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# Table of Contents

**Volume 7  Number 1  March 2017**

| Title                                                                 | Authors                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------|
| Knowledge and Practices of Dentists, Oral and Maxillofacial Surgeons of Cone Beam Computed Tomography (CBCT) and the Dentascanner in a Low Income Country: Case of Togo | M. Tchaou, H. Bissa, P. E. Pegbessou, A. Amadou, B. N’timon, M. Dansou, A.-R. Adam, L. Sonhaye, L.-K. Agoda-Koussema, K. Adjenou |
| Myocardial Segmentation of Area at Risk Based on Coronary Computed Tomography Angiography and Voronoi Diagram in Comparison with Magnetic Resonance Perfusion Imaging | N. Fukuyama, T. Kido, A. Kurata, Y. Tanabe, T. Kido, T. Yokoi, R. Ogawa, H. Nishiyama, T. Uetani, T. Mochizuki |
| Poor Reproducibility in the Evaluation of Paranasal Sinus X-Rays in Chronic Rhinosinusitis | A. Luukkainen, E. Terna, J. Numminen, A. Markkola, P. Dastidar, J. Jarnstedt, H. Huhtala, M. Karjalainen, K. Blomgren, P. Kauppi, M. Rautiainen, S. Toppila-Salmi |
| Voxel Placement Precision for GABA-Edited Magnetic Resonance Spectroscopy | X. Bai, A. D. Harris, T. Gong, N. A. J. Puts, G. B. Wang, M. Schär, P. B. Barker, R. A. E. Edden |
| Biometrics of the Cervical Spinal Canal and Cord by Computer Tomography in Togo | A. Amadou, L. Sonhaye, K. Apetse, K. Amoussou, M. Tchaou, B. N’timon, K. A. Agbangba, G. Watara, K. Adjenou |
| Cerebellar Haemangioblastoma Diagnosed as Giant Tuberculoma: Falacies of Magnetic Resonance Spectroscopy—Case Report | B. B. Sharma, N. Bhardwaj, S. Dewan, M. R. Aziz, S. Sharma, S. Singh |
| Cystic Mediastinal Schwannoma Presenting as Pleural Effusion | K. Sidibé, R. Sani, Y. A. Lamrani, F. Z. Ammor, P. E. Ossibi, B. dit M. Traoré, B. Alami, M. Boubou, K. Mazaz, Y. Ouadnouni, M. Maâroufi |
| Safety and Diagnostic Image Quality of Ultravist* in an Unselected Sub-Set of Chinese Patients: Data Analyses from a Previous Post Marketing Surveillance | S. X. Zhang, C. H. Liang, Z. P. Li, J. Wang |
| Assessment of Image Quality Parameters for Computed Tomography in Sudan | H. Elnour, H. A. Hassan, A. Mustafa, H. Osman, S. Alamri, A. Yasen |
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Knowledge and Practices of Dentists, Oral and Maxillofacial Surgeons of Cone Beam Computed Tomography (CBCT) and the Dentascanner in a Low Income Country: Case of Togo

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Abstract

Background: In dental-maxillofacial imaging, 3D sectional imaging progressively replaces conventional 2D imaging in developed countries. They are based specially on Computed tomography (CT-Scan), with the Dentascan application and cone beam computed tomography (CBCT). In developing countries those technics are newly introduced. Aim: This study aimed at studying the knowledge and practices of dentist and oral and maxillofacial surgeons on sectional imaging such as Dentascan and Cone Beam Computed Tomography (CBCT). Materials and Methods: We conducted an anonymous survey among dentists and oral maxillofacial surgeons in Togo over one month. Results: The response rate was 78.79% (27/33). They were mainly male sex (sex ratio of 2.25 men for one woman). They were aged between 27 and 71 years old with an average of 49.69 years old. The majority (61.54%) had a professional experience over 20 years. The majority of respondents (65.38%) believed their level of knowledge about dental x-Ray was poor. Half of them (50%) confirmed that they had never asked for a Dentascan, and 15.38% asked from time to time for it and only two (7.69%) asked often for this test. 96.15% confirm they have no knowledge of the Dentascan. Regarding the CBCT, 84.62% didn’t ask for it because this technique did not exist in Togo before. 69.20% of respondents confessed to be interested in continuing training on sectional imaging. Conclusion: This study shows that sectional imaging is very little used by oral and dental practitioners in Togo because of the ignorance of the new techniques
and the absence of the CBCT. It is therefore necessary to promote the teaching of the new technique of sectional imaging in the training syllabus of oral and dental specialists and to initiate continuing medical training.

**Keywords**

Knowledge, Practice, Dentascan, Cone Beam Computed Tomography (CBCT), Dentist, Oral and Maxillofacial Surgeon, Togo

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### 1. Introduction

In dental-maxillofacial imaging, 3D sectional imaging progressively replaces conventional 2D imaging in developed countries with the recommendations of professionals after consensus conferences [1]. It is more often used for diagnosis in dental care, reconstructive dentistry, and pediatric dentistry [1] [2]. This preference is due to the solution of shot confusing problem awkward situation in 2D imaging. There are various techniques to generate three-dimensional images in dentistry. Conventional tomography depicts a defined layer of the body; structures outside of this layer appear out of focus [3]. Computed tomography (CT-Scan) represents layers in the axial, coronal or sagittal plane and can provide information about the topographical location of various structures to one another. The CT scanner works using a rotating radiation source and high tube voltages. X-rays are emitted in a fan-shaped beam to stationary detectors placed 360˚ around the patient. Each rotation of the tube records an axial slice of the volume being examined. The 3-D domain is axially moved and each new section is recorded. The coronal and sagittal slices are computed from the axial data [4].

Arai Y. *et al.* 1999 [5] first described the application of cone beam computed tomography (CBCT). In contrast to computer tomography the Arai group introduced an Ortho-CT using a conical beam of radiation. The radiation source and the detector rotate around the patient. From a single 360˚ rotation, the complete volume under investigation is recorded. The cone beam computed tomography can capture a cylindrical volume of variable size.

In Togo, the CT-Scan was introduced in 2000 with a sequential cutting device which lacked of dental imaging software. Since then, new faster devices, including helical scanners, multi cuts (4 to 16 cuts) equipped with Dentascan software were installed. This study comes as a result of the scarcity of the use of the Dentascan by dental surgeons in Togo. The objective of this study was to review the knowledge and practices of dentists, maxillofacial surgeons and stomatologists in Togo on sectional imaging namely the Dentascan and the CBCT.

### 2. Materials and Methods

It is an anonymous cross-sectional study conducted with dentists, and oral and maxillofacial surgeons, of Togo over a period of a month from August 31st, 2015 to September 30th, 2015, during a meeting organized by the Dentists, Oral and
Maxillofacial Surgeons Association. The survey was conducted on the basis of anonymous survey form, previously established and tested and distributed to practitioners. All the dentists, oral and maxillofacial Surgeons who agreed to respond to the survey had been included in the study. Only the correctly completed survey forms had been retained.

The collected information dealt with the following items: 1) the participant (age, sex, place of basic training or specialization, number of years of practice, mode of practice); 2) the practice of medical imaging (knowledge, use of x-ray device at the dental surgery, frequency of using Dentascan and CBCT, the indications of the Dentascan and the CBCT); and 3) the need for continuing training in 3D Imaging.

3. Results

Out of 33 practitioners in Togo according to the Dentist, Oral and Maxillofacial Surgeons Association, 27 forms had been returned to us and one had been rejected for incomplete information accounting for 26 forms selected. The response rate was 78.79%. Oral and maxillofacial surgeons were 02 (7.69%) while dentists were 24 (92.31%). There were 18 men (69.23%) and 8 women (30.77%) accounting for a sex ratio of 2.25 and aged between 27 and 71 years old with an average of 49.69 ± 9.93 years old. 23 practitioners were over 38 years old (88.46%). They were trained in Senegal (69.23%), Côte d'Ivoire (3.85%) and France (7.69%). Among them, five (19.23%) were trained outside of Africa and France, (Ukraine, Yugoslavia, Russia, Cuba).

61.54% of dentists and oral surgeons had more than 20 years of professional experience (Figure 1). 42.31% of the respondents practiced their profession only in private health center against 38.46% who practiced only in public. Those who practiced both in public and private er presented 19.23%. 25 out of 26 practitioners accounting for 96.30% had admitted that they had at least one x-ray device in their office. Table 1 displays the x-ray devices practitioners have at their disposal. No Dental clinic had CT-Scan or the CBCT in Togo.

The Assessment by themselves of their own level of knowledge about dental radiology had enabled to notice that 18 practitioners (65.38%) had poor knowledge, 3 (11.54%) had good knowledge and 04 (15.38%) had average knowledge. Only one (3.85%) had a very good knowledge.

Table 1. X-ray devices practitioners have at their disposal in their dental clinics.

| X-ray Devices | Number | Percentage (%) |
|---------------|--------|----------------|
| Retro-alveolar X ray Machine | 23 | 88.46 |
| Orthopantomogram | 09 | 34.62 |
| Retro-alveolar X ray machine + Orthopantomogram | 07 | 26.92 |
| Teleradiography | 02 | 07.69 |
| CT-Scan | 00 | 00 |
| CBCT | 00 | 00 |
About the quality of radiologic images they have been receiving from various imaging centers in Togo, 7.69% said they were very satisfied; 38.50% were satisfied; 23.10% were fairly satisfied; 7.69% were not satisfied and 23.10% were neutral.

As far as the quality of radiological reports received from imaging departments are concerned, 3.85% said to be very satisfied; 38.50% were satisfied; 23.10% were fairly satisfied; 7.69% were not satisfied and 23.10% were neutral.

Half of the respondents (50%) confirm they had never asked for Dentascan; 15.38% asked from time to time for it and only two (7.69%) asked often for it (Table 2). This is also noticeable in the assessment of their knowledge about Dentascan; a practitioner (3.85%) considered he had a good/sufficient knowledge, against 25 (96.15%) who considered their knowledge poor.

Regarding the CBCT, only 4 (15.38%) had exceptionally asked for it; the rest had (84.62%) never. None of the participants had good knowledge about the CBCT during our study, 38.50% had insufficient/poor knowledge of this technique while 42.30% had poor knowledge, and 15.38% did not know about it. According to practitioners, the indications of the Dentascan were maxillofacial traumas (34.62%), followed by the exploration of the temporomandibular joint (15.38%), dental trauma (15.38%), orthodontic assessment (15.38%) and pre-implantation assessment (7.69%). 69.20% of the respondents said to be very interested in continuing training on sectional imaging (Dentascan and CBCT); 26.90% were fairly interested and 3.85% were not interested at all.

4. Discussion

The response rates in our study was 78.79%, close to that usually obtained in similar surveys especially 72.73% in Iran in 2015 by Mehdizadeh M. et al. [6] and 74% in Norway in 2014 by Hol C. et al. [7]. Our sample is small, 26 participants in all. This could be explained by a very low number of practitioners of oral and
Table 2. Frequency of Dentascan demand made by dentists, maxillofacial surgeon and stomatologists.

| Frequency          | Number | Percentage (%) |
|--------------------|--------|----------------|
| Never              | 13     | 50.00          |
| Exceptionally      | 3      | 11.54          |
| Very rarely        | 2      | 7.69           |
| Rarely             | 2      | 7.69           |
| From time to time  | 4      | 15.38          |
| Often              | 2      | 7.69           |
| **Total**          | **26** | **100.00**     |

dental survey in Togo. As a matter of fact, only 33 people practice this profession in Togo for a population estimated at 7.5 million [8] accounting for an average density of 1 dentist for more than 227,000 people, whereas in France, the average density was 63.1 dentists for 100,000 inhabitants in metropolitan France in 2013 [9].

The practitioners’ population of oral and dental surgery in Togo is older than that of Switzerland, Turkey, despite the fact that life expectancy is shorter in Togo: 64.5 years old in Togo in 2015 against 83.13 years old in Switzerland. Actually, the average age was 49.69 years old, with extremes of 27 and 71 years old against an average of 45.3 years old and extremes of 25 and 75 years old in Switzerland [10] and 37.14 years old, with extremes of 20 and 63 in Turkey [11]. The main reason for this difference is to be searched in the non-renewal of the specialists. For lack of training in Togo, and the scarcity of scholarships few people are interested in that field which cost a lot abroad. This is also noticeable through the analysis of the years of professional experience. In fact, more than half of dental surgeons (61.54%) had more than 20 years of professional experience. The predominance of male recorded in our study is also found in almost all of the studies [2] [10] [12].

Practitioners in Togo use very few cut imaging in their daily practice compared to those of European countries. This can be explained on the one hand by the absence or low availability of these imaging techniques in Togo; In fact the CBCT does not exist in Togo yet, however the Dentascan is available but it is only 5 CT-Scan devices across all the country and on the other hand by the ignorance of the Dentascan existence, the lack of information and sensitization on the part of dentists whose practice is much more private. They did not even talk to patients about CBCT because this technique did not exist yet. However in Switzerland, 19.2% of dentists were able to use CBCT on the spot, 40.8% of respondents asked for CBCT examination in second position, 4.9% asked for the conventional scanner, 34.2% would ask for a CBCT or a scanner depending on the situation, 11.1% said that they did not resort to any of the two options [10]. In Iran, 33.7% of practitioners suggest scanner to their patients, 18.8% suggest CBCT, and 46.3% had never suggested CBCT [6].
The Dentascan was the only technique in 3D cut imaging in oral and dental surgery available in Togo, and yet, its use is rare. Indeed, it was asked only twice in trimester by 15.38% of practitioners while two respondents (7.69%) said having asked for it more than once a month. Half of practitioners never used this technique in Togo whereas in Turkey, only 33.7% of them never used it [11].

The CBCT which is a rare technique in Togo is the most preferred one in other countries. It is the case in India where 72.7% of dentists preferred CBCT to scanner according to Sudhakara [13]. The fact that cut imaging is less used could be explained by the lack of sensitization and the poor knowledge in dental radiology in general, with those 65.38% who considered their knowledge poor. As for the CBCT, none of them did not assert having knowledge in that domain. As to the Dentascan, only one (3.85%) said to have good knowledge of this technique. This poor knowledge of cut imaging can be explained not only by the advanced age of practitioners who during their period of studies did not have access to these techniques because they are not developed yet, but also by the lack of continuing training. These two channels are the appropriate ways to acquire basic know-how and to update one’s skills. For instance the observations made in Turkey show that 55.9% of dentists had knowledge about CBCT [11]; that knowledge was acquired by 59.9% of respondents during basic training at the faculty, 31% in seminars and 20.9% on the internet [14]. It is the same in Switzerland where half of dentists who took part in the study had confessed having received a good training in the field of medical imaging and 44.2% have acquired their knowledge during their basic training [10].

According to practitioners in Togo, trauma represents 34.62% of indications for 3D sectional imaging, 7.79% for implantology, whereas implantology alone accounted for 63.40% in Switzerland [10] and 62.5% in Iran [6]. According to directives in Switzerland in 2015, the CBCT is mainly used for implant treatment [2]. This evidence still confirms the ignorance of indications of the different techniques of sectional imaging of practitioners in Togo.

In view of knowledge deficiency recorded, 69.20% of practitioners expressed their interest in receiving a continuing training on the Dentascan/CBCT. This rate is higher than that of Switzerland (42%) [10]. One of the solutions would be to introduce in the teaching curriculum of the basic training, the new imaging techniques and to update those lecturers knowledge in accordance with the new techniques evolution. That is the wish of dentistry’s students (91%) in Turkey who wanted that learning unit of the CBCT to be accessible at the dentistry Faculty [14] and in India where 49.1% of students wanted that training on the CBCT should be incorporated in the basic clinical training in dentistry [13].

5. Conclusion

Dental imaging is an essential tool for diagnostic and therapeutic orientation in the oral and dental surgery field. In Togo, sectional imaging is less used by practitioners of oral and dental medicine because of the ignorance of the new techniques existence and the absence of the CBCT. This ignorance stems from the
lack of sectional imaging course in the training syllabus at the time when most of those practitioners whose experience is more than 20 years were being trained and the lack of continuing medical education that would allow them to update their knowledge and to learn about the interests of new techniques. Therefore, it is necessary to promote the teaching of the new cut imaging technique in the training syllabus of oral and dental diseases specialists, and to initiate continuing medical training on that subject.

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Myocardial Segmentation of Area at Risk Based on Coronary Computed Tomography Angiography and Voronoi Diagram in Comparison with Magnetic Resonance Perfusion Imaging

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Abstract

Purpose: To assess the clinical feasibility of automated segmentation of the myocardial area at risk (MAAR) using coronary computed tomography angiography (CT-MAAR), as compared to stress magnetic resonance myocardial perfusion imaging (MR-MPI). Materials and Methods: Thirty patients who underwent coronary computed tomography angiography (CTA) and stress MR-MPI were retrospectively evaluated. The myocardial territory of the left ventricle (LV) distal to coronary artery stenosis (≥50% or ≥70% stenosis on coronary CTA) was three-dimensionally quantified using a Voronoi diagram. The ratio of all stenosis-related territories to the LV volume was defined as CT-MAAR (%-LV volume). The proportion of segments with perfusion defects in stress MR-MPI to the total of 16 segments (range: 0% - 100%; with a 6.3%-interval scale) was defined as the reference. Correlation was assessed using Spearman’s test. The capability of CT-MAAR to predict the ischemic burden was assessed. Results: Stress MR-MPI depicted a median ischemic burden of 25.2% (range: 18.9% - 44.1%) in 30 patients without myocardial infarction. When CTA stenosis criteria of ≥50% (n = 30) and ≥70% (n = 27) were applied to estimate CT-MAAR (%-LV volume), the median CT-MAAR values were 48.2% (31.6% - 64.3%) and 32.5% (23.7% - 51.9%), respectively. The correlations between the CT-MAAR values and the MR-based ischemic burden were significant (0.73 and 0.97 for ≥50% and ≥70% stenosis, respectively). CT-MAAR predicted the MR-based ischemic burden within ±1 segment of %-LV (6.3%) in 40% (12/30) of patients with ≥50% stenosis, and in 81.5% (22/27) of...
patients with ≥70% stenosis. **Conclusions:** Comprehensive assessment of resting coronary CTA combined with Voronoi diagram-based myocardial segmentation may help predict the myocardial ischemic burden in patients with severe coronary CTA stenosis.

**Keywords**
Computed Tomography, Ischemia, Myocardial Area at Risk

1. **Introduction**

Coronary computed tomography angiography (CTA) is widely used in clinical practice for assessing obstructive coronary artery disease (CAD), because of its high sensitivity and negative predictive value [1] [2] [3]. However, because of the limited spatial resolution, further evaluation, such as invasive coronary angiography (ICA) or stress myocardial perfusion imaging (MPI), is often required in the diagnostic workflow of coronary artery disease (CAD) [4]. Stress MPI, using single-photon-emission computed tomography (SPECT) and magnetic resonance imaging (MR), can non-invasively detect and quantify ischemic myocardium as a standard reference [5] [6], and is useful as the ischemic ratio of the left ventricular (LV) myocardium provides important information for diagnostic and therapeutic purposes in patients with CAD [7].

Furthermore, the Voronoi diagram is a type of centerline method that divides space (i.e., volume) by seeded points or lines [8], and is utilized in industry and geography. In diagnostic imaging, a previous study has shown the usefulness of this algorithm for liver segmentation, based on CT portal venography [9], and a recent study has reported that ICA-based stenosis-related CT myocardial territory correlates with the SPECT-based myocardial area at risk (MAAR) [10]. Coronary CTA stenosis-related CT myocardial territory is an assumption of the maximum MAAR that is obtained from a resting coronary CTA dataset. Stress MR-MPI has a high spatial resolution and yields better diagnostic performance in assessing multi-vessel disease in comparison with SPECT-MPI [11] [12]. Thus, this study aimed to assess the clinical feasibility of applying automated segmentation of MAAR using coronary CTA, as compared to stress MR-MPI.

2. **Materials and Methods**

2.1. **Study Design**

This retrospective observational study was approved by the local ethics committee (clinical research 1509002). The need for informed consent was waived because of the retrospective nature of the study. From June 2009 to March 2016, we retrospectively collected the records of 91 consecutive patients who underwent coronary CTA and stress MR-MPI within an interval of less than 6 months. All patient information was protected in compliance with the guidelines pro-
vided by the institutional review board. The flow chart for patient selection is shown in Figure 1. Patients with myocardial ischemia diagnosed by stress MR-MPI were excluded if they fulfilled the following criteria: 1) no invasive coronary angiography (ICA) available; 2) previous history of revascularization therapy, such as coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI); 3) heart valve disease; 4) cardiomyopathy; 5) total coronary artery occlusion confirmed by ICA and 6) poor image quality of coronary CTA.

2.2. Coronary CTA

We used a 256-slice (128 multi-detector row) CT (Brilliance iCT; Philips Healthcare, Cleveland, OH, USA) and an automatic dual-head injector (Stellant Dual Flow; Nihon MEDRAD K.K., Osaka, Japan). All patients received 1.2 mg (i.e., 2 puffs) of sublingual nitroglycerin (Myocor spray; Astellas Pharma, Tokyo, Japan). For patients with a resting heart rate of more than 60 beats/min, an intravenous beta-blocker (0.125 mg/kg of landiolol hydrochloride, Corebeta; Ono Pharmaceutical Co., Osaka, Japan) was administered 5 min before the timing-bolus scan, to reduce the heart rate. Coronary CTA was performed with iohexol (Omnipaque; 350 mg iodine/mL; Daiichi Sankyo, Tokyo, Japan) or with iopamidol (Iopamiron; 370 mg iodine/mL; Bayer Yakuhin, Osaka, Japan) at an injection rate of 5.0 - 5.5 mL/s for 10 s, followed by a saline chaser (20 mL, 5.0 - 5.5 mL/s). The scan parameters were as follows: retrospective electrocardiogram-gated mode (heart rate >60 beats/min) or prospective electrocardiogram-gated mode (heart rate ≤60 beats/min); tube voltage, 120 kV; effective tube current time-product, 800 - 1300 mAs/rotation with dose modulation; gantry rotation

![Figure 1. Flowchart of the study participants. CABG, coronary artery bypass grafting; CM, cardiomyopathy; CTA, computed tomography angiography; CTO, total coronary artery occlusion; HVD, heart valve disease; MI, myocardial infarction; ICA, invasive coronary angiography; MR-MPI, magnetic resonance myocardial perfusion imaging; PCI, percutaneous coronary intervention.](image-url)
time, 0.27 s/rotation; collimation, 2 × 128 × 0.625 mm with a dynamic z-focal spot; 250-mm display field of view; 0.8/0.4-mm slice thickness/overlap; and 512 × 512 image matrix. Image reconstruction was performed individually to reduce motion artifacts, with 0.8-mm slice thickness and 0.4-mm intervals using hybrid iterative reconstruction (iDose4 level 4; Philips Healthcare, Cleveland, OH, USA) and a medium-smooth cardiac kernel.

2.3. Stress Cardiac MR-MPI

We used a 3-T MR system (Achieva 3.0 T Quasar Dual; Philips Healthcare, Cleveland, OH, USA) equipped with a 32-element cardiac phased-array coil. Using an established comprehensive cardiac MR protocol [13], stress and rest MR perfusion and late images were obtained. For the stress image, pharmacological hyperemia was induced with an adenosine triphosphate infusion (0.16 mg·min⁻¹·kg⁻¹) for ≥3 min. Stress and resting MR perfusion images (for 35 s) were obtained from three short-axis images of the basal, mid-, and apical LV, using a two-dimensional (2D) T1 turbo field-echo sequence with k-space and time broad-use linear acquisition speed-up technique (k-t BLAST), after the injection of gadopentetate dimeglumine (0.05 mmol/kg; Magnevist; Schering, Berlin, Germany), followed by a 30-mL saline chaser, at an injection rate of 4 mL/s. Late images were obtained 10 min after the resting image using an inversion-recovery 3D T1 turbo field-echo sequence. The inversion time was individually determined using the Look-Locker sequence.

2.4. Invasive Coronary Angiography

ICA was performed following the standard institutional catheterization approach. Quantitative coronary analysis was performed by an independent cardiologist (T.U., 15 years of experience), who was blinded to other results, using commercially available software (CAAS5.9; Pie Medical Imaging, Maastricht, the Netherlands). Coronary artery stenosis ≥50% and ≥70% were considered as significant and obstructive CAD, respectively. When multiple stenoses were seen in two or more segments, the proximal stenosis was defined as the culprit stenosis. All coronary artery segments and stenotic lesions (≥50% stenosis) were classified by the main coronary vessels: the left anterior descending artery (LAD), including diagonal branches, the left circumflex artery (LCX), including the high lateral branch and ramus intermedius, and the right coronary artery (RCA), based on the American Heart Association guidelines [14].

2.5. MR-Based Ischemic Burden

The 16-segment model, excluding the apex, was applied [15]. The perfusion images were visually analyzed by two observers (T.K. and R.O., with 3 years and 8 years of experience in cardiac MR, respectively). These observers were blinded to all other data. If a perfusion defect in the LV myocardium was present in four or more cardiac cycles in the stress image, but not present in the resting image, it was considered to be a stress-induced perfusion defect [16]. When a segment
with ≥50% of stress-induced perfusion defect was seen along the circumferential direction of the LV short axial image, corresponding to significant ICA stenosis by vessel-based analysis, it was defined as the ischemic segment in this study. Discrepancies between the opinions of the first two observers were solved by a third senior observer (T. K., with 15 years’ experience). In the late image, a segment with any late gadolinium enhancement was defined as a segment with myocardial infarction, irrespective of the presence or absence of myocardial ischemia. Patients with any segments showing late gadolinium enhancement were excluded from the study. The ratio of the number of segments with myocardial ischemia to the total of 16 segments was defined as the standard reference in this study (range: 0% - 100% with a 6.3%-interval scale). The vessel-based analysis of the 16-segment model was based on a standardized myocardial segmentation [15].

2.6. Assessment of Coronary CTA

All CTA images were evaluated by two observers (Y.T. and T.Y., who had 4 years and 2 years of experience in cardiac CT, respectively) using a commercially available workstation (Aquarius intuition; TERARECON, Inc., Tokyo, Japan). First, an overall assessment of image quality was performed at the subject level to assess misalignment of the coronary arteries between the slabs and discontinuity of coronary vessels due to motion artifacts and arrhythmia. If any of the aforementioned requirements were unsuitable, the patient was excluded from the study. Using a single dataset of coronary CTA with sufficient image quality, stenosis severity per segment was semiquantitatively assessed using the standard guidelines for reporting coronary CTA [17]: “non-CAD”, 0% - 49%; “moderate”, 50% - 69%; “severe”, 70% - 99%; and “occluded”, 100%. The unassessable calcified segments were assumed to indicate severe stenosis. When multiple stenoses were found in the same coronary segment and vessel, the proximal stenosis was considered to be the culprit stenosis. Discrepancies were solved by consensus. Coronary artery segmentation was applied, in addition to ICA.

2.7. CTA-Based MAAR

The same two observers evaluated the coronary CTA-based myocardial territory using dedicated software (TVA; TERARECON Inc. Tokyo, Japan). Post-processing of Voronoi diagram-based myocardial segmentation using coronary CTA was shown in Figure 2. In a series of Voronoi diagram-based myocardial segmentations based on a single CT dataset, the LV myocardium was automatically extracted using basic cardiac function analysis, and the coronary arteries were extracted in a semiautomatic manner. The software three-dimensionally integrated the two datasets and quantified the LV territories distal to any point on coronary CTA irrespective of coronary stenosis severity.

For this study, the stenosis-related CT myocardial territory was quantified at both levels of stenosis (≥50% and ≥70% on coronary CTA). The discrepancies of the stenosis-related CT myocardial territories were individually reviewed and
solved by consensus. The two sums of all stenosis-related CT myocardial territo-
ries (i.e., the ratio of the LV volume at risk to the whole LV volume) were calcu-
lated using the two standards of the CTA stenosis (≥50% and ≥70%) as signifi-
cant and obstructive CTA stenosis-based CT-MAAR, respectively.

2.8. Statistical Analysis

Categorical variables were expressed as proportions and continuous variables
were Altman plotting expressed as the mean ± the standard deviation or as the
median (interquartile range), as appropriate. With regard to coronary CTA ste-
nosis severity and the stenosis-related CT myocardial territory for stenotic le-
sions ≥50%, the intra- and inter-observer reproducibility of the two operators
were assessed using Spearman’s test and Bland-Altman plotting.

Correlations between CTA-based MAAR and MR-based ischemic burden
were evaluated with Spearman’s test. The ability of CTA-based MAAR to esti-
mate the MR-based ischemic burden within ±6.3%, corresponding to a single
segment of the LV (100/16 = 6.3) in the assessment of MR-based ischemia, was
calculated. All analyses were performed using JMP version 11 (SAS Institute,
Cary, NC, USA). For all analyses, p < 0.05 was significant.

3. Results

3.1. Patient Characteristics

Of the 50 patients, 20 were excluded for the following reasons: no ICA (n = 6),
previous revascularization therapy (CABG, n = 1; PCI, n = 5), valvular heart
disease (n = 3), cardiomyopathy (n = 2), total coronary artery occlusion (n = 2), and poor image quality on MR-MPI (n = 1) or on coronary CTA (n = 1). Thirty patients were finally analyzed (24 men and 6 women; mean age, 67.5 ± 7.9 years). The patient characteristics are listed in Table 1. ICA revealed 60 coronary artery lesions with >50% stenosis and 28 coronary artery lesions with >70% stenosis. The numbers of diseased vessels were 29 in the LAD, 18 in the LCX, and 13 in the RCA, respectively. The ICA-based diagnosis was single-vessel disease (n = 16), double-vessel disease (n = 12), and triple-vessel disease (n = 2). The median MR-based ischemic burden was 25.2% (18.9% - 44.1%).

3.2. Coronary CTA Analysis

A total of 438 segments were assessed. The intra- and inter-observer agreement for the semiquantitative assessment of stenotic severity on coronary CTA was 0.71 and 0.67, respectively. The by-consensus diagnosis per segment was as follows: non-CAD stenosis (n = 361), moderate stenosis (n = 30), severe stenosis (n = 28), occluded lesions (n = 3), and unassessable calcified segments (n = 16). When using the CTA stenosis criterion of ≥50%, 77 lesions in 30 patients met the criteria for significant CTA-based MAAR. However, when using the CTA stenosis criterion of ≥70%, 47 lesions in 27 patients met the criteria for obstructive CTA-based MAAR.

3.3. Stenosis-Related CT Myocardial Territory

Seventy-seven coronary CTA lesions with a stenosis of ≥50% were assessed. Voronoi-based segmentation was successfully performed for all lesions. The representative for Compute cases are shown in Figure 3 and Figure 4. The intra- and

Table 1. Patient characteristics.

|                          | N = 30 |
|--------------------------|--------|
| Male/female              | 24 (80.0%)/6 (20.0%) |
| Age (years)              | 67.5 ± 7.9 |
| Hypertension             | 13 (43.3%) |
| Hyperlipidemia           | 14 (46.7%) |
| Diabetes mellitus        | 8 (26.7%) |
| Smoking                  | 12 (40.0%) |
| Family history of CAD    | 8 (26.7%) |
| Time between coronary CTA and MR-MPI (days) | 29 (11.5 - 49) |
| Calcium score (Agatston score) | 405.4 (95.4 - 1031.8) |
| *Number of diseased vessels confirmed with ICA | 46/90 |
| *Single-vessel disease   | 16 |
| *Double-vessel disease   | 12 |
| *Triple-vessel disease   | 2 |

CAD = coronary artery disease; CTA = computed tomography angiography; MR-MPI = magnetic resonance myocardial perfusion imaging; ICA = invasive coronary angiography; presented as N (%), mean ± SD or median (interquartile range), unless otherwise stated. *Invasive coronary angiography stenosis of ≥50% are significant stenosis.
Figure 3. Dataset of a 59-year-old man with effort angina. (a) Stress magnetic resonance myocardial perfusion imaging (MR-MPI) shows perfusion defects in the anteroseptal segments (yellow arrowhead). The MR-MPI-based myocardial ischemic burden was estimated to be 18.9%; (b)-(c) Coronary computed tomography (CT) angiography shows single-vessel disease with severe stenosis in the left anterior descending coronary artery (LAD, blue arrowhead); (f) The CT-based myocardial area at risk using Voronoi diagram-based myocardial segmentation was 23.8%. RCA, right coronary artery; LCX, left circumflex artery.

Figure 4. Dataset of a 71-year-old man with effort angina. (a) Stress magnetic resonance myocardial perfusion imaging (MR-MPI) demonstrates defects in the lateral segments (yellow arrowhead). The MR-MPI-based myocardial ischemic burden was estimated to be 18.9%; (b)-(d) Coronary computed tomography (CT) angiography shows single-vessel disease with a severe stenosis in the left circumflex (LCX, blue arrowhead); (e) The CT-based myocardial area at risk was quantified as 19.5%. LAD, left anterior descending coronary artery; RCA, right coronary artery.

Inter-observer agreements of the significant CTA-related myocardial territories were 0.99 and 0.99, respectively. The mean differences for intra- and inter-observer measurements of CT-based MAAR were 0.004% (95% confidence interval [CI], −0.053% to 0.045%) and −0.003 (95% CI, −0.030% to 0.024%), respectively.

Using the standard of ≥50% CTA stenosis, the median value of significant CTA-based MAAR was 48.2% (range: 31.6% - 64.3%). Marked CTA stenosis-based CT-MAAR correlated with MR-based ischemic burden statistically significantly ($r = 0.73; p < 0.001$) (Figure 5(a)). CT-MAAR predicted the ischemic
Figure 5. (a) and (b) The relationship and difference between myocardial area at risk assessed using computed tomography (CT-MAAR) and the magnetic resonance myocardial perfusion imaging (MR-MPI)-based ischemic burden. For the standard computed tomography angiography (CTA) stenosis criterion of ≥50%, the correlation coefficient was 0.73 ($p < 0.001$). For the standard CTA stenosis criterion of ≥70%, the correlation coefficient was 0.97 ($p < 0.001$). CTA, computed tomography angiography; LV, left ventricle; %LV, the ratio of all stenosis-related territories to the left ventricle myocardial volume.

burden as assessed with MR to within ±6.3% in 40% (12/30) of patients, but overestimated the area at risk by 6.3% in 60% (18/30) patients.

Using the standard of ≥70% CTA stenosis, the median value of obstructive CTA stenosis-based CT-MAAR was 32.5% (range: 23.7% - 51.9%). The correlation between obstructive CTA stenosis-based CT-MAAR and MR-based ischemic burden was statistically significant ($r = 0.97, p < 0.001$) (Figure 5(b)). CTA stenosis-based MAAR could predict the ischemic burden within ±6.3% of that assessed using stress MR-MPI in 22 patients (81.5%) and overestimated the area at risk by 6.3% in 5 patients (18.5%).

4. Discussion

In this study, we showed that: 1) the reproducibility of the procedural steps for assessment of the CTA-based MAAR was good, and that 2) severe coronary CTA stenosis-based MAAR more accurately estimated the MR-based myocardial ischemic burden than did moderate stenosis.

Stress MR-MPI has been established as a useful diagnostic tool for detecting obstructive CAD [11]. The high spatial resolution of MR-MPI enables the delineation of subendocardial ischemia and myocardial infarction in patients with CAD [18]. Therefore, a comprehensive cardiac protocol involving the use of stress MR-MPI is helpful for diagnosing and managing CAD, even in patients with multivessel disease [19]. Stress MPI is essential for assessing the MAAR; therefore, many researchers have investigated stress-induced myocardial perfusion abnormalities using SPECT, MR, and CT [20] [21] [22].

By using a Voronoi diagram, CTA-based myocardial segmentation can indicate the theoretical maximum potential myocardial territory to a seeded point on the coronary CT angiogram. A recent study has demonstrated the high reproduc-
cibility of CTA-based LV myocardial territory and the good correlation of CT-based MAAR with SPECT-based MAAR [10]. SPECT has been established as a clinical standard because of the substantial evidence supporting its use in the diagnosis and management of CAD [5] [20] [23]. However, some studies [11] [12] have discussed the potential disadvantages of SPECT as compared to MR-MPI, such as its lower spatial resolution and visualization of relative myocardial perfusion abnormalities.

Some researchers have reported clinical application of Voronoi diagrams in cardiovascular imaging [24] [25] [26]. Termeer et al. [25] utilized the Voronoi algorithm for estimating the MAAR on a 2D bull’s eye map of the 17-segment model. Kang et al. [26] agreements of recently reported that the impact of coronary stenosis severity as assessed by intravascular ultrasound on the dependent myocardial territory is related to the severity of the invasive fractional flow reserve.

We considered that the CTA stenosis-based CT MAAR might contain some artificial post-processing. The study evaluated the intra- and inter-observer agreements of the CTA stenosis semi-quantification and (0.71 and 0.67, respectively) and those of the stenosis-related myocardial segmentation (0.99 and 0.99, respectively). These may indicate that the former is potentially variable, while the stenosis-based myocardial segmentation on CT scans is highly reproducible, although the region of interest for coronary CTA stenosis was manually placed. A previous study reported the relationship between the extent of the severity of coronary artery stenosis on CT to myocardial ischemia as assessed with stress SPECT-MPI [27]; however, our study revealed the clinical significance of the CTA-based MAAR, according to coronary artery stenosis severity, by quantifying the individual stenosis-related myocardial territory, using the MR-based ischemic burden as the reference. In clinical practice, massive calcification, coronary stents, and intermediate stenosis remain a challenge for coronary CTA [2] [28]. The present study may show the additional value of this method for further examinations, such as stress MPI and invasive examination in the assessment of myocardial ischemia.

The present study has several limitations. First, the study population was relatively small. Second, stress MR-MPI as a reference was obtained with three cardiac short axial images, assessed using a conventional 16-segment model (excluding the apex), with a step-formed ordinal scale per 6.3%, independent from the morphological volume-based or the transmural extent-based evaluation. It is to be noted that these differences between CT-MAAR and stress MR-MPI might potential place a limitation on the evaluation of CT-MAAR in the study. Third, this study excluded patients with myocardial infarction because a myocardial scar may influence the quantification of CT-MAAR, by affecting the volumetric estimation of CT-MAAR, and the true extent of myocardial ischemia. Fourth, the CT-MAAR was estimated based on the anatomical location of coronary stenosis, independent of whether the lesion was diagnosed as hemodynamically significant. Fifth, the precision of the ischemic burden in stress MR-MPI was not
objectively validated on anatomical territory that corresponded to coronary artery stenosis. Further studies with a large number of patients will be required to clarify the significance of these findings in clinical practice.

5. Conclusion

Voronoi diagram-based myocardial segmentation has the potential for predicting the MAAR in patients with obstructive coronary stenosis on CTA. The estimation of MAAR using resting coronary CTA may provide useful information in clinical decision-making.

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Poor Reproducibility in the Evaluation of Paranasal Sinus X-Rays in Chronic Rhinosinusitis

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Abstract

Objective: The aim of this study was to evaluate intra- and inter-observer reproducibility of sinus x-rays in comparison to sinus computed tomography (CT) in chronic rhinosinusitis (CRS) patients. Methods: This was a prospective controlled study for which 14 adult CRS patients were recruited. Patients underwent a sinus multi-detector CT scan as well as additional sinus x-rays at the same time. Symptom interview and skin prick tests were performed. Lund-Mackay (LM) scores and 43 other findings in paranasal sinuses were analyzed by three blinded observers from CT-scans and x-rays. We compared agreement between sinus CT and x-rays (intra-observer reproducibility) and between three observers (inter-observer reproducibility) by Cohen’s kappa. Results: In at least 90% of the cases, the status of 47/49 structures was detectable in CT scans, whereas the status of only 8/49 structures was detectable in x-rays. The majority of the 25 visualized structures had poor intra-observer and inter-observer reproducibility. Conclusion: Only a few structures can be visualized in paranasal sinus x-rays and compared to paranasal sinus CT-scans, their reproducibility is poor. Our results strongly support the current consensus of radiation dose reduction by limiting the number of x-rays.

*The authors contributed equally to this work.
Keywords
Sinusitis, Paranasal Sinus, Computed Tomography, Magnetic Resonance Imaging, X-Ray

1. Introduction
Chronic rhinosinusitis (CRS) is a multifactorial and variable disease with a prevalence of 10.9% [1]. Computed tomography (CT) scans and/or nasal endoscopy are the recommended imaging modality for CRS [1]. Correlation between sinonasal symptoms and endoscopic or radiologic signs is poor [2]. The main findings of CRS are mucosal changes within the ostiomeatal complex and/or sinuses [1]. Paranasal sinus anatomical variants are very common and several critical anatomical structures (such as big vessels, orbit and central nervous system) are closely located to the sinonasal surgical area [3] [4].

CRS surgery has improved many patients’ quality of life with hard to treat CRS [1]. Imaging of the nose and paranasal sinuses has progressed rapidly during the past decade. CT can demonstrate sinus anatomy specifically as well as anatomical variants and other important structures, when preparing for surgery or evaluating the cause of long lasting sinus symptoms. X-rays are not recommended for CRS imaging [2]. A simple radiogram of the nose and paranasal sinuses carries a radiation dose of 0.03 mSv (four days of natural background radiation). Although x-rays are inferior to CT in detecting bony structures and mucosal changes, little comparative data exists on the agreement between sinus CT and x-rays [2].

Despite the novel low dose sinus CT scan modalities, the number of performed sinus x-rays is high in Finland (13.1 per 1000 inhabitants in 2011, according to the statistics of the Radiation and Nuclear Safety Authority) [5]. The aim of this prospective controlled study was to evaluate intra- and inter-observer reproducibility of sinus x-rays in comparison to sinus CT, in order to contribute to the need for reduction of unnecessary radiation.

2. Materials and Methods
2.1. Ethical Consideration
The study was approved by the ethics committee of the Pirkanmaa Hospital District (no 96032) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983. Written informed consent was obtained from each participant. Volunteer patients were exposed to an extra radiation dose of 0.02 years (6 days of natural background radiation in Finland).

2.2. Patients
This study was carried out in the Department of Otorhinolaryngology, at Tampere University Hospital, Finland from 2006 to 2015. A random sample of 14
adult CRS patients, who also had a history of AR and requiring sinus CT scans during 2007-2011, were enrolled. 3 (21%) out of 14 patients also had concomitant asthma. Having another severe disease was an exclusion criterion. 2 (85.7%) out of 14 patients reported as having other diseases (one had arrhythmia, one had resolved melanoma). None of the patients reported using regularly other medication than those due to inflammatory airway diseases. There was no patient record report of any other diseases, nor of psychiatric/psychologic disorders. Patient data was collected from medical records and by a questionnaire at the time of sinus CT scans, as previously described [6]. Follow-up data was collected from patient records of the Tampere University Hospital or Tampere City Hospital in 2015. The median (min-max) follow up time was 6.0 (0 - 8) years after sinus CT scans were performed. None of the subjects had undergone aspirin desensitization, allergen immunotherapy or anti IgE therapy prior to or during sinus CT scans or during follow-up.

2.3. CT Scans

Patients underwent routine sinus multiple detector CT scans for clinical purposes. Two different CT scanners were used: GE LightSpeed 16 (GE Healthcare, Milwaukee, Wisconsin) and Philips Brilliance 64 (Philips, Best, Netherlands). Patients were scanned in a supine position with a kilovoltage of 120 kV and a milliampere second of 100 mAs. With the GE scanner, slice thickness was 0.625 mm with coronal reconstructions at 1.5 mm and a radiation dose of 0.8 mSv. With the Philips scanner, slice thickness was 0.9 mm with coronal reconstructions at 0.9 mm and a radiation dose of 0.9 mSv. Both were three dimensional (3D) in nature without any gaps. In all cases, imaging was performed using a bone filter technique. Scans covered the entire sinonasal area in both axial and coronal directions, starting from the nasal tip and ending at the posterior wall of the sphenoid sinuses.

2.4. X-Rays

X-rays were performed at the same time as sinus CT scans. Two X-ray projections, Waters and PA-projection (Caldwell), were taken with Philips Pendo Diagnost (Philips, Best, Netherlands) skull unit in a sitting position. Imaging parameters were 85 kV, 12 mAs with Waters, and in PA-projection 85 kV and 8 mAs. The images were captured using photostimulable phosphor plates, pixel size 0.1 mm and read with AGFA CR 25 CR (Agfa-Gevaert N. V. Mortsel, Belgium) system. The radiation dose of x-rays with two projections was 0.06 mSv.

2.5. Evaluation of CT Scans and X-Rays

CT scans and x-rays were observed by three independent observers blinded to each other and to patient history data: an experienced head and neck radiologist (AM), an experienced Ear Nose Throat (ENT)-and rhinosurgeon (JN), and a fifth year ENT resident (ST-S). Examination of the same patient’s images took place at least a week apart. The three observers filled a 49-item form of sinonasal
structures from both CT-scan and x-ray bilaterally for each patient (Table 3). Each structure listed in the form could be scored by 2 - 5 different listed choices. Before evaluation of the CT scans, all choices were discussed between observers. Before this study, the observers had participated a pilot study with 15 CT scans [6]. The radiologist did not respond to the question: “Need for septoplasty”.

2.6. Data Analysis
Statistical analysis was carried out by SPSS Base 15.0 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Cohen’s kappa was used to compare the degree of agreement between CT scans and x-rays (e.g. intra-observer agreement); and the inter-observer agreement of x-rays. The calculation is based on the difference between how much agreement is actually present compared to how much agreement would be expected to be present by chance alone. The established interpretation of Kappa-value is classified into 6 subgroups: Poor < 0.2, Fair 0.21 - 0.4, Moderate 0.41 - 0.6, Good 0.61 - 0.8 and Very Good 0.81 - 1.0. A value under zero means that the agreement is worse than that by chance [7]. Two-tailed P-values of <0.05 were considered statistically significant.

3. Results
3.1. Patient Characteristics
Patient characteristics are shown in Table 1. The median (min-max) age was 36.9 (20.0 - 54.3) years. 57.1% of patients underwent sinonasal operation within a year after the CT scans (Table 1). 2 (14.3%) of the patients reported suffering from diseases besides CRS ± AR ± asthma with regular need for medication. One of the patient reported having melanoma and the other patient cardiac arrhythmia.

3.2. Visualized Structures in X-Rays
The number of visualized structures in x-rays was 25, e.g. the structures that were visualized in at least one patient’s paranasal sinus x-rays, whereas the number of visualized structures in at least one patient’s CT scan was 49 (Table 2). The visualized 25/49 structures in x-rays were Lund-Mackay (LM)-scores (except ostiomeatal unit), mucosa and size of paranasal sinuses, mucosa of inferior and middle turbinates, nasal mucosal oedema and septal abnormalities (Table 2). Yet, reliability to even detect these structures in most cases of x-rays was poor (Table 2). In at least 90% of the cases, the status of 47/49 structures was detectable in CT scans, whereas for x-rays it was only 8/49 (Table 2). Several diagnostically and surgically important structures were not visible in x-rays, such as ostiomeatal complex, insertion of the uncinate process, lamina papyracea and anterior ethmoid artery (Table 2).

3.3. Intra-Observer Agreement
We compared the degree of agreement between x-rays and CT scans of the 25 structures that were visualized in x-rays. In general, the intra-observer agree-
Table 1. Characteristics of the patients.

|                      | Chronic rhinosinusitis patients |
|----------------------|----------------------------------|
|                      | n = 14                           | %          |
| Gender               |                                  |            |
| Male                 | 2                                | 14.3       |
| Female               | 12                               | 85.7       |
| Age                  |                                  |            |
| <45 years            | 11                               | 78.6       |
| ≥45 years            | 3                                | 21.4       |
| Smoking              |                                  |            |
| No                   | 9                                | 64.3       |
| Ex                   | 3                                | 21.4       |
| Current              | 1                                | 7.1        |
| Unknown              | 1                                | 7.1        |
| Allergic rhinitis    |                                  |            |
| No                   | 2                                | 14.3       |
| Yes                  | 11                               | 78.6       |
| Unknown              | 1                                | 7.1        |
| SPT positivity       |                                  |            |
| No                   | 3                                | 21.4       |
| Only pollen(s)       | 5                                | 35.7       |
| Only animal dander(s)| 1                                | 7.1        |
| Multiple allergen types| 5                               | 35.7       |
| Asthma               |                                  |            |
| No                   | 10                               | 71.4       |
| Yes                  | 3                                | 21.4       |
| Unknown              | 1                                | 7.1        |
| Nasal polyps         |                                  |            |
| No                   | 12                               | 85.7       |
| Yes                  | 1                                | 7.1        |
| Unknown              | 1                                | 7.1        |
| AERD                 |                                  |            |
| No                   | 13                               | 92.9       |
| Yes                  | 0                                | 0.0        |
| Unknown              | 1                                | 7.1        |
### Continued

| Other diseases | No   | 12   | 85.7 |
|----------------|------|------|------|
| Yes            | 2    | 14.3 |

#### Current use of intranasal corticosteroids

|                | No | 1   | 7.1 |
|----------------|----|-----|-----|
| Yes            | 12 | 85.7|
| Unknown        | 1  | 7.1 |

#### ≥1 peroral corticosteroid course(s) during the past 1 year

|                | No | 13  | 92.9|
|----------------|----|-----|-----|
| Yes            | 0  | 0.0 |
| Unknown        | 1  | 7.1 |

#### Previous sinonasal operation(s)

|                  | No | 11  | 78.6|
|------------------|----|-----|-----|
| Yes              | 2  | 14.3|
| Unknown          | 1  | 7.1 |

#### Radiological signs in CT scans of previous sinus operation

|                        | No | 11  | 78.6|
|------------------------|----|-----|-----|
| Yes                    | 3  | 21.4|

#### Total Lund-Mackay score of CT scans

| Score Range | No | 7   | 50.0|
|-------------|----|-----|-----|
| 0 - 3       | 7  | 50.0|
| 4 - 12      | 0  | 0.0 |
| 13 - 24     |    |     |

#### Sinonasal operation performed within a year after the CT scans

|                | No | 5   | 35.7|
|----------------|----|-----|-----|
| Yes            | 8  | 57.1|
| Unknown        | 1  | 7.1 |

#### ≥1 sinonasal operation(s) during the 6-year follow-up

|                | No | 12  | 85.7|
|----------------|----|-----|-----|
| Yes            | 1  | 7.1 |
| Unknown        | 1  | 7.1 |

#### Number of antibiotic courses during the past 2 years, median (min-max)

|                        | 6.0 (2 - 15) |
|------------------------|--------------|

#### Duration of symptoms in years, median (min-max)

|                      | 2.5 (0.3 - 25.0) |
|----------------------|------------------|

#### Current symptoms by VAS, mean (min – max)

| Symptom               | Score Range       |
|-----------------------|-------------------|
| Sense of smell        | 3.7 (0.0 - 7.3)   |
| Post-nasal drip       | 5.5 (1.0 - 8.1)   |
| Obstruction           | 6.1 (0.7 - 9.8)   |
| Facial pain           | 5.5 (2.4 - 9.9)   |

Abbreviations: SPT = skin prick test; AERD = patient-reported aspirin exacerbated respiratory disease; CT = computed tomography; VAS= visual analogue scale (0 - 10). ¹At least one peroral corticosteroid treatment during the last 12 months. ²Self-reported and patient-record information.
Table 2. The list of visualized or non-visualized sinonasal structures of paranasal sinus x-rays.

| Non-visualized in x-rays | Non-visualized in CT-scans | Non-visualized cases% | Visualized in x-rays | Visualized in CT-scans | Visualized cases% |
|--------------------------|---------------------------|-----------------------|----------------------|-----------------------|------------------|
| Atrophy-normal hypertrophy of inferior turbinate | 0.0 | 28.6 | Anterior ethmoidal artery | 25.0 | 100.0 |
| Atrophy-normal hypertrophy of middle turbinate | 3.6 | 50.0 | Atrophy-normal hypertrophy of superior turbinate | 21.4 | 100.0 |
| Hypoplasia/normal/hyperplasia of anterior ethmoidal sinus | 0.0 | 14.3 | Contact to middle turbinate of orbital lamina of ethmoidal bone | 0.0 | 100.0 |
| Hypoplasia/normal/hyperplasia of frontal sinus | 0.0 | 14.3 | Frontal recess | 0.0 | 100.0 |
| Hypoplasia/normal/hyperplasia of maxillary sinus | 0.0 | 14.3 | Infraorbital cell | 0.0 | 100.0 |
| Hypoplasia/normal/hyperplasia of posterior ethmoidal sinus | 0.0 | 14.3 | Keros classification | 0.0 | 100.0 |
| Hypoplasia/normal/hyperplasia of sphenoid sinus | 0.0 | 14.3 | Lund-Mackay ostiomeatal unit | 0.0 | 100.0 |
| Lund-Mackay anterior ethmoidal sinus | 0.0 | 0.0 | Mucosa of pneumatized middle turbinate | 0.0 | 100.0 |
| Lund-Mackay frontal sinus | 0.0 | 7.1 | Mucosa of pneumatized superior turbinate | 0.0 | 100.0 |
| Lund-Mackay maxillary sinus | 0.0 | 0.0 | OMC region, accessory maxillary sinus ostium | 7.1 | 100.0 |
| Lund-Mackay posterior ethmoidal sinus | 0.0 | 7.1 | OMC region, hiatus | 0.0 | 100.0 |
| Lund-Mackay sphenoid sinus | 0.0 | 3.6 | OMC region, infundibulum | 0.0 | 100.0 |
| Mucosa of nasal cavity (extent of edema) | 0.0 | 14.3 | OMC region, maxillary antrum | 0.0 | 100.0 |
| Mucosa of nasal cavity (normal-polypous) | 0.0 | 14.3 | OMC region, pneumatized superior attachment of uncinate process | 0.0 | 100.0 |
| Need for septoplasty | 0.0 | 35.7 | OMC region, prominent ethmoid bulla | 0.0 | 100.0 |
| Septal deviation obstructing middle meatus | 0.0 | 32.1 | OMC region, superior attachment of uncinate process | 7.1 | 100.0 |
| Septum, crest | 0.0 | 17.9 | Optic nerve | 0.0 | 100.0 |
| Septum deviation | 0.0 | 21.4 | Sphenethmoidal recess | 3.6 | 100.0 |
| Septum turbinate | 0.0 | 32.1 | Paradoxical middle turbinate | 0.0 | 100.0 |
| Septum, spur | 0.0 | 21.4 | Paradoxical superior turbinate | 7.1 | 100.0 |
| Sinus mucosal abnormalities of anterior ethmoidal sinus | 0.0 | 7.1 | Pneumatized middle turbinate | 0.0 | 100.0 |
| Sinus mucosal abnormalities of frontal sinus | 0.0 | 17.9 | Pneumatized superior turbinate | 7.1 | 100.0 |
| Sinus mucosal abnormalities of maxillary sinus | 0.0 | 3.6 | Previous sinus surgery performed | 0.0 | 100.0 |
| Sinus mucosal abnormalities of posterior ethmoidal sinus | 0.0 | 7.1 | Thickness of orbital lamina of ethmoidal bone | 0.0 | 100.0 |
| Sinus mucosal abnormalities of sphenoid sinus | 0.0 | 10.7 | | | |

The CT scans and x-rays were taken from 14 patients with chronic rhinosinusitis symptoms. Each patient underwent CT scans and x-rays at the same time. The columns show in alphabetical order the evaluated 49 structures from paranasal sinus CT-scans and x-rays. Visualized in x-rays = the 25 structures that were visualized in at least one patient’s paranasal sinus x-rays (left column); Non-visualized in x-rays = the 24 structures that were non-visualized in paranasal sinus x-rays of all cases (right column); OMC = Ostiomeatal complex; Not detectable = the percentage of the observer’s responses “The status of the structure is not detectable” of both sides. 1Evaluated by the ENT surgeon. Other structures evaluated by the radiologist.
ment was poor (kappa < 0.2) in the majority of structures, such as LM scores. Moderate and good agreement was only achieved for gross anatomical structures on the right hand-side only, concerning respectively, nasal septum deviation and size of the frontal sinus (Table 3). Fair or poor agreement was observed for the rest of the structures.

3.4. Inter-Observer Agreement

The 25 structures that were visualized in x-rays were evaluated by a radiologist, an ENT surgeon and an ENT resident. The inter-observer agreement between radiologist and ENT resident for x-rays was poor (kappa ≤ 0.02) in 88% of the structures and fair (kappa 0.21 - 0.4) for the rest (12%) of the structures. The agreement between radiologist and ENT surgeon for x-rays was poor or fair in 80% of the structures and the agreement between ENT surgeon and ENT resident was poor or fair in 92% of the structures.

4. Discussion

This study was carried out to evaluate intra- and inter-observer reproducibility of sinus x-rays in comparison to sinus CT scans. When this study was started, multi-detector CT scans had a high radiation dose (in average 0.9 mSv) and x-rays were still relative widely used due to a clearly smaller radiation dose (in average 0.03 mSV per image). After this, low-dose CT scans (such as cone beam CT scans) have emerged (radiation dose between 0.08 - 0.27 mSv) and hence have largely replaced both sinus x-rays and high-dose sinus CT scans [8]. The number of performed sinus x-rays is still high in Finland [5]. Consequently, this study could contribute to the reduction of unnecessary radiation.

Our main finding was that a small proportion of structures can be visualized in x-rays; and x-ray evaluations have poor reproducibility. CRS specific changes that should be observed in CT-scans including degree of opacification of the paranasal sinuses and/or obstruction of the ostiomeatal complex cannot be visualized or only poorly in simple x-rays, making CRS diagnosis unreliable [1]. Similarly, others found in a small study that engorged turbinates and opaque nasal fossa could be observed from paranasal sinus x-rays. In the x-rays of 19.7% of patients with nasal and/or paranasal symptoms during at least 8 weeks, no changes were observable [9].

Intra-observer agreement was fair to poor regarding most of the 25 structures that could be visualized in plain x-rays. Similarly to us, others report in a study with 47 patients with acute rhinosinusitis that plain sinus radiograms have a low sensitivity for detecting sinus inflammatory changes in other paranasal sinuses besides the maxillary sinus, in comparison to CT-scans [10].

Inter-observer agreement was poor for the majority of structures that could be visualized by the radiologist, ENT surgeon and ENT resident. Very good inter-observer agreement was only achieved in regard to structures that could not be visualized, between ENT resident and surgeon.
Table 3. Comparison of the degree of intra-observer agreement from paranasal sinus x-rays and computed tomography (CT)-scans.

| Structure                                      | Right kappa | P      | Left kappa | P      |
|------------------------------------------------|-------------|--------|------------|--------|
| Lund-Mackay frontal sinus                     | −0.057      | <0.001 | −0.050     | <0.001 |
| Lund-Mackay anterior ethmoidal sinus          | 0.109       | 1.00   | 0.243      | 0.357  |
| Lund-Mackay posterior ethmoidal sinus         | 0.155       | <0.001 | 0.200      | <0.001 |
| Lund-Mackay sphenoid sinus                    | −0.148      | <0.001 | 0.323      | 0.286  |
| Lund-Mackay maxillary sinus                   | 0.125       | 0.560  | 0.087      | 1.00   |
| Sinus mucosal abnormalities of frontal sinus  | −0.120      | 1.00   | 0.192      | 1.00   |
| Sinus mucosal abnormalities of anterior ethmoidal sinus | 0.155 | <0.001 | 0.114      | 1.00   |
| Sinus mucosal abnormalities of posterior ethmoidal sinus | 0.142 | <0.001 | 0.067      | 1.00   |
| Sinus mucosal abnormalities of sphenoid sinus | 0.058       | <0.001 | 0.233      | 1.00   |
| Sinus mucosal abnormalities of maxillary sinus| 0.355       | <0.001 | 0.339      | <0.001 |
| Hypoplasia/normal/hyperplasia of frontal sinus| 0.650       | <0.001 | 0.344      | <0.001 |
| Hypoplasia/normal/hyperplasia of anterior ethmoidal sinus | 0.000 | <0.001 | 0.000      | <0.001 |
| Hypoplasia/normal/hyperplasia of posterior ethmoidal sinus | 0.000 | <0.001 | 0.000      | <0.001 |
| Hypoplasia/normal/hyperplasia of sphenoid sinus | 0.192 | <0.001 | 0.208      | <0.001 |
| Hypoplasia/normal/hyperplasia of maxillary sinus | 0.000 | <0.001 | 0.000      | <0.001 |
| Need for septoplasty¹                           | 0.114       | 1.00   | 0.114      | 1.00   |
| Septal deviation obstructing middle meatus    | 0.079       | 1.00   | 0.114      | 1.00   |
| Septum turbinate                               | 0.000       | <0.001 | 0.000      | <0.001 |
| Septum deviation                               | 0.462       | <0.001 | 0.385      | <0.001 |
| Septum, crest                                  | 0.133       | <0.001 | −0.061     | 1.00   |
| Septum, spur                                   | 0.023       | <0.001 | −0.094     | <0.001 |
| Atrophy-normal-hypertrophy of inferior turbinate | 0.250 | <0.001 | 0.381      | 0.019  |
| Atrophy-normal-hypertrophy of middle turbinate | −0.083 | 0.143 | −0.051     | <0.001 |
| Mucosa of nasal cavity (extent of edema)      | 0.030       | 0.250  | −0.054     | <0.001 |
| Mucosa of nasal cavity (normal-polypous)      | 0.175       | <0.001 | −0.054     | 1.00   |

The CT scans and x-rays were taken from 14 patients with chronic rhinosinusitis symptoms. Each patient underwent CT scans and x-rays at the same time. Agreement is presented only of the 25 structures that were detected in x-rays (Table 2). The 24 structures that were not detectable in x-rays have been withdrawn from evaluation. The order of the structures is the same as they were in the evaluation form. Structures with substantial to almost perfect agreement level by Kappa-coefficient. ¹Evaluated by the ENT surgeon. Other structures evaluated by the radiologist.
Simple X-rays of sinuses are currently used to exclude acute sinusitis. Long-term smoking, decline in lung function and poor health-related quality of life are risk factors for exacerbation of asthma exacerbations and emergency room [11]. Prevalence of chronic rhinosinusitis is twice as common in asthmatics needing acute care compared to those without emergency room. However, CRS is not an independent risk factor for acute care. With progressing severe symptoms not responding to antibiotics and other forms of treatment, especially in this patient group, simple X-rays are in some cases used to evaluate the signs and extent of acute bacterial infection [12] [13].

The limitation of our study is the small sample size, which was due to ethical reasons and to difficulties in recruiting volunteer patients for additional x-ray images, carrying extra radiation. We acknowledge that small sample size hinders large scale extrapolation of results and selection bias may have occurred.

5. Conclusion

Only a very small number of structures can be visualized in paranasal sinus x-rays and their evaluation reproducibility is poor compared to paranasal sinus CT scans. Despite the small study sample size, our results strongly support the current European position paper on rhinosinusitis and nasal polyps consensus that sinus CT-scans are needed when estimating the need for surgical treatment of CRS (Figure 1).

Figure 1. 14 patients diagnosed with chronic rhinosinusitis, who underwent routinely multi-detector sinus computed tomography (CT) scans, were asked to take part in the study and to voluntarily undergo sinus x-rays in three projections at the time CT scans were taken. Three cases are presented in this panel. Coronal projection of CT scans of the three cases ((c), (f), (i)). Waters projection of the x-rays of the same cases ((a), (d), (g)); and Caldwell projection of the x-rays of the three cases ((b), (e), (h)). Lateral projections of the x-rays are not shown. Patient 1: thickened mucosa of the inferior wall of the maxillary sinuses and narrowly open ostiomeatal complexes are visualized in CT scans (c), whereas they are not visualized in the x-rays ((a)-(b)). Patient 2: thickened mucosa of the maxillary sinuses and anterior ethmoidal cells, air bubbles within the fluid of right maxillary sinus, obstructed ostiomeatal complex are visualized in CT scans (f), whereas thickened mucosa of the maxillary sinuses is only visualized in x-rays ((d)-(e)). Patient 3: thickened mucosa of the maxillary sinuses and anterior ethmoidal cells, and signs of previous middle mental antrostomies are visualized in CT scans (i), whereas thickened mucosa of the maxillary sinuses is poorly visualized in x-rays ((g)-(h)).
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Voxel Placement Precision for GABA-Edited Magnetic Resonance Spectroscopy

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Abstract

The purpose of the present study was to assess the reproducibility of voxel placement for GABA-edited MRS. GABA-edited MRS data were acquired in 13 healthy volunteers from (3 cm)3 voxel; and within the same session a second acquisition was independently prescribed. A three-dimensional voxel mask image was reconstructed in T1-image-space using the SVMask tool (in house software). Reproducibility of voxel placement was assessed using the Dice overlap coefficient, both within-subject and between-subject following co-registration of T1 images and transformation of voxel mask images to standard space. Within-subject overlap coefficients were 86% ± 5%. Between-subject overlap coefficients were 75% ± 10%. For the two voxel locations considered (occipital and sensorimotor), voxel overlap was very similar. Between-subject values are higher due to between-session effects, anatomical variability and volume mismatch in standard space. While surprisingly low in terms of volume overlap, the overlap coefficients correspond to acceptable linear displacements.

Keywords

MRS, Voxel Placement, Precision, Voxel Prescription, Registration

1. Introduction

1H magnetic resonance spectroscopy (MRS) is a non-invasive technique that allows for the quantitative investigation of a number of in vivo metabolites, such as N-acetyl aspartate, creatine and choline, commonly interpreted as markers for
neuronal integrity, energetic status and membrane turnover respectively [1]. Recently, there has been significant interest in using edited MRS to reveal signals from less concentrated metabolites, such as GABA [2] [3], glutathione [4] and ascorbate [5]. Due to the fundamental insensitivity of MRS, larger measurement volumes are required for these edited experiments, typically on the order of (3 cm)$^3$ compared to (2 cm)$^3$ or less for traditional single-voxel MRS [6].

In cohort MRI studies, one common post-processing step is the co-registration of images either to each other, or to a standard-space template. Co-registration of images across a cohort allows comparisons between images to be drawn for anatomically equivalent regions, limited only by the quality of co-registration. In contrast, MRS is usually performed as a single-voxel measurement, and placement of voxels involves planning on the basis of predefined anatomical or functional landmarks. This is an irreversible anatomical judgment that cannot be mitigated by post-processing co-registration. For single-voxel acquisitions, the measurement acquired corresponds to the region prescribed without any further spatial resolution, or opportunity for spatial realignment. Conclusions drawn from MRS studies are usually based upon the functional role of a particular anatomical structure, and there is generally an implicit assumption that voxel placement is accurate and reproducible. To date, a landmark-based approach is the main method for edited MRS voxel placement. Given the reliance on anatomical landmarks, it is therefore particularly important to assess the reproducibility of voxel placement in MRS studies [7], especially for edited MRS experiments.

To our knowledge, no previous study has investigated the placement reliability of voxel for edited MRS, compared with traditional MRS. The increase in voxel size required for edited MRS of less concentrated metabolites may have several impacts on placement precision: displacement of the voxel by a fixed distance will have a relatively smaller impact on the voxel contents; larger voxels may suffer from additional anatomical restrictions; and operator care or judgment may be influenced by the size of the voxel to be planned. One further development that is relevant for studies of GABA is the increasing adoption of functionally motivated measurement regions, as opposed to anatomically defined studies. Tolerance of placement variance might be greater for a fronto-parietal region than a primary sensorimotor region, both because of the greater specificity of the functional definition and the qualitative difference in the conclusions likely to be drawn from such a study.

In this current study, the reproducibility of voxel placement for two anatomically defined and functionally motivated, regions of interest (occipital and sensorimotor), commonly used in MRS studies of sensory and motor function [8] [9] [10] [11], was assessed. Using the Dice overlap coefficient (DOC), placement precision both within-subject within-session, and between-subject was investigated. Differences between within- and between-subject results are discussed in terms of the interpretation of individually different anatomy and the limitations of the DOC.
2. Methods

2.1. Participants

13 healthy male subjects (all right handed, age 30 ± 6.1 years old) participated in the study. Only male participants were included to mitigate gender effects on brain anatomy and voxel localization. Written informed consent was obtained for each participant under the approval of the local Institutional Review Board prior to testing.

2.2. Edited-MRS

Data were acquired on a Philips 3T “Achieva” MRI scanner (Best, the Netherlands) using a 32-channel head coil for receive and body coil for transmit. For each participant, sagittal 1 mm³ isotropic T1-weighted (T1w) images (MP-RAGE) were acquired and resliced in axial and coronal views (TR = 7.99 ms, TE = 3.76 ms, Flip angle = 8°). GABA-edited MRS voxels were manually placed in two regions (with the visualized voxel in Figure 1 correct for the 3 ppm GABA signal) viewing all 3 planes by a single experimenter. A (3 cm)³ voxel was placed on the right sensorimotor cortex (SM1, Figure 1(b)) and was centered on the central sulcus posterior to the hand-knob [12] in the axial plane; the voxel was rotated to align with the cortical surface by rotating in the coronal plane and subsequently in the sagittal plane. A second (3 cm)³ voxel was placed in the occipital cortex (OCC, Figure 1(c)), centered on the midline and rotated in the sagittal slice to align along the cerebellar tentorium and placed as posterior as possible without including the sagittal sinus or skull. Each voxel was placed twice in all participants. The first placement was part of a standard GABA-edited MEGA-PRESS scan with the following scan parameters: TE/TR = 68/2000 ms, 320 transients acquired with editing pulses placed at 1.9 (edit-ON) and 7.5 (edit-OFF) ppm, 2 k bandwidth and VAPOR water suppression (as described in [8]). The second placement was only performed to log voxel location parameters, although minimal MRS data were acquired (a 12-second water acquisition). Prior to the second placement, voxel location and angulations were zeroed so that the voxel was centered approximately in the center of the brain without rotation, and independent placement was again performed on the basis of the landmarks described above. All voxel placements were performed by a single experimenter and participants were not removed from the scanner in between the first and second voxel placement. No additional information (e.g. screen shots of the first placement) was used for the second placement. A total of 51 MRS voxels’ data, from 13 participants were included in this study (1 subject’s second SM1 voxel was unavailable).

2.3. Analysis

The following image analysis pipeline was used (Figure 2):

1) Generation of the MRS voxel mask (Figure 2(a)). Each MRS acquisition volume was reconstructed as a binary mask in the image matrix of the T1w image of the same subject using the SVMask tool (in house software), which ex-
tracts the required geometric information from MRS and MRI file headers.

2) Brain extraction (Figure 2(b)). Skull-stripping of 3D T1w images was performed using the Brain Extraction Tool (BET, v2.1) [13], from the FSL suite.

3) Image co-registration (Figure 2(b)). T1w images were co-registered to (2 mm)$^3$ MNI standard-space brain using FMRIB’s Linear Image Registration Tool (FLIRT, v6.0) [14].

4) Voxel transformation to standard space (Figure 2(c)). For each subject, the transformation matrix determined in step 3 was applied to all the voxel masks generated in step 1 to give voxel masks in standard space (as shown in Figure 1).

2.3.1. Within-Subject Overlap

The quantification of voxel overlap within subjects between the two scans was performed using the Dice overlap coefficient (DOC [15]). The DOC is defined as the intersection volume, divided by the mean volume of the two voxels; it ranges between 0 and 1, where 1 represents perfect overlap. For example, A might refer to the first OCC voxel mask and B to the second OCC voxel mask:

$$\text{DOC} = \frac{2(A \cap B)}{A + B}.$$

Within-subject voxel overlap DOC was calculated using FSL tools in subject-space (rather than standard space), prior to step 2 above (as shown in Figure 2(a)).

2.3.2. Between-Subject Overlap in Standard Space

Between-subject voxel placement reliability was calculated using the first-placement voxel masks for each region from the 13 participants, registered to standard space. For each of the thirteen subjects, another subject was selected randomly (without replacement and prohibiting double comparisons e.g. 1-8 and 8-1) to generate thirteen unique pair-wise comparisons. The DOC was calculated for OCC and SM for each of these pairs. This process was repeated five times, so that in all 65 between-subject overlap coefficients were calculated for each region.

![Figure 1](image1.png)

*Figure 1.* MRS voxel placement. A single-subject voxel, shown in white, is superimposed on the average template brain, in standard space. Both occipital (a) and sensorimotor (b) regions are considered.
### 2.3.3. Voxel Density Images
In standard space, an image was calculated of the sum of the voxel masks of all subjects (separately for OCC and SM voxel). For each point in space, this image reflects how often that point is included in the different subjects’ MRS voxels.

### 3. Results

#### 3.1. Within-Subject Voxel Overlap
The overlap between the first and second voxel prescriptions for each subject were 87% ± 5% in the occipital region and 86% ± 5% in the SM region ([Figure 3](#)). The displacement between the centers of the two voxels was 2.6 ± 1.2 mm (mean ± standard deviation), with very similar average displacements for both the OCC and SM locations (2.66 mm for SM and 2.63 mm for OCC).

#### 3.2. Between-Subject Voxel Overlap
Mean between-subject voxel overlap was 75% ± 10% in OCC and 78% ± 7% in SM (as shown in [Figure 3](#) and [Figure 4](#)). Due to substantial variation in brain volume between subjects (from 1.05 liter to 1.50 liter for males [16]), the volume of the MRS voxels is scaled in standard space through the registration process. Voxel volumes were scaled relative to the mean by −13% to +15% (standard deviation 9%). The mean pair-wise volume mismatch is 11%.

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**Figure 2.** Schematic outline of the registration framework. Numbered steps correspond to the list in Analysis Methods above. (a) Voxel header information is used to reconstruct a voxel mask image (step 1). Masks from the two voxel placements (per region) are then compared to give the within-subject DOC; (b) T1W images are skull stripped (step 2) and co-registered to a standard-space template (step 3); (c) The co-registration transformation is applied to voxel masks (step 4), to allow between-subject DOC comparisons.
4. Discussion

It is a tacit assumption of the majority of single-voxel MRS studies that metabolite concentrations are measured from equivalent regions in each subject. It is therefore somewhat surprising that the fidelity of voxel placement has only occasionally been investigated in the literature [7] [17]. In order to evaluate the repeatability of voxel placement for MEGA-PRESS GABA scans, this study calculated the DOC both within-subject and, after image co-registration, between-subject. The primary results suggest the within-subject DOC is 85% in both occipital and sensorimotor measurement regions, and that the between subject DOC is 75% for a $3 \times 3 \times 3$ cm$^3$ voxel.

Figure 3. Overlap coefficients (DOC) calculations of MRS voxels within- and between-subjects. OCC = occipital; SM = sensorimotor.

Figure 4. Voxel density images. All the OCC (a) and SM (b) voxels are transferred to one standard space. The degree of spatial overlap illustrates the repeatability of MRS voxel placement procedures.
At first glance, these overlap numbers are surprisingly low; however, 85% overlap is equivalent to 5% (or 1.5 mm of one direction of a (3 cm)³ voxel) displacements along each of the three spatial directions, without any variability in rotations. The mean displacement between voxel centers is 2.6 mm, equal to the diagonal of a 1.5 mm cube, suggesting that displacement accounts for the majority of the overlap loss, with only minor losses due to rotation. Given that voxels are placed using T1w images with 1-mm-isotropic resolution, precision better than 1 mm in each direction would not be expected. Similarly, the 75% overlap between subjects corresponds to a 9% (or 2.7 mm) displacement along all three axes—again not substantially greater than the (2 mm)³ matrix on which co-registration was performed.

Some limitations arise from the choice of the Dice coefficient (DOC). Firstly, the DOC only reports on the overlap between the tissues contained in different voxels, and cannot address the impact that any change in voxel contents has on measured GABA concentration. Secondly, it is difficult to interpret the difference in DOC from within-to-between-subjects comparisons (85% vs. 75%). Some of this reduction in overlap is “real”, reflecting the operator’s variable interpretation of individual anatomy, while some of it is artifactual reflecting imperfections in co-registration on a (2 mm)³ matrix.

A further limitation of using the Dice coefficient in standard space is that two voxels with identical position and orientation that originate from different-sized brains will not give overlap of 100% due to a volume mismatch in standard space. In this special case, the Dice coefficient is less than 1 by half the fractional difference in volume between the brains. This suggests that the mean volume mismatch in our cohort (11%) therefore accounts for about half of the additional between-subject overlap loss compared to within-subject. Thus, while the DOC reflects the mathematical overlap between voxels, in standard space it does not report simply on operator reliability. One might even suggest that voxel volume should be scaled relative to total brain volume when MRS scans are prescribed (which would likely result in increased DOC), but this has signal-to-noise (SNR) and data quality implications also. Additional limitations are the consideration of only two voxel positions, the lack of within-subject between-session data, and the single operator prescribing voxels. Although the strong agreement between the two regions studied suggests that the findings may be generalizable, these results are likely to be affected to some degree by several factors including the complexity of the prescription protocol including the number of rotations, reproducibility of subject placement in the scanner (i.e. brain orientation in the anatomical images), and ease of identification of landmarks used (which may differ due to lesions, atrophy or normal/abnormal anatomical variation). Additional advances in co-registration, as well as an in-depth investigation of the effect of small changes in voxel tissue composition on GABA levels, would allow for a better understanding of the effect of small changes in voxel placement within and between subjects. Furthermore, we restricted our investigation to single-prescriber, single-scanner and single-session. For longitudinal or mul-
ti-center studies, the effects of multi-prescriber, multi-scanner, and multi-session on voxel localization and overlap would need to be investigated as well.

In practical terms, this study shows that voxel placement to a precision of 2 - 3 mm in three directions is possible, with care. Although these results give surprisingly low Dice coefficients of ~75%, this level of precision is approximately equal to the ability of subjects to remain motionless during the 10-minute scan. This agreement is only possible due to the rigorous specification of voxel placement protocol, including three-dimensional position and rotation information. Of particular note is the need to specify the order of multiple voxel rotations (which do not commute) for voxels. A range of voxel overlaps have been shown previously, from 57% within-subject for a small (15 mm)$^3$ parietal voxel [7] to 86% for a slightly larger (20 mm)$^3$ posterior cingulate voxel [17]. There is some evidence that automated voxel placement protocols, which typically calculate voxel location parameters from parameters co-registering images to standard space within-session, can perform as well as human operators and remove some variance [17], and prospective voxel placement correction has been demonstrated with a navigator-based acquisition [18]. Another methodological improvement is the use of voxel density maps (as used in Gaetz et al. [19]) to simultaneously display the position of MRS voxels and the placement precision across subjects.

5. Conclusion

In conclusion, the percentage of equivalent tissue included by 3 × 3 × 3 cm$^3$ MRS voxels in different subjects is surprisingly low at 75%. However, this corresponds to displacements of less than 3 mm along three axes, which seems to be relatively good agreement, and some fraction of this overlap loss is caused by brain volume mismatches. Within-subject agreement is ~85%, again low at first glance, but equivalent to acceptable 3D displacements of 1.5 mm in all three directions.

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Biometrics of the Cervical Spinal Canal and Cord by Computer Tomography in Togo

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Abstract

Studies on the canal dimensions of the cervical spinal are rare in Africa. The aim of this study is to provide normal values of the cervical spinal canal and spinal cord dimensions of adult people in Togo. It was about a twelve-year prospective study conducted in the main Hospitals of Campus Teaching Hospital. This study involved people of more than 18 years who neither presented any clinical signs nor spinal defect. The distances measured were antero-posterior 1 (APD1) and inter-pedicular (IPD) of the cervical spinal canal, the antero-posterior 2 (APD2) and the transverse (TD) diameters of the cervical spinal cord, followed with APD2/APD1 (R1) and TD/IPD (R2) research reports. The mean age was 38 ± 9.34 years old. The average of APD1 of the cervical spinal canal stood at 15.41 ± 0.55 mm, with a minimum of 10.48 ± 0.57 mm and a maximum of 25.00 ± 2.60 mm. The IPD average stood at 23.27 ± 1.67 mm with a minimum of 13.68 ± 1.46 mm and a maximum of 33.68 ± 1.46 mm. The average of DAP2 was 11.66 ± 0.66 mm, with a minimum of 10.7 ± 0.66 mm and a maximum of 12.77 ± 0.66 mm. The DT average stood at 15.55 ± 1.46 mm, with a minimum of 14.03 ± 2.43 mm and a maximum of 17.63 ± 1.82 mm. The ratio R1 (APD2/APD1) average was 0.80 ± 0.04, with a minimum of 0.76 ± 0.06 and a maximum of 0.85 ± 0.07. The ratio R2 (TD/IPD) average stood at 0.69 ± 0.14, with a minimum of 0.5 ± 0.12 and a maximum of 0.84 ± 0.08. The cervical spinal canal and the cervical spinal cord diameters in Togo are not significantly different from those described above.

Keywords

Cervical Spinal Canal, Cervical Spinal Cord, Biometrics, CT Scan-Togo
1. Introduction

Spinal stenosis is a major predisposing factor for cervical myelopathy and spinal cord injury [1] [2]. The spinal canal can be tightened congenitally or take the tight form by arthritic injuries resulting in its strong biomechanical implication [3]. The information with regard to the accurate dimensions of the spinal canal is important to suggest the diagnosis for the constitutional tight canal and the spinal surgery. Thus the scanning plays a crucial role for measuring the lumbar canal and the canal tightness diagnosis. The Computer Tomography (CT Scan) and the Magnetic Resonance Imaging (MRI) are the most efficient and the most used imagery tools to diagnose the tightness of the cervical canal. It is seldom to encounter studies that deal with the normal dimensions of the cervical spinal canal and cervical spinal cord in Black Africa. Hence, few studies have assessed the dimensions of the spinal cord, either in terms of MRI or CT Scan. So, we undertook this work to determine in, by CT scan, the biometrics of the cervical spinal canal and cervical spinal cord of adult people in Togo, and then assess the ratio between the cervical spinal cord and cervical spinal canal.

2. Material and Method

It was prospective study carried out over a twelve-month (12) period at the university hospital center of the campus. It concerns CT Scans of adults people of more than 18 years, who did not present any clinical sign of neck pain or cervicobrachial neuralgia. We excluded from our study the cervical spinal which presented malformation, degenerative, infectious, rheumatic, traumatic lesions or spinal surgery backgrounds.

The studies have been carried out on General Electric’s CT Scan. The volume acquisition has been realized on the cervical spinal. The stocked images have been processed on the image processing console with the measurement tools that facilitate the enlargement and rotation.

The measurement of the dimensions of the cervical spinal canal and spinal cord was realized on pedicular axial CT Scan cuts.

The distances measured were the antero-posterior (APD1) and inter-pedicular (IPD) diameters of the cervical spinal canal, as well as the antero-posterior (APD2) and transverse diameters (TD) of the spinal cord. Then we assessed APD2/APD1 (R1) and TD/IPD (R2) ratio.

APD1 has been measured between the posterior edge of the vertebral body and the fore junction of the blades (Figure 1).

IPD represents the longest distance between two pedicles (Figure 1).

APD2 has been measured between the anterior and the posterior edges of the spinal cord (Figure 2), at the same level as the APD1, in order to assess their ratio (R1).

TD has been measured between the right and the left edges of the spinal cord (Figure 2), at the same level as the IPD, in order to assess their report (R2).

The data have been processed and analyzed with Epi info 7 and Microsoft Excel software.
Figure 1. Measurements of anteroposterior diameter (APD1) and interpedicular diameter (IPD) of cervical spinal canal.

Figure 2. Measurements of anteroposterior diameter (APD2) and transverse diameter (TD) of cervical spinal cord.

3. Results

Our study involved 350 CT Scans of the cervical spinal. The mean age stood at 35 ± 10.55 years old. Both genders were involved, with 217 men (62%) and 133 women (38%).

The average of the APD1 stood at 14 ± 2.1 mm, with a minimal average of
12.7 ± 1.5 mm and a maximal average of 18.3 ± 1.9 mm. The highest average was at C1 and the lowest at C3, C4 and C5 (Table 1).

The IPD average was 24 ± 1.3 mm, with a minimal average of 22.2 ± 1.8 mm, and a maximal average of 26 ± 1.9 mm. We found the highest average at C1 and the lowest at C2 and C3 (Table 2).

The APD2 average was 11.66 ± 0.66 mm, with a minimal average of 9.1 ± 0.67 mm and a maximal average of 10.5 ± 1.5 mm. The highest average was found at C1 then at C2. From C3 to C7, the averages were slightly lower, but substantially equal (Table 1).

Table 1. Measures of Antero-Posterior Diameters (APD1) of the cervical spinal canal and the cervical spinal cord (APD2), and the ratio of the APD1 on the dural sac APD.

| SPINAL CANAL (APD1) | SPINAL CORD (APD2) | RATIO 1 (R1) |
|---------------------|---------------------|-------------|
| Min - Max | Mean | Min - Max | Mean | Min - Max | Mean |
| C1 | 15.4 - 21 | 18.3 ± 1.9 | 8.5 - 14 | 10.5 ± 1.5 | 0.43 - 0.68 | 0.54 ± 0.09 |
| C2 | 12.3 - 17.7 | 15.5 ± 2.2 | 7.4 - 11.1 | 9.33 ± 1.3 | 0.49 - 0.67 | 0.58 ± 0.07 |
| C3 | 10.3 - 14.2 | 12.7 ± 1.4 | 7 - 10.5 | 8.6 ± 1.0 | 0.43 - 0.67 | 0.55 ± 0.07 |
| C4 | 10 - 15 | 12.7 ± 1.5 | 7 - 10 | 8.6 ± 0.9 | 0.44 - 0.65 | 0.54 ± 0.05 |
| C5 | 11.1 - 14.6 | 12.6 ± 1.3 | 7.7 - 10 | 8.9 ± 0.6 | 0.46 - 0.64 | 0.54 ± 0.05 |
| C6 | 11.6 - 14.4 | 13.3 ± 1.3 | 7.2 - 11.6 | 9 ± 1.3 | 0.48 - 0.64 | 0.56 ± 0.06 |
| C7 | 11.2 - 14.7 | 13.1 ± 1.2 | 8 - 10 | 8.7 ± 0.6 | 0.44 - 0.77 | 0.55 ± 0.1 |
| General average | 12.7 ± 1.5 | 9.1 ± 0.67 | 14 ± 2.1 | 11.66 ± 2.5 | 0.57 ± 0.05 |

P values are higher than 0.05: absence of statistically significantly difference of diameters and the ratio between the male and female sex.

Table 2. Measures of the Inter-Pediculaire Diameter (IPD) of the cervical spinal canal and the Transverse Diameter (TD) of the cervical spinal cord, and the ratio of the IPD on the TD.

| SPINAL CANAL (IPD) | SPINAL CORD (TD) | RATIO 2 (R2) |
|---------------------|---------------------|-------------|
| Min - Max | Mean | Min - Max | Mean | Min - Max | Mean |
| C1 | 22 - 28.6 | 26 ± 1.9 | 11 - 17.7 | 14.63 ± 2.5 | 0.51 - 0.7 | 0.57 ± 0.05 |
| C2 | 20 - 26.4 | 22.2 ± 1.8 | 10.4 - 15 | 12.8 ± 1.5 | 0.55 - 0.66 | 0.6 ± 0.04 |
| C3 | 20.3 - 24.6 | 22.5 ± 1.2 | 10.4 - 13.6 | 12.3 ± 1.3 | 0.6 - 0.78 | 0.67 ± 0.05 |
| C4 | 22.4 - 26.4 | 24 ± 1.2 | 10 - 15.7 | 13.1 ± 1.5 | 0.6 - 0.79 | 0.68 ± 0.05 |
| C5 | 22.3 - 27.4 | 24.5 ± 1.8 | 7.7 - 10 | 9 ± 0.6 | 0.61 - 0.8 | 0.7 ± 0.06 |
| C6 | 22 - 28.4 | 24.5 ± 1.9 | 11.5 - 16.5 | 13.7 ± 1.5 | 0.6 - 0.75 | 0.67 ± 0.05 |
| C7 | 22 - 25.3 | 23.6 ± 1.3 | 10.3 - 17.7 | 13 ± 2.4 | 0.57 - 0.9 | 0.66 ± 0.09 |
| General average | 22.2 ± 1.8 | 9 ± 0.6 | 24 ± 1.3 | 12.64 ± 1.77 | 0.57 ± 0.05 |

P values are higher than 0.05: absence of statistically significantly difference of diameters and the ratio between the male and female sex.
The TD average stood at 12.64 ± 1.77 mm. The Minimal TD average was 9 ± 0.6 mm and the maximal average was 14.63 ± 2.5 mm. The highest average was at C1 and the lowest at C5 (Table 2).

The average of R1 was 0.55 ± 0.01, with a minimal average at C4 and C5 (0.54 ± 0.05 mm) and maximal average at C2 (0.58 ± 0.07). All R1 were lower than 0.8 at all levels (Table 1).

The R2 average R2 stood at 0.65 ± 0.04, with a minimal average at C1 (0.57 ± 0.05 mm) which progressively increased to C5 (0.7 ± 0.06 mm) and then decreases to C7 (0.65 ± 0.04 mm). The R2 were lower than 0.9 at all levels (Table 2).

While comparing the measurements of the cervical spinal canal (APD1 and IPD) and the spinal cord (APD2 and TD), as well as R1 and R2 between the two genders, we found that there is no significant difference (Table 3).

4. Discussion

Knowing the normal values of the spinal canal is important, because it enables to detect central canal stenosis by reduction of the canal caliber [4].

The antero-posterior diameter of the cervical spinal canal (APD1) is important in traumatic, degenerative and inflammatory situations, and a small diameter of APD1 is associated to the increase of lesions occurrence [5]. Generally, it is admitted that a cervical canal stenosis exists when the APD1 of the cervical canal is under the threshold of 12 mm [5] [6]. The global average of the APD1 cervical spinal canal in our study stood at 14 ± 2.1 mm, with a larger APD1 at C1 and the lowest at C3, C4 and C5. We noticed a decrease of APD1 from C1 to C5. Singh et al. [7], as well as Gupta et al. [8] in India found an average higher (17.05 ± 1.61 mm) than ours. The average of our study is close to that of Lee et al. [9] in Korea, to Taitz [10] in South Africa and Gepstein [11] in Israel. Few studies [4] [10] found the smallest APD1 at C3. Some studies [7] [9] [12] found a smallest

| SPINAL CANAL | SPINAL CORD | RATIOS |
|--------------|-------------|--------|
|              | APD1        | IPD    | APD2 | TD   | R1   | R2   |
| C1           | 0.93        | 0.99   | 0.96 | 0.96 | 0.94 | 0.96 |
| C2           | 0.97        | 0.99   | 0.90 | 0.94 | 0.90 | 0.94 |
| C3           | 0.99        | 0.98   | 0.90 | 0.91 | 0.94 | 0.95 |
| C4           | 0.96        | 0.99   | 0.92 | 0.94 | 0.95 | 0.95 |
| C5           | 0.95        | 0.99   | 0.98 | 0.95 | 0.92 | 0.96 |
| C6           | 0.95        | 0.99   | 0.95 | 0.93 | 0.94 | 0.97 |
| C7           | 0.94        | 0.96   | 0.96 | 0.94 | 0.96 | 0.95 |

P values are higher than 0.05: absence of statistically significantly difference of diameters and the ratio between the male and female sex.
APD1 at C4. For most studies [7] [8] [10] [11] [13], the smallest APD1 would stand at C5. It necessary to consider that regardless of the type of population, the smallest APD1 would stand generally in C3, C4 or C5 as we mention it in our study. Singh et al. [7] found a decrease of the APD1 from C1 to C5. UlbriCH [14] noted a lowering from C1 to C6. Other studies [13] [15] noticed a fall from C1 to C4 with an increase to C5 and a decrease to C6. Our study as well as Singh et al. [7] has not found any statistical significant difference between the APD1 of the cervical spinal canal of men and those of women. However, Evangepolos et al. [13] noticed a significant difference between the genders at C1. The comparison of the APD1 of our study with those of Singh et al. [7] on the one hand and with those of Evangepolos et al. [13] on the other hand, revealed that the differences are not statistically important. As for Taitz [10], the APD1 would be larger with White people than Black people, without any important difference. It is thus considered that the cervical spinal canal biometrics would not be in relation with the phenotype. Measurements from Asians, Europeans and Africans would be the same. According to the study of Chazono et al. [16], a possible ethnic difference of the APD1 would exist, with a larger APD1 with Europeans and Americans than with Asians.

With regard to the interpedicular diameter of cervical spinal canal (IPD), our study found out a global average of 24 ± 1.3 mm with a variation from 22.2 ± 1.8 mm to 26 ± 1.9 mm. We observed a higher average at C1 and lower average at C2 and C3. The averages of our study are comparable to that of Chazono et al. [16], who found out averages varying from 22.6 mm à 27.5 mm, with a minimal average at C3 for Asian people (22.6 mm) and a maximal average in C5 for European and American people (27.5 mm). As for Chazono et al. [16], many studies found out the lowest IPD at C3 and the highest at C5. Like our study, Chazono et al. [16], have not found any significant statistical difference of IPD between ethnic groups.

Few studies concerning the measurement of the cervical spinal cord exist [14]. Studies [17] revealed that the average of antero-posterior diameter of the cervical spinal cord (APD2) varies between 5 mm and 6 mm. Our study found out an average of APD2 higher than 11.66 mm ± 0.66 with a variation from 9.1 mm ± 0.67 à 10.5 mm ± 1.5. Yet, the diameters measurement of the cervical spinal cord only would not enable to determine a cervical spinal cord compression. But when the measurement of the cervical spinal cord is coupled with that of the cervical spinal canal, it is possible to calculate the gap or to establish the relationship between the two. Tierney et al. [2], in their study, measure the gap between the spinal cord and the spinal canal by calculating the difference between the two. Our study considered the relationship between the cord and the canal, with a global average ratio of 0.55 ± 0.01, minimal at C4 and C5 (0.54 ± 0.05 mm) and maximal at C2 (0.58 ± 0.07) in the antero-posterior plan. In the transverse plan, the global average ratio was 0.65 ± 0.04, with a minimal average at C1 (0.57 ± 0.05 mm) which was increasing progressively until C5 (0.7 ± 0.06 mm); then it decreases to reach C7 (0.65 ± 0.04 mm). There is no study concerning the
relationship between the cord and the medullar canal regardless of in the antero-posterior plan or in the transverse plan. It is acknowledged that the spinal cord compression is due to an inadequacy between the cord and the medullar canal [18]. The gap around the spinal cord would diminish at the level of the cervical low segment [2], increasing the risk of medullar compression at this level [19] [20]. In our study, the smallest antero-posterior ratio stands in C4 and C5, and the largest ratio stands in C2. With regard to transverse plan report, our study found out an increase of the ratio from C1 to C5, then a decrease from C5 to C7. The assessment of the gap around the cord would be more contributing than the diameters of the canal and the spinal cord and the medullar canal in the determination of the spinal cord compression [21].

5. Conclusion

CT scan can provide accurate cervical spinal canal and spinal cord measurements that could serve as a useful guide in the determination of the cervical canal stenosis. The dimensions of the cervical spinal canal and spinal cord in healthy individuals are dependent on spinal level. The consideration of these normal values should help radiologists and clinicians to interpret CT scan.

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Cerebellar Haemangioblastoma Diagnosed as Giant Tuberculoma: Falacies of Magnetic Resonance Spectroscopy—Case Report

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Abstract

Background: Posterior fossa haemangioblastoma tumors are slightly rare and these originate from the brain blood vascular network. Cerebellum and brain stem are the commonest places of occurrence. These are benign and produce symptoms quite late because of their slow growing asymptomatic nature.

Case report: We present 24-years old female who was wrongly diagnosed as having giant tuberculomas of the posterior fossa by MR spectroscopy. Contrast enhanced computerized tomography (CECT) and magnetic resonance imaging (MRI) studies had shown the results more in favor of tuberculoma. She was given anti-tubercular therapy (ATT) but without any much improvement. The condition aggravated by causing obstructive hydrocephalus at the level of fourth ventricle. The patient was operated upon for the mass lesion and on histopathology; it was proved to be a case of cerebellar haemangioblastoma.

Conclusion: MR spectroscopy can sometimes be misleading and can lead to mismanagement. The reliability of spectroscopy is debatable and has to be decided on the merits along with clinical symptomatology.

Keywords

Haemangioblastoma, MR Spectroscopy, CECT, MRI, ATT, Hydrocephalus

1. Introduction

Haemangioblastomas constitutes 8% - 12% masses of the posterior fossa masses as compared to 1% - 2.5% of all the brain tumors. These are benign tumors but
derive their blood supply from the pial vessels. These often produce symptoms by compressing the neighboring structures [1]. Haemangioblastomas are twice common in men than women and majority of these falls in 20 - 40 years age group. These have been labeled as WHO grade I benign tumors originating from the blood vessels. Sometimes the inferences of the imaging modalities can confuse the diagnosis which leads to the mismanagement as was in our case.

2. Case Report

24-years female reported to the outpatient department with complaints of headache of one year duration. She had occasional difficulty of balancing herself while walking. There was history of off and on low grade fever with slight evening rise in nature. She was diagnosed as posterior fossa giant tuberculomas on the basis of imaging studies and biomedical investigations. Pre-operative non contrast computerized tomography (NCCT) of head had shown posterior fossa mass which was compressing upon fourth ventricle leading to hydrocephalus (Figure 1(a) and Figure 1(b)).

Post contrast study had shown enhancement of the solid part with cystic component as hypo dense region (Figure 2).

MRI studies have shown a mixed intensity structure with avid enhancement of the mural nodule. Spectroscopy of the tumor had shown lipid and lactate peaks without any significant choline rise. NAA peak was decreased with increased Choline/Creatinine ratio. Though the possibility of haemangioblastoma was kept, but as per the laboratory investigations, spectroscopy and presentation she was labeled as a case of giant tuberculomas (Figures 3(a)-c, Figure 4(a) and Figure 4(b) and Figures 5(a)-c)).

She was put on ATT for six months after these findings. However the condition deteriorated and the patient had to undergo surgical excision of the mass. Histopathological findings confirmed the diagnosis of Hemangioblastoma. The

![Figure 1.](image)

NCCT head axial sections: (a) at third ventricle level (white arrow) which shows moderate hydrocephalus (white stars); (b) at slightly lower level with mass lesion in the posterior fossa having mixed solid and cystic components (white inverted arrow).
Figure 2. CECT brain axial section: There is enhancement of the solid part of the tumor (horizontal arrow) in the posterior fossa with surrounding hypodense area (white star).

Figure 3. MR study of the same patient: (a) T1W axial section shows mixed intensity lesion (inverted white arrow) with compression of fourth ventricle (thin horizontal white arrow); (b) T2W axial section shows hyperintensity in the posterior fossa depicting peritumoral oedema predominantly on right side with hypointense peripheral solid lesion (inverted black arrow). Frontal horns on both sides shows dilatation (white arrow); (c) T1W post contrast sagittal section shows intense enhancement of the solid component (inverted white arrow) with dilatation of ventricular system (white star).

Figure 4. MR Spectroscopy: (a) T1W post contrast axial section with single voxel study; (b) MR spectroscopy shows increased lipid and lactate peaks. N-acetylaspartate peak is decreased with increased Ch/Cr peak.
specimen was predominantly constituted abundant vacuolated stromal cells with capillary network (slides not available). Post operation CT scan was done after one month had shown encouraging result without any residual tumor.

Post surgical recovery was uneventful and the patient had been kept on six monthly follow up.

3. Discussion

Haemangioblastomas are slow growing tumors with tendency to rupture. These remain undiagnosed for a long time because of their asymptomatic nature. This has got a close association to the tune of 25% with von Hippel Lindau disease and rest 75% are of sporadic in nature [2]. Common complaints are headache in 70% of the cases and 50% report with hydrocephalus. These tumors cause disturbances in movements, equilibrium and muscle tone because of cerebellar involvement. The coordination of movements is always affected. There can be sudden bleeding inside the cranial cavity because of the rupture which is a medical emergency. These can cause hydrocephalus because of compression over the CSF pathway.

Magnetic resonance imaging and computerized tomography imaging are the modalities of choice for their evaluation. On CEMRI and CECT of the brain these are well demarcated cystic masse with mural nodule and non enhancing wall [3]. Mural nodule within this cystic mass enhances vividly [4]. MR spectroscopy of haemangioblastoma shows high lipid peak without any lactate peak. Coline peak is raised with low creatinine/phosphocreatinine ratio. N-acetylaspartate (NAA) is absent which indicates of non neurogenic origin of these tumors. MR spectroscopy in our present case had shown increased lipid peak, decreased NAA peak and increased Choline/Creatinine ratio and this was the reason for labeling her as a case of giant tuberculomas [5] [6] [7].

Management is always by surgical intervention and Gamma knife radio surgery has become the fashion of the day. The tumors can partially be drained before surgery as these constitute mixed pattern of solid and cystic. Pre surgical embolisation is done to minimize the blood loss and neat surgical excision [8].
Recurrence is seen in 25% of the cases associated with von Hippel-Lindau syndromes.

4. Conclusion

Hemangioblastomas can be best diagnosed by the modalities like CECT and MR contrast studies. But sometimes spectroscopy can mislead the issue of final diagnosis as happened in this case.

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Consent of the Patient

Written consent of the patient was taken for publishing this case.

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Cystic Mediastinal Schwannoma Presenting as Pleural Effusion

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Abstract

Cystic schwannoma represents a neurogenic tumor of the mediastinum rarely reported in literature. Its rupture in the pleural cavity remains exceptional. We hereby report the case of a patient who presented with pleurisy for which diagnostic imaging including thoracic MRI revealed a cystic schwannoma ruptured in the pleura. This case, to the best of our knowledge, represents the very first of its kind reported in literature.

Keywords

Posterior Mediastinum, Schwannoma, Neurogenic Tumor, Computed Tomography, Magnetic Resonance Imaging

1. Introduction

Schwannomas are rare nerve tumors, accounting for 2% of neurogenic mediastinal tumors [1]. This tumor, usually poly-lobulated, rounded and well encapsulated, is generally located in the para vertebral groove around the intercostal nerve [2]. It is often discovered fortuitously as it is usually asymptomatic, or even more rarely in the event of compression of adjoining organs [1].

We deem highly interesting to report the case of a large cystic mediastinal schwannoma ruptured in the pleura, whose diagnosis was suspected on CT and confirmed on magnetic resonance imaging.

2. Case Report

Mrs. MS, 40-year-old female with no prior clinical history, referred to our unit
for diagnostic imaging. Extensive diagnostic imaging was required for a gradual worsening of a sub-acute chest pain with pleural effusion on plain chest X-ray dating few weeks prior to her referral.

Physical examination found a conscious patient, having a febrile with dyspnea and good general condition. Plain chest X-ray showed a right side opacity occupying almost the entire right lung space consistent with abundant pleural effusion.

Further work was done with thoracic CT revealing a voluminous heterogeneous cystic lesion of the left para vertebral foramen with posterior mediastinum extension, widening of D10-D11 foramen, a scalloping effect on the left vertebral pedicle and abundant left pleurisy (Figure 1). In the presence of a cystic lesion of costo-vertebral location with associated mediastinal extension and pleural effusion, the diagnosis of a schwannoma ruptured into the pleura was suspected.

To further confirm the diagnosis, MRI was considered necessary to study its endocanal extension. It revealed a large solido-cystic lesion taking up para vertebral space and extending through the left D10-D11 intervertebral foramen and to the ipsilateral pleural space.

Solid component appeared hypo-intense T1-T2 and was slightly enhanced after contrast medium injection. Cystic component had a parietal discontinuity coming into contact with ipsilateral pleural cavity with abundant effusion at this level (Figure 2).

Pathology examination generally reveals spindle shaped cells, with palisade nuclei and hyalin inclusions associated with cystic and ischemic zones. An intense and diffuse staining with PS100 (K1 67 in 10%) could be observed on immunohisto-chemistry (Figure 3).

The diagnosis of cystic mediastinal schwannoma ruptured into the pleural cavity was retained and the patient was referred for surgery where a complete tumor resection had been performed. Immediately postoperative recovery was uneventful with good clinical course up to date.

**Figure 1.** Chest CT scan, lung and thoracic cage window with iodinated contrast medium injection: large solido-cystic para spinal lesion of posterior mediastinum (a), enlarging the foramen between D10 and D11 with a scalloping effect on the left vertebral pedicle (b) (arrowhead) and associated abundant pleurisy.
Figure 2. Thoracic MRI (from left to right) sequences T2, T1 and T1 with gadolinium showing a large lesion solido-cystic of the left para vertebral foramen and process extending through to the left D10 foramen and the ipsilateral pleural space and whose solid component appears hypo intense T2 and T1 ((a) and (b)) enhanced significantly following contrast (c) (arrowhead). The cystic component has a parietal discontinuity contacting the ipsilateral pleural cavity with pleurisy.

Figure 3. Pathology image showing spindle shaped cells with palisade nuclei, associated cystic and necrotic zones of ischemia (a) with intense staining with PS100 (KI67 à 10%) on immuno-marking (b).

3. Discussion

Schwannoma, also called neuroma is a rare tumor representing only 2% of all neurogenic mediastinal tumors [1] [3] [4]. This tumor, made up of cells forming the Schwann sheath, usually affects young adults between 20 and 50 years, with a female predominance, as was the case in our patient. [5] The circumstances of discovery are in most cases fortuitous with symptoms in relation to compression of adjoining structures. It could present as dyspnea or most often as cough associated with chest pain [3] [5].

In the case of our patient notwithstanding, the discovery of a schwannoma after rupture into the pleural cavity constitutes a rare clinical phenomenon. Thus representing to the best of our knowledge of recent literature, the first case of mediastinal cystic schwannoma ruptured in the pleura whose clinical setting was dominated by gradual onset of dyspnea.

In the presence of a mediastinal schwannoma, thoracic CT should be considered as an essential first-line imaging tool. It allows characterization of the lesion by determining its size, its outline, but above all, it confirms the presence of a cystic component or otherwise. Contrast medium injection improves its sensi-
tivity as it shows a significant enhancement of the solid component vis-a-vis the cystic component as was the case in our patient [3] [4] [6] [7]. MRI allows the study of its links with adjacent mediastinal structures as well as foraminal and endocanal extension as evidenced in our patient where foraminal extension was detected on MRI [8].

Given all the above clinical and radiological arguments we concluded the diagnosis of cystic mediastinal schwannoma ruptured in pleura. The patient was referred for surgical management.

4. Conclusion

This case relates a particular mode of revelation of cystic mediastinal schwannoma whose rupture constitutes its main peculiarity. In the presence of a cystic lesion of the posterior mediastinum, the diagnosis of a nerve tumor in the mediastinum such as schwannoma should be considered. Diagnostic workup should include not only a CT scan but also an especially MRI as its enhanced resolution, facilitating the positive diagnosis while eliminating other differential diagnosis such a hydatid cyst especially in endemic areas.

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Safety and Diagnostic Image Quality of Ultravist® in an Unselected Sub-Set of Chinese Patients: Data Analyses from a Previous Post Marketing Surveillance

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Abstract

Background: Iopromide (Ultravist®) has been shown to be a very safe CM agent in previous post-marketing surveillance studies on Western and Asian populations. Our study aimed to analyse data pertaining to the safety, tolerability and diagnostic image quality of Iopromide in an unselected sub-set of the Chinese population. Methods: we analysed data for Chinese ambulatory and in-patients who received Iopromide for an imaging procedure (in accordance with the local package insert and routine clinical practice), as part of an international post-marketing surveillance study. Use of premedication was at the discretion of the attending physician. Patient demographics, clinical history, type of examination, contrast quality and tolerability, including pre-specified adverse drug reactions, were recorded. All statistical analyses were descriptive. Results: case report forms for 20,000 Chinese patients (61.3% men) were analysed, of whom 153 patients (0.77%) had risk factors for idiosyncratic contrast media reactions (at-risk group). Use of premedication, most commonly corticosteroids, was recorded for 5658 patients (28.3%) and 86 at-risk patients (56.2% of the at-risk group), respectively. The mean (± standard deviation) dose of iodine administered was 29 ± 5.5 g. During the physician’s evaluation of image parameters, contrast quality was considered to be “good” (64.7%) or “excellent” (29.3%) in the majority of patients. 571 patients (2.9%) experienced at least one adverse drug reaction [most frequently nausea (0.70%) and dysgeusia (0.62%)], which were typically transient and of mild intensity. Two serious adverse drug reactions were reported [edema (n = 1), decreased blood pressure and dyspnea (n = 1)]. The incidence of adverse drug reactions was increased in the at-risk group versus the overall patient popula-
tion, and tended to reduce with premedication (mainly corticosteroids). Conclusions: Iopromide was well tolerated and proved to be an efficient contrast agent in a large, non-selected sub-set of Chinese patients undergoing different types of diagnostic imaging procedures.

Keywords
Contrast Media, Iopromide, Adverse Drug Reaction, Chinese Sub-Population, Post-Marketing Surveillance

1. Introduction
Iodinated contrast media (CM) have been administered safely in millions of people worldwide [1], and constituted a crucial tool that is frequently used for imaging procedures carried out during diagnostic clinical practice. The first iodinated CM to be used for the purpose of diagnostic imaging was sodium iodide (1920), subsequent to which Sodium and Meglumine salts of tri-iodinated benzoic acid derivatives were developed in the 1950s. These CM were hyperosmolar (>1400 mOsm/kg), with an osmolality five to eight times that of blood [2]. Since then, low osmolality (600 - 850 mOsm/kg), non-ionic CM agents have been developed and Iopromide is one such example. The safety and tolerability of this agent has already been evaluated in previous post-marketing surveillance studies carried out on Western as well as Asian populations [3]. Currently, several different CM are available and while the use of iodinated CM has proved relatively safe [4] [5] [6] [7] [8], adverse drug reactions (ADRs) to these agents, although extremely rare, have been documented before. Risk factors such as a history of CM reactions, allergy and asthma increase the incidence of ADRs associated with their use [1] [9] [10].

Numerous iodinated CM are currently available in China, such as Iodixanol (Visipaque) and Iopromide (Ultravist®; Bayer Healthcare Pharmaceuticals), among others [11]. While their safety profiles have already been established as part of routine clinical trials that preceded their marketing and commercialization; extensive post marketing surveillance on a large number of patients is required in order to identify and determine the frequency of all extremely rare adverse drug reactions that may occur. To our knowledge, such a non-interventional study that seeks to quantify the rate of ADR and AE occurrence due to Iopromide use in an unselected Chinese population has not been conducted so far. The patient population analysed in this manuscript was recruited during the execution of a large, international, multi-centre, post marketing surveillance carried out in order to assess the safety and tolerability of Iopromide in various populations. The majority (44.6%) of patients who enrolled were from centres in China, and this study focuses on the detailed analysis of data from these Chinese patients in order to determine the safety and tolerability of Iopromide based on patient parameters such as pre-existing risk factors and use of pre-medication.
Additionally, a subjective analysis of diagnostic image quality based on the investigators’ evaluation has also been included in our analyses.

2. Methods

2.1. Study Design and Conduct

The rationale, design and conduct of the study from which data were collected and analyzed has previously been reported in detail [12]. Briefly, Data analysed in this manuscript were obtained during the conduct of a prospective, phase IV post-marketing surveillance study [Iopromide (UltrAvist)—to Gain further information on tolerability and safety in X-ray Examination (IMAGE) study] (ClinicalTrials.gov identifier: NCT00876083) conducted in 21 countries in Europe and Asia and sponsored by Bayer HealthCare Pharmaceuticals, Berlin, Germany. Patients undergoing an X-ray or computed tomography (CT) examination, for which the investigator had elected to use Iopromide, were eligible. The 44,835 patients who comprised the overall patient population, a majority, i.e., 20,000 (44.6%) were from China, with 56 centres in China participating in the study. Iopromide was administered in a routine manner, based on investigator discretion and procedure requirements and in accordance with recommendations in the local package insert.

2.2. Ethical Approval

This study was non-interventional and was conducted in a routine clinical setting in accordance with local and international legal and ethical requirements, which did not necessitate the provision of written informed consent from Chinese subjects.

2.3. Observational Plan

Investigators used case report forms (CRF) to capture demographic data, patient clinical history (including risk factors), drug administration, type of examination, contrast quality and tolerability, as previously described [12]. Briefly, CRFs recorded patient parameters such as demographics, concomitant diseases, pre-and concomitant medications, examination region, indication, contrast medium volume, type of application and examination, contrast quality, and adverse events. Paper CRFs were converted to electronic CRFs using a double data entry process and validated electronic edit checks were performed on all CRFs. In case any queries arose regarding the information recorder in the CRFs, they were redirected to the investigator wherever necessary. Investigators assessed image quality according to five qualitative categories: excellent, good, adequate, non-diagnostic and not specified.

2.4. Iopromide Administration

Patients requiring administration of iopromide for an imaging procedure were considered eligible for inclusion. The administration of Iopromide and any premedication was at the discretion of the investigator, providing it was in ac-
cordance with the local package insert. Two formulations of iopromide were compared in this study, Ultravist®-300 [1 mL contains 623 mg of iopromide (equivalent to 300 mg iodine)] and Ultravist®-370 [1 mL contains 769 mg of iopromide (equivalent to 370 mg iodine)].

2.5. Adverse Events and Adverse Drug Reactions

Investigator-observed adverse events (AEs) and pre-specified ADRs of interest that occurred within the observation period (30 - 60 min according to the local packaging information) were recorded in a separate questionnaire, and as free text, in terms of symptoms, onset, duration, intensity, and causal relationship (see [12] for further details). The intensity of each event was classified by investigators as mild, moderate, or severe (In line with the recommendations of the ACR Manual on Contrast media [20]). Mild symptoms included scattered urticaria, pruritus, rhinorrhea, nausea, brief retching, and/or vomiting, diaphoresis, coughing and dizziness. Moderate symptoms included persistent vomiting, diffused urticaria, headache, facial edema, laryngeal edema, mild bronchospasms or dyspnea, palpitations, tachycardia or bradycardia, hypertension and abdominal cramps. Severe symptoms included life-threatening arrhythmias (i.e., ventricular tachycardia), hypotension, overt bronchospasm, laryngeal oedema, pulmonary oedema, seizures and syncope. In addition, events were designated as serious if they met one of the following criteria: resulted in death; were life-threatening; required inpatient hospitalization/prolongation of current hospitalization; resulted in persistent or significant disability/incapacity; or resulted in a congenital anomaly/birth defect. ADRs of special interest included injection site warmth and/or feeling hot, nausea and/or vomiting, urticaria, erythema, rash and/or papular rash, cough and/or sneezing, dyspnea and/or bronchospasm, and changes in blood pressure (increase and/or decrease). ADRs were compared between all patients and at-risk patients (those with history of bronchial asthma, allergies, and/or contrast media reaction). Injection site warmth, feeling hot or injection site pain of mild intensity were defined (post-hoc) as tolerance indicators. No laboratory tests were required.

Patients were also asked to complete questionnaires to record AEs. Special attention was paid to ADRs among patients with risk factors for idiosyncratic CM reactions, specifically asthma, allergy and/or prior history of the occurrence of such reactions (at-risk group).

2.6. Statistical Analysis

Results are reported for all evaluable patients in the Chinese population, i.e. eligible patients with documented evidence of receiving iopromide. Qualitative descriptive statistical analyses were conducted.

3. Results

Patient demographics and clinical characteristics of the Chinese subpopulation included in this study are presented in Table 1. The majority of patients were
Table 1. Patient demographics and clinical characteristics.

| Demographic Characteristics                        | All patients (N = 20,000) |
|----------------------------------------------------|--------------------------|
| Sex, n (%)                                         |                          |
| Male                                               | 12,260 (61.3)            |
| Female                                             | 7740 (38.7)              |
| Not specified                                      | 2 (0.01)                 |
| Mean age, y (SD)*                                  | 54 (15.4)                |
| Age category, n (%)                                |                          |
| <18 y                                              | 355 (1.8)                |
| 18 - 39 y                                          | 2837 (14.2)              |
| 40 - 59 y                                          | 9088 (45.4)              |
| 60 - 79 y                                          | 7005 (35.0)              |
| ≥80 y                                              | 676 (3.4)                |
| Not specified                                      | 39 (0.20)                |
| Patients with any concomitant disease, n (%)†      | 9042 (45.2)              |
| Reduced general condition                          | 3483 (17.4)              |
| Hypertension                                       | 1581 (7.9)               |
| Coronary heart disease                             | 1417 (7.1)               |
| Diabetes mellitus                                  | 541 (2.7)                |
| Autoimmune disorder                                | 214 (1.1)                |
| Renal insufficiency                                | 193 (1.0)                |
| Cardiac arrhythmia                                 | 166 (0.83)               |
| Thyroid disorder                                   | 93 (0.47)                |
| Allergy                                            | 82 (0.41)                |
| Asthma                                             | 69 (0.35)                |
| Heart failure                                      | 36 (0.18)                |
| Dehydration                                        | 7 (0.04)                 |
| History of contrast media reaction                 | 3 (0.02)                 |

*N = 19,961 patients; †Multiple responses possible (MedDRA preferred terms). SD: Standard deviation.

Male (61.3%) and the mean age was 54 years. Approximately half the patient population (n = 9042, 45.2%) had at least one concomitant disease, most commonly a reduced general condition (17.4%), hypertension (7.9%) and coronary heart disease (7.1%). Risk factors for idiosyncratic CM reactions were reported for 153 patients (0.77% of the total; constituting the at-risk group). Premedication was recorded in 5658 patients overall (28.3%), including over half (n = 86, 56.2%) of the at-risk group (Figure 1). As premedication, corticosteroids were the most frequently prescribed drugs (84.4% and 89.5% of all patients and the at-risk group received premedication, respectively).
3.1. Radiological Examinations and Iopromide Administration

There were a total of 20,000 radiological examinations in which Iopromide was used as a CM agent in the Chinese population included in this study. Iopromide was administered via intravenous injection in 19,935 patients (99.7%) and via intra-arterial injection in the remainder (n = 65, 0.33%). The most frequent examination was multi-slice computerized tomography (99.5%). The most frequent means of administration was automatic injection (99.7%). The mean [± standard deviation (SD)] dose of iodine administered was 29 ± 5.5 g and the median flow rate was 3 mL/s. Ultravist®-300 was the most commonly used formulation of iopromide (Table 2).

3.2. Primary Outcome Measures: Treatment-Emergent Adverse Events and Adverse Drug Reactions

3.2.1. Treatment-Emergent Adverse Events

A total of 580 patients (2.9%) experienced at least one AE (Table 3), most commonly gastrointestinal disorders (n = 206, 1.0%), nervous system disorders (n = 152, 0.76%), general disorders and administration site conditions (n = 136, 0.68%), skin and subcutaneous tissue disorders (n = 107, 0.54%) and respiratory, thoracic and mediastinal disorders (n = 32, 0.16%). The most frequent AEs (annotated as per the MedDRA preferred term) were nausea, dysgeusia and feeling hot. The incidence of injection site pain and/or warmth was low, with a frequency of 0.01% and 0.02%, respectively.

3.2.2. Adverse Drug Reactions

ADR findings were similar to the overall AE profile, since only 14 of the 672 reported events were found to be unrelated to the administration of Iopromide. The overall incidence of ADRs was 2.9% (571 patients), the most frequent reac-
Table 2. Dosage and administration of iopromide.

| Dosage and Administration Parameters       | All patients (N = 20,000) |
|-------------------------------------------|---------------------------|
| Iopromide concentration, n (%)            |                           |
| Ultravist®-300                             | 12,979 (65.0)             |
| Ultravist®-370                             | 7018 (35.0)               |
| Not recorded                               | 3 (0.02)                  |
| Route of administration, n (%)             |                           |
| Intravenous                                | 19,935 (99.7)             |
| Intra-arterial                             | 65 (0.33)                 |
| Means of administration, n (%)             |                           |
| Manual injection                           | 50 (0.25)                 |
| Infusion                                   | 1 (0.01)                  |
| Automatic injection                        | 19,949 (99.7)             |
| Median flow rate, mL/s (range)             | 3.00 (0.1 - 20.0)         |
| Mean iodine dose, g (SD)                   | 29 (5.5)                  |
| Category of iodine dose (g), n (%)*        |                           |
| ≤20                                       | 684 (3.4)                 |
| 20 - 40                                    | 18,861 (94.3)             |
| 40 - 60                                    | 445 (2.2)                 |
| >60                                       | 10 (0.05)                 |

*Dose of iodine (g) was calculated as follows: For patients who received Ultravist®-300: [300 (mg iodine/mL)*applied volume (mL)]/1000. For patients who received Ultravist®-370: [370 (mg iodine/mL)*applied volume (mL)]/1000. SD: Standard deviation.

Table 3. Proportion of patients experiencing treatment-emergent adverse events, *by system organ class and preferred term, after iopromide administration.

| Adverse Events (MedDRA preferred term)                                 | Number of patients, n (%) |
|------------------------------------------------------------------------|---------------------------|
| Patients with any adverse event                                       | 580 (2.9)                 |
| Gastrointestinal disorders                                             | 206 (1.0)                 |
| Nausea                                                                 | 144 (0.72)                |
| Vomiting                                                               | 75 (0.38)                 |
| Nervous system disorders                                               | 152 (0.76)                |
| Dysgeusia                                                              | 126 (0.63)                |
| Dizziness                                                              | 26 (0.13)                 |
| General disorders and administration site conditions                  | 136 (0.68)                |
| Feeling hot                                                            | 119 (0.60)                |
| Skin and subcutaneous tissue disorders                                 | 107 (0.54)                |
| Rash                                                                   | 69 (0.35)                 |
| Pruritus                                                               | 23 (0.12)                 |
| Respiratory, thoracic and mediastinal disorders                        | 32 (0.16)                 |

*Only those adverse events reported by more than 0.1% of patients are presented.
More patients receiving Ultravist®-300 experienced ADRs compared with those receiving Ultravist®-370 (3.4% and 1.9%, respectively). The majority of ADRs were of mild (n = 525) or moderate (n = 43) intensity and resolved without sequelae, and there were no clinically relevant sex or age-related trends (data not shown). Three ADRs were of severe intensity. Excluding tolerance indicators such as any occurrence of injection site warmth, feeling hot or injection site pain, (of mild intensity only), the overall incidence of ADRs was 2.4% (469 patients) and the corresponding value in the at-risk sub-group was 8.5% (13 patients; Figure 2). Two serious ADRs were reported following the administration of Ultravist®-300 [oedema (n = 1) and decreased blood pressure and dyspnea (n = 1)].

Findings for ADRs of special interest are summarised in Table 4. 119 patients (0.60%) reported injection site warmth/and or feeling hot, including one patient in the at-risk group (0.65%). Nausea and/or vomiting were reported in 200 patients from the overall population and in 4 at-risk patients (1.0% and 2.6%, respectively), and urticaria, erythema, rash and/or papular rash were reported in 94 and 4 patients, respectively (0.47% and 2.6%). Further analysis showed that at-risk patients who received premedication had a lower incidence of ADRs versus at-risk patients who received Iopromide alone (Table 5).

![Figure 2](image-url). Proportion of patients experiencing adverse drug reactions after Iopromide administration: all patients combined and only the at-risk subgroup. Caption: graph showing the occurrence of adverse drug reactions in the at-risk group versus the total patient population. All ADRs occurred more frequently in the at-risk group of patients.

### Table 4. Iopromide-related adverse drug reactions of special interest.

| ADR of special interest                     | Patients, n (%) | At-risk patients (N = 153) |
|--------------------------------------------|-----------------|----------------------------|
| Injection site warmth/and or feeling hot   | 119 (0.60)      | 1 (0.65)                   |
| Nausea and/or vomiting                     | 200 (1.0)       | 4 (2.6)                    |
| Urticaria, erythema, rash and/or papular rash | 94 (0.47)       | 4 (2.6)                    |
| Cough and/or sneezing                      | 20 (0.10)       | 3 (2.0)                    |
| Dyspnea and/or bronchospasm                | 11 (0.06)       | 1 (0.65)                   |
| Blood pressure increase and/or decrease    | 6 (0.03)        | 0                          |
Table 5. Incidence of adverse drug reactions after iopromide administration, (with and without premedication), in the at-risk subgroup.

| ADR Description | At risk population, n (%) Premedication (N = 86) | No Premedication (N = 67) |
|-----------------|-------------------------------------------------|---------------------------|
| Any adverse drug reaction | 6 (7.0) | 8 (11.9) |
| Nausea | 3 (3.5) | 0 (0) |
| Vomiting | 1 (1.2) | 0 (0) |
| Feeling hot | 1 (1.2) | 0 (0) |
| Dizziness | 1 (1.2) | 1 (1.5) |
| Dysgeusia | 0 (0) | 1 (1.5) |
| Dyspnea | 1 (1.2) | 0 (0) |
| Sneezing | 0 (0) | 3 (4.5) |
| Pruritus | 0 (0) | 3 (4.5) |
| Rash | 1 (1.2) | 2 (3.0) |
| Urticaria | 0 (0) | 1 (1.5) |

3.3. Secondary Outcome Measures: Contrast Quality

Overall, contrast quality was considered by investigators to be “good” (64.7%) or “excellent” (29.3%) in the majority of patients. Contrast quality was comparable for the two Ultravist® formulations used, with 27.9% and 32.0% as “excellent” for Ultravist®-300 and Ultravist®-370 66.4% and 61.5% of investigators rating it as “good” respectively. Approximately 5% of examinations were reported as “adequate”. Images were non-diagnostic for only one patient (of 20,000).

4. Discussion

To our knowledge, this is the first analysis of the safety and diagnostic image quality of the non-ionic, iodinated CM-Iopromide-in a routine clinical setting in a large group of Chinese patients. Indeed, we found that the safety profile of Iopromide was excellent in this population, with only very few patients experiencing ADRs that were typically transient and of mild intensity. The incidence of injection site pain and/or warmth was also low, indicating a good tolerability profile as well. Overall, our findings are consistent with earlier reports of favourable safety and tolerability profile of Iopromide in Western populations [3] [13] [14]. Our results are also in agreement with the results from a previous large-scale post-marketing surveillance study that included Asian patients and which concluded that the safety of Iopromide in routine clinical practice was comparable with the published safety profiles of other non-ionic, iodinated contrast agents [3]. In addition, a large-scale comparative study concluded that the use of non-ionic CM significantly reduced the incidence of ADRs when compared to ionic CM, including those categorised as severe and potentially life-threatening [4]. Moreover, in the present study, the contrast quality of Iopromide was considered to be “excellent” or “good” by investigators in the majority
of patients, and this was comparable for the two Ultravist® formulations investigated.

Allergy, asthma and a history of CM reactions are risk factors for idiosyncratic reactions to Iopromide, and 153 of the 20,000 Chinese patients (0.77%) were considered to be at risk of such reactions. The incidence of ADRs (excluding tolerance indicators) in this sub-group was higher compared with the total patient population, but such results were not entirely unexpected. Indeed, patients with asthma, previous reactions to CM, a history of allergy, pre-existing illness (diabetes mellitus, renal or cardiac impairment, myelomatosis and sickle-cell anemia), and children are generally at increased risk of developing ADRs [3] [4] [7] [8] [15] [16]. These differences may be attributed to a higher proportion of at-risk patients experiencing allergy-like gastrointestinal (nausea/vomiting), cutaneous (erythema, urticaria, rash) or respiratory (coughing, sneezing) reactions. Moreover, nausea and vomiting could also be anxiety-related [17]. Additionally, there may be a genetic component, given that Asian patients (mainly of Japanese heritage) are more likely to experience delayed skin reactions after administration of non-ionic iodinated CM [18] [19].

The American College of Radiology’s Manual of Contrast media recommends that corticosteroids should comprise an essential component of the premedication protocol in at-risk patients [20]. Notably, in our study, the incidence of ADRs of special interest showed a favourable reduction with premedication (most frequently corticosteroids) in at-risk patients. This finding is in contrast to what was previously reported for Western and Asian populations in the post marketing surveillance study conducted by Kopp et al., where the use of pre-medication did not have a favourable impact on the incidence of ADRs in the at-risk population. In our analyses, the benefits of premedication were most pronounced in terms of a reduction in the incidence of sneezing, pruritus, urticaria and rash. However, “breakthrough” ADRs still occurred in some patients, and this finding is consistent with previous studies [21]. While a controversy remains regarding the use of premedication for patients at high risk of an ADR [1] [9], the present study appears to support the recommendation to use appropriate premedication in Chinese patients at risk of such reactions.

Study strengths include the population size and the fact that the study conduct mirrored routine clinical practice, with the inclusion of patients at risk of idiosyncratic CM reactions. However, the non-interventional design is a possible limitation; as such studies tend to detect a lower incidence of ADRs compared with randomized controlled trials. There could also be other sources of bias along with a lack of cardiac and renal monitoring that have not been accounted for during the analysis.

5. Conclusion

Iopromide, when given according to the prescribing information, is well tolerated among Chinese patients undergoing computed tomography and other diagnostic imaging procedures that require the use of contrast agents. Data from
this study supports its efficiency in 20,000 Chinese patients and confirms the very low risk of ADR occurrence associated with the use of Iopromide.

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**Conflicts of Interest**

Zhang Shuixing, Liang Changhong and Li Ziping received travel support from Bayer Healthcare Pharmaceuticals.

Wang Jary is an employee of Bayer Healthcare Pharmaceuticals.

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Assessment of Image Quality Parameters for Computed Tomography in Sudan

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Abstract

X-ray-computed tomography (CT) has become one of the most important investigation procedures worldwide. The study aimed to assess image quality parameters, mainly noise, and radiation doses during abdominal examination. This study examined the diagnostic parameters (kilo voltage, tube current time product, slice thickness, and pitch) and their effects on image quality as well as the radiation doses received from computed tomography scanners using phantom. The study carried out in four CT centers in Sudan. The study applied prospective and experimental methods. The study demonstrated there was a linear correlation between diagnostic parameters and image noise. The reduction in milli-ampere second and peak kilo voltage increased the image noise. Moreover increasing the pitch led to an increase in the image noise, whereas increasing the slice thickness, reduced the image noise. There was also a linear relationship between kilo voltage and radiation dose at Elnileen diagnostic center characterized by an increase kilo voltages values which led to an increase in the radiation dose by 92% and a reduction in the image noise by 83%. However, at Antalya medical center, increasing in kilo ampere second and peak kilo voltage increased the image noise. Moreover increasing the pitch led to an increase in the image noise, whereas increasing the slice thickness, reduced the image noise. There was also a linear relationship between kilo voltage and radiation dose at Elnileen diagnostic center characterized by an increase kilo voltages values which led to an increase in the radiation dose by 92% and a reduction in the image noise by 83%. However, at Antalya medical center, increasing in kilo voltage values led to an increase in the radiation dose by 35% and a reduction in the image noise by 26%. Also increasing in milli-ampere second values led to an increase in the radiation dose by 49% and a reduction in the image noise by 46% in a phantom compared with an increase in radiation dose by 82% and a reduction in the image noise by 51% in patients. The study found that an optimal protocol for adult abdominal scan at Antalya medical center was 4.22 HU for image noise and 10.45 mGy for radiation dose when using 120 kVp, 300 mAs, 5 mm slice thickness and pitch of 0.8. At Elnileen diagnostic center, however, the optimal protocol was 5.4 HU for image noise and 5.4 mGy for radiation dose using 130 kVp, 50 mAs, 10 mm slice thickness and pitch of 2. In addi-
tion, the quality control tests for image quality parameters carried out at the two centers were performed by using the Chat Phan phantom and all the tests were within the acceptable limits, according to Sudan Atomic Energy Commission (SAEC) Standardizations. The study concludes with a number of recommendations, such as; the necessity for an extensive collaboration among manufacturers, radiologists, technologists and physicists to find a plan to decrease patient radiation dose (ALARA Principle) from computed tomography scanner.

**Keywords**

CT, Image Quality, Patient Dose

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### 1. Introduction

X-ray-computed tomography (CT) has rapidly evolved in terms of both technical performance and clinical use. It has become one of the most important of all x-ray procedures worldwide [1]. The CT technique has been introduced into many medical applications and it is accepted as a useful method in diagnostic imaging owing to the fact that it provides three-dimensional image reconstructions with low contrast detectability, fast volume coverage, easy hardware implementation and considerable spatial resolution [2] [3] [4] [5].

The components of CT image quality are noise, slice thickness (Z-axis resolution), low contrast resolution and high contrast resolution. While image quality has always been a concern for the physics community, clinically-relevant image quality has become important to get clear diagnostic findings for early detection of serious diseases. Image quality can be defined in terms of image noise, which limits low contrast resolution, and spatial resolution.

To optimize image quality, patient dose and relevant issues such as CT dosimetry should not be ignored as obtaining high quality images is always associated with high patient doses.

In Sudan, as far as the authors’ knowledge, few studies regarding CT image quality and patient doses have been published locally and worldwide. This study, therefore, would have a good contribution to the existing literature.

The main purpose of this study is to assess image quality parameters and patient dose parameters, in order to optimize imaging procedure.

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2. Materials and Methods

This prospective, analytical and experimental study deals with diagnostic parameters of the computed tomography scan to evaluate the image quality in CT images. The study was carried out in Sudan at Khartoum State in the CT departments of Antalya medical center, Enileen diagnostic center and Al Amal diagnostic center. The data was collected from June 2014 to August 2016. A special data collection sheet was designed by the authors after was approved by the research ethics committee at each center. The inclusion criteria of the study variables that were measured are, the diagnostic parameters (kVp, mAs, slice thickness and pitch), and the radiation dose [CT dose indices volume (CTDIvol) and dose length product (DLP) and image noise (SD)]. The authors concentrated on image noise as an image quality parameter because it is a key parameter in assessing CT image quality according to previous studies [2] [3] [4] [7] [9] [13] [17] [18] [20].

Before data collection, extensive quality control (QC) tests were performed in all the CT departments in our study. The QC tests used both Catphan 600 and Catphan 500/600 (The Phantom Laboratory, Salem NY, USA) phantoms. Catphan 500/600 is a CT quality assurance phantom suitable to test low contrast detectability, spatial resolution, noise, slice thickness and homogeneity. It is specially designed to evaluate image quality for CT. Different tests can be performed, evaluating the homogeneity, the noise level, the modulation transfer function and the visibility of low contrast details (Laboratory 2006). The evaluation method of interest in this study was measuring the noise level along with routine quality control tests performed by local quality control (QC) committee, the QC tests for this study was carried out by Sudan Atomic Energy Commission (SAEC) and all departments have successfully passed the extensive tests.

The CTDIvol and DLP based on the manufacturer’s data were used for estimation the radiation dose in axial images of the rando-phantom.

The corresponding CTDIvol and DLP of each acquisition condition indicated on the monitor screen were recorded. The CTDIvol and DLP obtained by the standard protocol were compared with that obtained by other protocols.

In order to perform the experiments with doses and noise levels representative of routine phantom values, thirteen clinical data of normal liver examinations performed by the same CT department and scanning parameters were recorded. The radiation dose and the level of the noise were chosen as they are the most important quality parameters and have a direct effect on the quality of the image.

Seven additional abnormal examinations including liver metastases (hyper vascular) were performed. For each patient, one region of interest (ROI) was chosen from one liver metastasis and another ROI from a homogeneous normal
area adjacent to the liver. The mean CT number and SD then recorded to calculate contrast to noise ratio (CNR) as follows: CNR = (CTL − CTM)/SDM, where CTL is the mean CT number of the normal liver and CTM is the mean CT number of the metastasis and SDM is the SD of the metastasis liver.

So the contrast-to-noise ratio was defined as the difference between the mean CT attenuation values of the right lobe of the liver and the background references divided by image noise [9].

The statistical analysis was performed using the software statistical package for the social science (SPSS) version 18.0. The relationship between SD and tube current-time product settings and the relationship between CNR and CTDIvol were investigated using the linear regression analysis and Pearson correlation coefficient (r). To optimize the technical factors (kVp, mAs, ST and pitch) as a function of CTDIvol and SD, taguchi setting was used.

3. Results and Discussion

3.1. Results

The results show in Table 1 and Table 2. Figures 1-9.

![Figure 1](image)

Figure 1. Correlation of kVp with CTDIvol in Elnileen center.

| Parameters | Low resolution (large slice thickness ≥ 5 mm) | High resolution (low slice thickness ≤ 5 mm) |
|------------|-----------------------------------------------|---------------------------------------------|
| ROI/Hospital | NILE | ANT | ALAMAL | NILE | ANT | ALAMAL |
| Iso center | 4.59 | 2.3 | 2.2 | 26.56 | 1.2 | 2.5 |
| 0 degree | 3.57 | 1.9 | 3.2 | 19.8 | 1.2 | 1.3 |
| 90 degree | 3.83 | 1.8 | 2.9 | 19.1 | 1.1 | 1.9 |
| 180 degree | 4.13 | 1.7 | 3.4 | 19.6 | 1.9 | 2.5 |
| 270 degree | 4.37 | 2.3 | 2.5 | 20.9 | 1.4 | 2.2 |
| Standard deviation | 4.098 | 2 | 2.84 | 21.192 | 1.36 | 2.08 |

| Table 2. Unit’s specifications. |
|--------------------------------|
| Center | manufacturer | Installation date | Max No of slices | No of tube exposures | Max kV | Max mA |
| NIL | Siemens | 2008 | 16 | 16423 | 130 | 450 |
| ANT | GE | 2011 | 16 | 9653 | 140 | 300 |
| ALAMAL | Toshiba | 2010 | 64 | 11794 | 140 | 500 |
Figure 2. Correlation of mAs and DLP.

\[ y = 81.257\ln(x) - 325.9 \]
\[ R^2 = 0.6889 \]

Figure 3. Correlation of Pitch and CTDI\textsubscript{vol}.

\[ y = 10.996\ln(x) + 8.5935 \]
\[ R^2 = 0.5618 \]

Figure 4. General correlation between noise and pitch.

Figure 5. General correlation of kV\textsubscript{p} and Noise (SD).
Figure 6. The adjusted factor of (ST) and kilo voltage kVp versus CTDIvol (GE scanner).

Figure 7. The adjusted factor slice thickness (ST) and kVp versus CTDIvol (Siemens Scanner).

Figure 8. The adjusted factor slice thickness (ST) and kilo voltage kVp versus DLP (GE scanner).
3.2. Discussion

The low contrast detectability is dependent on how much noise is present in the image. One way of quantifying the contrast in an image is to determine the contrast-to-noise ratio, which provides a value describing the quality of an image. In this study, the noise was determined by measuring noise at Region of interest ROIs at the centers and peripheries, as shown in table one for slices less and more than 5 mm (Table 1). This is considered to be acceptable according to SAEC standardizations that were obtained from the international atomic energy agency IAEA.

Two diagnostic parameters were evaluated to obtain a minimum image noise or an optimal radiation dose. The best minimum image noise was obtained by having a slice thickness of 5 mm and kVp of 120 at Antalya center (GE scanner) (Table 2). However, at Elnileen diagnostic center (Siemens scanner) the minimum image noise was obtained by having a slice thickness of 10 mm and kVp of 130 at Antalya center (GE scanner). The different values are due to differences in multi detector scanner types between the two centers. In addition, at Antalya center, the optimum CTDIvol (9.76 mGy) was obtained with 120 kVp and slice thicknesses of 5 mm. At Elnileen diagnostic center, however, the optimum CTDIvol (3.17 mGy) was obtained with 110 kVp and slice thicknesses of 8 mm. Finally (Figure 1 and Figure 2), at Antalya medical center, the optimum dose length product DLP (88 mGy·cm) was obtained when 120 kVp was used with 5 mm slice thickness. However, at Elnileen Diagnostic center, the optimum DLP (67 mGy·cm) was obtained with 110 kVp and 8 mm slice thickness.

Other adjustment factors were (pitch & kilo voltage). At Antalya Medical center, the minimum image noise was obtained by using the pitch of 1.3 with 120 kVp. However, at Elnileen diagnostic center, 130 kVp and pitch of 2 provided the minimum image noise.

Moreover, at Antalya medical center, the optimum CTDIvol (10.45 mGy) was obtained with 120 kVp and pitch of 1.3. However, at Elnileen diagnostic center, 110 kVp and pitch of 1.5 provided the optimal CTDIvol (3.66 mGy). Finally, the optimal DLP (88 mGy·cm) at Antalya medical center (Figure 8 and Figure 9),
was obtained with 120 kVp and pitch of 1.3). At Elnileen diagnostic center, however, 110 kVp and pitch of 1.5 were used to obtain the optimal DLP (69 mGy·cm).

The relationship between tube current-time product (mAs), tube kilo voltage (kVp) and image noise (SD) were evaluated. It showed that a reduction in mAs and kVp increases the image noise. This is consistent with studies done by Seung-Wan 2010 and Reid et al 2010; they found that doses increased linearly with an increase in mAs and by the power function of kVp for increases in kVp. They also found that the image noise decreases as a function of kVp and mAs and increases as a function of the phantom diameter.

Also the relation between slice thickness (ST) (Figure 7 and Figure 8), pitch (P) and image noise showed that as pitch increases (Figures 3-5), the image noise decreases, and approximately inversely nonlinear relationship between slice thickness and image noise, i.e. increasing slice thickness decreases the image noise. For some manufacturers of multi detector scanners, the slice thickness is independent of the table speed based on the interpolation algorithm used. This is in line with a study done by Brochure. 2001 who showed that an increase in slice thickness leads to an improvement in the noise level and a reduction in the spatial resolution. He also found that decreasing the pitch decreases the duration of the patient exposure to radiation, and hence the patient dose per slice and image noise increase. This agrees with previous studies done by Yu-Chun Lin, Rehani et al and Reid et al 2010. They found that increasing the pitch increases the doses to the patients.

4. Recommendations

This study recommends the following:

First of all, further studies are required to optimize protocols in different CT examination in multi-detector CT. Secondly, further studies are required to look at the effect of the patient age (pediatric and adult). Finally, developing a CT training program in quality assurance program, targeted for technologists, radiologist, physicists and CT scanner manufacturer. It is necessary for manufacturers, radiologists, technologists and physicists to work side by side to find a plan to decrease patient radiation dose (ALARA Principle) from CT scanner.

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