RESEARCH ARTICLE

Four-dimensional CT angiography (4D-CTA) in the evaluation of juvenile nasopharyngeal angiofibromas: comparison with digital subtraction angiography (DSA) and surgical findings

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Objectives: To explore the value of four-dimensional CT angiography (4D-CTA) in the preoperative evaluation of juvenile nasopharyngeal angiofibromas (JNAs) using 320-row volume CT.

Methods: 4D-CTA and DSA data of 18 patients with histopathologically proven JNAs were retrospectively reviewed. The location, extent, feeding vessels and stage of JNAs were assessed by two radiologists independently and blindly. The agreements between both reviewers and between 4D-CTA and surgical findings for assessing the above indicators were analysed, respectively. The radiation dose and the number of feeding arteries between 4D-CTA and digital subtraction angiography (DSA) were also compared.

Results: 4D-CTA showed high diagnostic consistency with surgical pathology for JNAs with consistent rates of 96.2 and 100% in both reviewers, respectively. The effective dose of 4D-CTA was significantly less than that of DSA ($p < 0.001$). Good agreements between 4D-CTA and surgical findings and between the two reviewers were found in the assessment of the location, extent and stage of JNAs. 4D-CTA showed that 15 lesions were supplied strictly by the external carotid artery circulation and 3 by the external and internal carotid artery supply, which was in accordance with DSA. There were no significant differences in the main arterial feeder number obtained by 4D-CTA and DSA between different observers (all $p > 0.05$).

Conclusions: 4D-CTA can provide a reliable preoperative diagnosis and assessment of JNAs, which is useful for determining the surgical strategy and management of this condition.
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Keywords: four-dimensional CT angiography (4D-CTA); juvenile nasopharyngeal angiofibromas; digital subtraction angiography; 320-row volume CT

Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is an uncommon benign and highly vascularized tumour with a propensity to local invasiveness and an adolescent male's predilection, comprising 0.5% of all head and neck tumours.¹ Due to the highly vascular nature

of most JNAs, an open or closed biopsy should not be attempted.² Diagnosis of JNAs predominantly relies on the knowledge of clinical manifestations as well as cross-sectional imaging techniques such as conventional CT and MRI.³ Because of their vascular nature, occurrence site and local destruction, the management for JNAs is of great challenge to surgeons.² Traditionally, these tumours were surgically resected with an open

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procedure in concert with neck dissection and clamping of the external carotid artery (ECA).⁴ Currently, a pre-surgical embolization for JNA through digital subtraction angiography (DSA) was usually performed to reduce intraoperative blood loss, followed by resection via endoscopic or open surgery.^{2,3,5} However, DSA is a relatively expensive, time-consuming and invasive technique, which will carry a high incidence of silent embolic events and a small risk of transient or permanent neurologic deterioration.⁶⁻⁹ Therefore, non-invasive imaging modalities that can supply preoperative meticulous evaluation of JNAs, including the precise location, extent, and feeding artery of the lesion, are crucial for planning the surgical approach and anticipating areas of increased vascularity and bleeding.

MRI angiography (MRA) and three-dimensional CT angiography (3D-CTA) are two common non-invasive modalities, which can noninvasively evaluate the anatomic details and show the feeding artery of the lesion, but they provide limited information about flow dynamics within the lesion. Technological development of CT, especially the introduction of 320-row CT scanner which has a z-axis coverage of 16 cm and can acquire volumetric scans of the brain in subsecond time,¹⁰⁻¹² now permits dynamic imaging techniques of the whole brain to image the flow of contrast in the cerebral vasculature by running consecutive volumetric scans over a predetermined timeframe.¹⁰⁻¹⁴ Such time-resolved dynamic CTA also referred to as four-dimensional CTA (4D-CTA) is an advanced CT technique that combines the noninvasive nature of 3D-CTA with the dynamic acquisition of DSA, enabling the noninvasive evaluation of flow dynamics of the intracranial vasculature by multiple subsequent CT acquisitions or a continuous volume CT acquisition for a period of time.¹⁴⁻¹⁶

Although 4D-CTA using 320-row CT has been widely applied in neurovascular disease,^{13,14} to the best of our knowledge, there has been no systematic reports in the literature aiming to evaluate the diagnostic performance of 4D-CTA for comprehensive assessment of JNA. Thus, the purpose of this present study was to assess the value of 4D-CTA using 320-row volume CT in comparison with DSA results and surgically findings.

Methods and materials

Study patients

The institutional review board of our hospital approved this retrospective study, and the requirement for patient informed consent was waived due to the retrospective nature of this study. We performed a retrospective review of clinical and imaging data on the patients with clinically suspected JNAs who underwent 320-row CTA examinations in our institution for the 7-year period between February 2008 and March 2016. Ultimately, 18 patients with histologically proven JNAs, including 16 cases with primary JNAs (88.9%) and 2 with recurrent JNAs (11.1%) were enrolled into the study. Among

histologically proved JNAs, 17 patients were male and 1 was female, and the patient ages ranged from 8 to 53 years old with a median age of 18.5 years old. Epistaxis (83.3%) was most commonly observed, followed by nasal obstruction (72.2%). All patients underwent DSA for pre-surgical embolization followed by surgical resection.

CT protocol and image processing

The 4D-CTAs were performed with volumetric imaging mode using a 320-row volume CT scanner (Acquilion ONE, Toshiba Medical Systems, Nasu, Japan) by an experienced CT technician. The scanning parameters were as follows: scan range, 16 cm from skull base to the root of neck; gantry rotation time, 350 ms; slice thickness, 0.5 mm; field of view (FOV), 240 mm; tube potential, 120 kV; and tube current, 150 mA. After the delivery of 65 ml of 370 mg ml⁻¹ CT contrast agent - iopamidol (Isovue-370®, Bracco Diagnostics, Milan, Italy) at a flow rate of 5.0 ml s⁻¹, it should be followed by a saline flush of 30 ml at the same injection rate using a dual-head-power injector (Dual Shot GX, Nemoto Kyorindo, Tokyo, Japan). The scan was performed at 7 s post-injection. The dynamic CTA protocol consisted of 7 dynamic volumes; the total acquisition time was 25–35 s, and the acquisition interval was 2 s for pre-contrast and arterial phase scans and 4–6 s for venous-phase scans.

4D-CTA source data was transferred to an image processing workstation (Vitrea 2 software 6.02, Toshiba, Japan). Multiple pre-contrast CTA images were selected and averaged to reconstruct a mask image. The software subtracted the unenhanced mask image from the contrast-enhanced CTA images to ensure that only the vessels remained visible. Multiple subtracted images with high arterial contrast (four arterial phases) were selected; they were averaged to reconstruct a CTA image. Additional multiplanar reformation, curve planner reconstruction, maximum intensity projection and volume rendering were performed with 360° rotation in any plane on the workstation by an experienced radiologist.

DSA technique

After catheterization of the internal and external carotid arteries via right common femoral artery approach by Seldinger's technique, diagnostic biplanar intra-arterial DSA (Infinix-i, Toshiba Medical Systems, Japan) was performed by trained vascular surgeons. The goal of angiography was to identify ECA and internal carotid artery (ICA) tumour feeders and to identify any normal variant external or internal arterial anastomoses.

Image analysis

Two experienced radiologists, blinded to any information of the patients, independently evaluated the images of 4D-CTA and DSA. The radiologists recorded the

Table 1 A nomenclature for classifying Cohen's kappa coefficient (κ)

κ	Agreement
<0.40	Poor
0.40–0.75	Fair to good
>0.75	Excellent

Note: κ , Cohen's kappa coefficient; κ of 1.00, “perfect” agreement.

location, extent, feeding artery, and the stage of JNAs according to Radkowski's system.¹⁷

Radiation dose measurements

Dose reports of the 4D-CT and DSA were reviewed. The total volume CT dose index of 4D-CTA, the dose-length product (DLP) values of both modalities were retrospectively recorded. The effective dose was estimated by the product of the DLP value and the conversion factor of 0.0054 mSv/mGy·cm.^{18,19}

Statistical analysis

We used MedCalc for Windows 12 (Version 12.3.0; MedCalc Software, Mariakerke, Belgium) for statistical analysis. With regard to the measurements of “JNA presence”, “location & extent”, and “stage”, the diagnostic agreements between 4D-CTA and surgical findings (the reference standard) were assessed by using Cohen's kappa coefficient (κ), and then interobserver agreement for 4D-CTA was also evaluated by Cohen's kappa coefficient (κ). In addition, the difference of radiation dose between 4D-CTA and DSA was compared using a two-sample Student *t*-test. And the difference between 4D-CTA and DSA with respect to the number of feeding arteries was compared using the chi-square test. The adopted interpretation of κ was presented in

Table 2 Frequency of the invasion site of JNAs in 4D-CTA and surgical findings

Anatomical site	No. of patients (%)		
	Reviewer 1	Reviewer 2	Surgical findings
Pterygoid cannal	18 (100.00)	18 (100.00)	18 (100.00)
Nasopharynx cavity	17 (94.44)	17 (94.44)	17 (94.44)
Choanae	14 (77.78)	14 (77.78)	14 (77.78)
Pterygopalatine fossa	8 (44.44)	9 (50.00)	9 (50.00)
Paranasal sinus	6 (33.33)	6 (33.33)	6 (33.33)
Oropharynx	3 (16.67)	3 (16.67)	3 (16.67)
Infratemporal fossa	3 (16.67)	3 (16.67)	3 (16.67)
Pterygoid plate	2 (11.11)	2 (11.11)	2 (11.11)
Orbital apex	1 (5.56)	1 (5.56)	1 (5.56)
Cavernous sinus	1 (5.56)	2 (11.11)	2 (11.11)
Skull base	2 (11.11)	2 (11.11)	2 (11.11)

4D-CTA, four-dimensional CT angiography; JNA, juvenile nasopharyngeal angiofibroma; No. of patients, the number of patients.

Table 1. And reported *p* values were declared statistically significant when less than 0.05.

Results

High consistencies of 96.2 and 100% were found in both reviewers in the diagnosis of JNAs by means of 4D-CTA using surgical pathology as the reference standard. Additionally, excellent intermodality ($\kappa = 0.92$ and 1.00) and interobserver agreements ($\kappa = 1.00$ and 0.92) were found when determining the presence of JNA. The mean total DLP, CTDI and effective dose for 4D-CTA was 611.53 ± 14.90 mGy·cm, 11.29 ± 0.85 mGy and

Figure 1 Representative images of juvenile nasopharyngeal angiofibroma in a 15-year-old boy. Axial pre-contrast soft tissue window image of CT scan (a) showed a juvenile nasopharyngeal angiofibroma occupying the left nasal cavity and pterygopalatine fossa. Axial bone window image of CT scan (b) revealed the enlargement of pterygopalatine fossa and the erosion of pterygoid process. Axial contrast enhanced thin-section CT image (c) demonstrated the intensively but heterogeneously enhanced mass. Sagittal contrast enhanced multi-planar reconstruction image (d) provided a better visualization of the relationship between the masses and nasopharynx, exhibiting the mass spreading into the nasopharynx. Volume rendering (e) and curve planner reconstruction (f) from four-dimensional CT angiography indicated the enlarged maxillary artery predominantly supplied the mass.

Table 3 Staging or typing systems for juvenile nasopharyngeal angiofibromas in 4D-CTA and surgical findings

Stage	Definition	No. of patients (%)		
		Reviewer 1	Reviewer 2	Surgical findings
IA	Limited to nose and/or nasopharynx	3 (16.67)	3 (16.67)	3 (16.67)
IB	Extension into one or more sinuses	1 (5.56)	1 (5.56)	1 (5.56)
IIA	Minimal extension into pterygopalatine fossa	3 (16.67)	3 (16.67)	3 (16.67)
IIB	Occupation of the whole pterygopalatine fossa with or without erosion of the orbital apex	2 (12.50)	2 (12.50)	2 (12.50)
IIC	Infratemporal fossa with or without cheek or extension posterior to pterygoid plates	4 (22.22)	4 (22.22)	4 (22.22)
IIIA	Erosion of the skull base (middle cranial fossa/base of pterygoid, minimal intracranial)	3 (16.67)	2 (12.50)	2 (12.50)
IIIB	Erosion of the skull base, extensive intracranial with or without cavernous sinus	2 (12.50)	3 (16.67)	3 (16.67)

Note: 4D-CTA, four-dimensional CT angiography; No. of patients, number of patients.

Figure 2 Dynamic 4D-CTA (a) demonstrated that the branches of the external carotid artery supplied the tumour (arrows), which was in accordance with the result from DSA (b). 4D-CTA, four-dimensional CT angiography; DSA, digital subtraction angiography.

3.30 ± 0.08 mSv, respectively. And the effective dose for 4D-CTA was statistically less than that of DSA with 7.72 ± 2.41 mSv ($p < 0.001$).

Table 4 The diagnostic agreement between 4D-CTA and surgical findings assessed by Cohen's kappa coefficient (κ)

	Location and Extent	Stage
Reviewer 1	0.86	0.71
Reviewer 2	1.00	1.00

Note: 4D-CTA, four-dimensional CT angiography.

Table 5 Frequency of the blood supply pattern of JNAs in 4D-CTA and DSA

Feeding artery	No. of lesions			No. of arteries		
	Reviewer 1	Reviewer 2	DSA ^a	Reviewer 1	Reviewer 2	DSA ^a
External carotid artery	15	15	15	34	31	35
External and internal carotid arteries	3	3	3	7	8	8

4D-CTA, four-dimensional CT angiography; DSA, digital subtraction angiography; JNAs, juvenilenasopharyngeal angiofibromas; No. of patients, number of patients.

^aInterpretations of both reviewers for DSA were identical.

The frequency of the invasion sites of JNAs demonstrated in 4D-CTA was presented in Table 2 and the path of invasion could be best observed by means of the consecutive axial and sagittal MPR images (Figure 1). The classification of JNAs based on Radkowski's stage were summarized in Table 3. As shown in Table 4, both observers found excellent agreements between 4D-CTA and surgical manifestation for the assessment of tumour location and extent ($\kappa = 0.86$ and 1.00), and the interobserver agreement of 4D-CTA was also excellent ($\kappa = 0.86$). As for tumour "stage", fair to good agreement between 4D-CTA and surgical finding was found in Reviewer 1 ($\kappa = 0.71$), with excellent agreement achieved in Reviewer 2 ($\kappa = 1.00$). Interobserver agreement between the two observers for the assessment of tumour stage was fair to good by means of 4D-CTA ($\kappa = 0.71$).

As presented in Table 5, the demonstration of DSA revealed that 15 lesions were supplied strictly by the ECA circulation and had 35 feeding arteries with 3 lesions having both ECA and ICA supply and 8 feeding arteries. 4D-CTA depicted 15 lesions supplied strictly by the ECA circulation and 3 by ECA and ICA supply, which was in accordance with DSA. However, both reviewers found less feeding arteries when compared to DSA. There were no significant differences in the main arterial feeder number between the two observers using obtained from 4D-CTA and DSA (all $p > 0.05$) (Figure 2).

Discussion

In this study, we used 4D-CTA to evaluate patients with JNAs and found this CT technique was able to provide good diagnostic performances for JNAs by assessing the presence, location, extent and feeding artery of these entities precisely. Moreover, the effective dose was lower in 4D-CTA than DSA, indicating the possible application of this technique for clinical assessment of JNAs.

Nowadays, advanced imaging methods such as CT, MRI and DSA have been widely applied for the diagnosis of JNA.^{2,20} Previous studies have demonstrated that CT possesses the advantage of evaluating tumour location and extent as well as bone erosion whereas MRI is considered as the initial choice for these neoplasms in clinical routine.^{2,20} However, both of these two modalities cannot visually show the feeding artery of the tumour for pre-surgical embolization. DSA is considered to be the gold standard for detection of tumour feeding artery and is usually performed for tumour embolization, thus reducing the associated procedural risk for patients.^{2,21,22} The main drawbacks of DSA are the invasive procedure accompanied with possible complications.⁶⁻⁹ Noninvasive imaging modalities, particularly MRA and 3D-CTA, can allow simultaneous assessment of the anatomical details and feeding vessels for JNA, but lack the temporal dynamic information to characterize the tumour. More importantly, it is usually difficult to separate arteries from veins in both modalities. 4D-CTA is a novel technique which has the same capacity as a 3D-CT to demonstrate anatomical details but demonstrates the flow pattern of the lesion at different phases of contrast flow.¹⁴⁻¹⁶ Notably, by means of this method, artery-only images can be obtained after the subtraction of pre-contrast and optimal arterial contrast images, and then CTA images can be reconstructed. This technique has recently been widely used to study cerebral vessel disease,²³ showing the potential to provide precise evaluation for JNAs.

In the present study, 4D-CTA is effective for the diagnosis of JNA with a high consistent rates of 96.2 and 100% for both reviewer, respectively. Moreover, the effective dose of 4D-CTA was much less than that of DSA ($p < 0.05$), indicating 4D-CTA a preferred modality in the diagnosis of JNAs. Furthermore, as a non-invasive radiological technique, 4D-CTA can be executed as soon as possible when compared with DSA. In addition, metal artifacts can be minimized with the application of bone subtraction technique. This technique identifies bones as high-attenuation objects on the nonenhanced scan and removes these from the subsequent contrast-enhanced 4D sequence. As a result, only high-attenuation vessels with contrast enhancement can be reserved thus effectively reducing the artifacts. However, it should also be noted that DSA is commonly necessary for preoperative embolization. The total sum of radiation dose will increase significantly if both

4D-CTA and DSA are performed. Given that most patients with JNAs are adolescent, the high total radiation dose will limit the wide application of 4D-CTA in the clinical setting for JNAs. Previous studies have shown that proper image filtering such as iterative reconstructions allowed substantial dose reduction with preservation of or even increase in diagnostic image quality.²⁴⁻²⁶ Thus, the use of iterative reconstructions for 4D-CTA should be performed in further studies to reduce the radiation dose. Additionally, preoperative precise staging of JNAs is greatly important in planning the surgical approach and therefore different staging systems have been proposed.^{17,20,27-29} Our results suggest the clear superiority of 4D-CTA for the determination of the location, extent, and staging of the lesions, which showed good agreement between 4D-CTA and surgical findings and between different reviewers. It is noteworthy that this study is the first report investigating and finding the consistency between 4D-CTA and surgical findings.

As shown in this current study, no significant differences existed in the main arterial feeder number between different observers obtained from 4D-CTA and DSA (all $p > 0.05$) for the detection of the blood supply. Specifically, DSA revealed 15 lesions which were supplied strictly by the ECA circulation and had 35 feeding arteries, with 3 lesions having both ECA and ICA supply and 8 feeding arteries. And 4D-CTA revealed 15 lesions that were supplied strictly by the ECA circulation and 3 by ECA and ICA supply, which was in concert with DSA. Clinically, the diagnostic arteriogram was performed during the pre-surgical embolization procedure to delineate the specific blood supply to the tumour, allowing the surgeon to plan the surgical approach and anticipate areas of increased vascularity and bleeding.²¹ According to our study, it appears that 4D-CTA has the ability to provide precise analysis of feeding arteries. However, it should also be noted that both reviewers found less feeding arteries on 4D-CTA as compared to DSA, because some feeding arteries were too small to be detected by 4D-CTA. Given that only the main feeding arteries of the lesion should undergo the embolization, this limitation might not affect the surgical procedure. But our study still suggested that only a well-trained and rich experienced operator could make good use of 4D-CTA. Occasionally, when smaller arteries are not filled with contrast agents, they may not be well visualized. Meanwhile, we also found that the blood supply of partial JNAs was not only from ECA systems but also from ICA systems. This may be due to the fact that adjacent structures and blood vessels could provide a collateral source of blood supply for JNA, including branches of the ICA or contralateral carotid system when the tumour grows bigger.³⁰ Additionally, Mehan *et al*³¹ found that larger tumours of JNAs were more likely to be associated with ICA supply, suggestive of the positive correlation between the tumour sizes of JNAs with the ICA supply. However, due to the

small sample size of our study, an association between vascular supplies, stage and tumour size of JNAs on 4D-CTA was not investigated that would merit further exploration.

Our study has several limitations. Firstly, the patient number was small, although this is owing to the rare occurrence of JNA. To draw more definite conclusions, a multicentre study involving a larger number of patients is required. Secondly, 4D-CTA using volumetric imaging mode would increase additional exposure to radiation while the radiation dose is acceptable for the patients. Thirdly, conventional CT angiography with helical scanning mode was not employed in our study and not compared with 4D-CTA, because both of them had been proved to be useful in the diagnosis of vascular disease or tumours.³² Lastly, other advanced radiological techniques were not included in this study, such as contrast-enhanced MRA (CE-MRA).

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Comparative study between different modalities or imaging techniques should be performed in future investigation.

Conclusion

In conclusion, this is still the first systematic study demonstrating the application of 4D-CTA in assessing the rare condition, JNA. 4D-CTA appears to be a valid choice for precise diagnosing JNAs and preoperatively assessing the location, extent, stage and feeding artery of JNAs in a routine clinical setting.

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