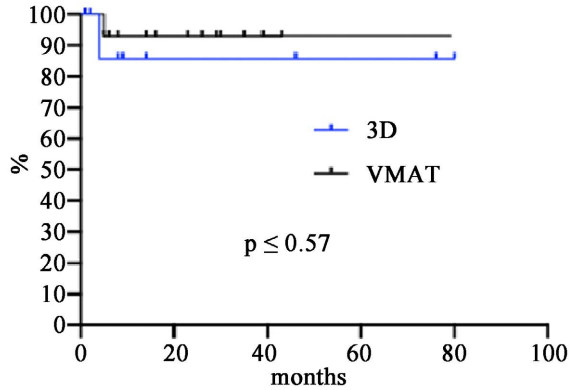

Figure 2. Progression-free survival in 3DC CRT and VMAT techniques. Abbreviations: 3D CRT: three-dimensional conformal radiation therapy, VMAT: Volumetric modulated arc therapy.

Table 4. Overall toxicity.

Toxicity		3D CRT (%)	VMAT (%)	p-value*
Acute	Oral Mucositis	5 (20.8%)	10 (41.6%)	p = 0.14
	Facial radioepithelitis	5 (20.8%)	6 (25%)	p = 0.03
Chronic	Craniofacial hypoplasia	2 (8.3%)	0 (0%)	p = 0.001
	Xerophthalmia	0 (0%)	2 (8.3%)	p = 0.002

*Difference in acute and chronic toxicity with statistical significance calculated by Fisher's exact test. Abbreviations: 3D CRT: Three-dimensional conformal radiation therapy, VMAT: Volumetric modulated arc therapy.

the absence of facial hypoplasia in the VMAT group (p = 0.001), on the other hand, xerophthalmia was not present in the 3DC group (0%), but it was present in 2 patients (8.3%) from the VMAT group (p = 0.002) (Table 4).

4. Discussion

The JNA is histologically benign, however, it presents a locally aggressive behaviour, with high morbidity given its destructive growth pattern and the mortality generated by haemorrhage [6] [7]. In our study, the main symptom was a nasal obstruction in accordance with the literature. Depending on its extension and severity, facial deformity, proptosis, cranial neuropathy, and intracranial haemorrhages may also occur [8] [9]. The median age of the patients in our study was 14 years, with a greater range of presentation from 9 - 17 years, similar to those reported by Tork *et al.* [10], with the difference that we only included pediatric patients.

Treatment of locally advanced JNA has long been a challenge in advanced tumours and the presence of skull base involvement or intracranial extension makes most patients not amenable to complete surgical resection [11] [12]. For an advanced disease with intracranial extension, even after surgical resection, recurrence is high due to incomplete resection [13]. Fagan *et al.* reported 37.5% recurrence after surgical excision of JNA with intracranial extension [5]. In our study, 17 (70.8%) patients complete and subtotal resecable on first line therapy.

Preoperative embolization is generally performed 24 to 72 hours before resection to prevent large intraoperative blood loss and to achieve a successful complete tumour resection [14] [15]. Only 37.5% of the total of our patients studied received embolization due to the lack of material and resources in our environment This is a big contrast to the publications of Tork *et al.* and Mallick *et al.*, in which embolization and maximum resection are contemplated in most cases [10] [16].

The use of adjuvant/radical radiation has remained controversial due to its expected long-term morbidity and the occurrence of a second primary neoplasm. In the last two decades, the introduction of sophisticated radiation delivery techniques has allowed investigators to utilize radiation and limit morbidity. In a review, Reddy *et al.* reported the efficacy of radiation in 10 patients with intra-

cranial extension, a total of 30 Gy was administered with a 3D megavoltage field design and with a median follow-up of 2.5 years, the authors reported a local control of 85% [3]. Lee *et al.* in a retrospective review analyzed the treatment outcomes of 27 patients treated with radiotherapy and reported a local control of 85% [4]. In our study, the local control rate was 85% and 95% for 3D vs VMAT, respectively, after a median follow-up of 14 months.

In our study, only grade I and II radiation-induced acute toxicity was observed (oral mucositis and facial radioepithelitis). Long-term disease control has reached a new horizon, with improvement in long-term morbidity. Two large series published by Chakraborty *et al.* and Kuppersmith *et al.* investigated the efficacy of radiation when delivered with conformal techniques [17] [18]. The authors highlighted the excellent preservation of critical normal organs and excellent disease control with doses administered in ranged from 34 to 45 Gy. [19]. Also, most recent reviews suggest that schedules below 36 Gy are associated with an increased risk of tumour recurrence [20]. In this study, the radiation dose ranged from 36 to 54 Gy with adequate tumour control.

In our current work, the dosimetric results are similar for both techniques and we associate it with the fact that our medical centre has an expert and consolidated group of physicists and engineers, regardless that the literature reports higher integral doses in modulated intensity [21].

Chakraborty *et al.* reported no long-term toxicities during its follow-up [17]. On the contrary, our series presents chronic toxicity manifested with a statistical difference in the craniofacial hypoplasia for its absence in the VMAT group and the xerophthalmia with statistical significance by the absence in the 3DC group explained by the reduced number of patients treated with this modality compared to VMAT, in addition to a cerebrospinal fluid fistula for both.

The main limitations of the present study are the retrospective nature, the number of subjects analyzed, the low performance of embolization related to the lack of coverage and the loss of follow-up due to migration to sites of origin.

We found that similar tumour control was obtained for 3D vs VMAT of 85% and 95%, respectively, for which reason radiotherapy with doses of 45 - 50 Gy is suggested, in our study with a dose of 46 Gy, and with acceptable 5-year chronic toxicity.

5. Conclusion

The present work shows the experience of 3DC and VMAT in patients with the diagnosis of JNA, documenting favourable results comparable to those reported in the world literature in terms of local control, and progression-free survival, having that there is no statistically significant difference between 3DC vs VMAT radiotherapy modalities ($p \leq 0.57$), however, the VMAT technique showed to decrease some chronic toxicities such as facial hypoplasia important for the aesthetics of the patient. It should be noted that more studies are needed to establish the most appropriate treatment technique; however, the rarity of this disease

will always be a limiting factor.

Standards of Reporting

The STROBE guidelines were followed.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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