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SDHD-related head and neck paragangliomas & their natural course

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Measurement of head and neck paragangliomas: is volumetric analysis worth the effort? A method comparison study

Abstract

Background: The aim of this study was to assess the reproducibility of different measurement methods and define the most workable technique for measuring head and neck paragangliomas, to determine the best method for evaluating tumour growth. The evaluation of tumour growth is vital for a "wait and scan" policy, a management strategy that became increasingly important.

Study design: Method comparison study.

Setting and participants: Thirty tumours, including carotid body, vagal body, jugulotympanic tumours and conglomerates of multiple tumours, were measured in duplicate, using linear dimensions, manual area tracing and an automated segmentation method.

Main outcome measures: Reproducibility was assessed using the Bland-Altman method.

Results: The smallest detectable difference using the linear dimension method was 11% for carotid body and 27% for vagal body tumours, compared with 17% and 20% for the manual area tracing method. Due to the irregular shape of paragangliomas in the temporal bone and conglomerates, the manual area tracing method showed better results in these tumours (26% and 8% versus 54% and 47%). The linear dimension method was significantly faster (median 4.27 versus 18.46 minutes, $p < 0.001$). The automatic segmentation method yielded smallest detectable differences between 39% and 75%, and although fast (2.19 ± 1.49 minutes), it failed technically.

Conclusions: Due to a relatively good reproducibility, fast and easy application, we found the linear dimension method to be the most pragmatic approach for evaluation of growth of carotid and vagal body paragangliomas. For jugulotympanic tumours, the preferred method is manual area tracing. However, volumetric changes of these tumours may be of less clinical importance than changes in relation to surrounding anatomical structures.

Introduction

Head and neck paragangliomas are neuroendocrine tumours related to the parasympathetic nervous system. Approximately 35% of head and neck paragangliomas are associated with hereditary syndromes. Mutations in subunit-D of the succinate dehydrogenase gene (SDHD) are the most common [1]. Inheritance of paragangliomas in SDHD-linked families is characterised by parent-of-origin-related tumorigenesis. Development of paragagangliomas after maternal transmission is extremely rare [2].

Surgery is the only definitive treatment for head and neck paragangliomas; however, due to location close to large vessels and lower cranial nerves, resection is challenging. This is especially true for jugular and vagal body paragangliomas; in the latter case, sacrificing the vagus nerve is almost inevitable [3]. Treatment of patients with hereditary syndromes, particularly SDHD-linked cases, is further complicated as these patients often develop multiple head and neck paragangliomas that may grow together and form a conglomerate. In addition, they are at risk for debilitating bilateral lower cranial nerve impairment. With the evolvement of radiotherapy and stereotactic radiosurgery, local control rates vary from 76% to 100% while the complication rate is significantly lower compared to surgery. Although risk of radiation induced malignancy is low, it should be considered, especially in younger patients [3–5].

Surgery and radiotherapy thus carry disadvantages and head and neck paragangliomas generally show a very favourable natural course. This has led our institution, among others, to advocate an initial policy of "watchful waiting". Only tumours that cause complaints, (impending) cranial nerve impairment or exhibit progressive growth are treated. A "wait and scan" strategy is not the first choice in hormonally active and malignant paragangliomas or in case of skull base lesions with significant intracranial extension [1, 3, 4, 6–9].

A "wait and scan" treatment strategy has become increasingly important as pre-symptomatic testing for causative gene defects in family members of paraganglioma patients has increased the detection of very small and predominantly asymptomatic paragangliomas [10].

For the surveillance of these tumours, it is essential to determine whether presumed growth is true tumour progression or could still be explained by measurement variation alone (i.e., reproducibility). Several measurement methods are available for the assessment of tumour volume, these include linear dimension methods, manual area tracing and automated segmentation techniques.

Three previous studies that addressed growth of paragangliomas used linear dimensions [6–8]. However several studies comparing linear dimension methods with volumetric analysis in the assessment of growth of other tumours, for example schwannomas and meningiomas, concluded that volumetric analysis is more accurate [11–14]. Although head and neck paragangliomas are usually well defined, they are not always homogeneously enhancing and due to their hypervascularity often difficult to delineate from carotid arteries and the jugular vein. These features hamper the use of automated techniques and make manual area tracing more laborious.

To the best of our knowledge, no study has yet compared linear dimension measurements and volumetric analysis in head and neck paragangliomas. The aim of this study was to assess the reproducibility of these methods and define the most workable technique for measuring head and neck paragangliomas, taking also practicability into account.

Methods

Ethical considerations

This method comparison study was approved by the review board of the department of Radiology, of the Leiden University Medical Center.

Patients

A database detailing all SDHD mutation carriers tested in the Leiden University Medical Center before 1, July 2012 and their affected family members (obligate SDHD mutation carriers) was ranked by follow-up time. The 10 carotid body paragangliomas, 10 vagal body paragangliomas and 10 jugulotympanic paragangliomas with the longest follow-up were selected. Furthermore, nine conglomerates, consisting of a total of 20 paragangliomas (five conglomerates of carotid and vagal body tumours, two vagal and

jugulotympanic conglomerates and two conglomerates consisting of carotid body, vagal body, and jugulotympanic tumours) were included. The 50 paragangliomas included in this study were from 26 patients, and the most recent MRI scan of the head and neck region was retrospectively analysed.

MRI technique

We used 3D Time of Flight MR angiography with gadolinium, as this method was previously indicated the modality of choice for detection of head and neck paragangliomas [15]. Examinations completed between June 2006 and December 2012 were performed on a 1.5T (Philips Medical Systems, Best, the Netherlands) using a head and neck coil (repetition time/echo time, 21/7 ms; flip angle, 20; slice thickness, 0.75 mm; field of view, 210 mm; matrix, 256 x 256; reconstructed voxel size, 0.82/0.82/0.75 mm) or on a 3T (Philips Medical Systems) using a neurovascular coil (repetition time/echo time, 20/3.5 ms; flip angle, 15; slice thickness, 0.75 mm; field of view, 200 mm; matrix, 384 x 384; reconstructed voxel size, 0.39/0.39/0.75 mm).

Measurements

All measurements were taken twice by a trained first observer (BLH), with an interval of at least 4 days, and subsequently verified and, if necessary, corrected by an experienced head and neck radiologist (BMV, 12.5 years of experience). The time required to take measurements was also recorded, by observer 1 during the second session of measurements.

Tumour volume (cm^3) was calculated using linear dimensions, computer-assisted manual area tracing method and automatic segmentation tool. A Vitrea workstation version 6.0.1540.7188 (Vital images, Minnetonka, Minnesota, USA) was used for all measurements. For the linear dimension method, the largest diameter in the axial plane (A) was measured using a linear digital caliper tool, followed by the diameter perpendicular to A in the same plane (B). Finally, the largest craniocaudal diameter (C) was measured in the sagittal plane (figure 3.0.1 a & b). Tumours were assumed to be ellipsoid and volume was therefore estimated using the equation:

$$Volume(V) = \frac{4}{3}\pi(\frac{1}{2}A * \frac{1}{2}B * \frac{1}{2}C) \tag{3.1}$$

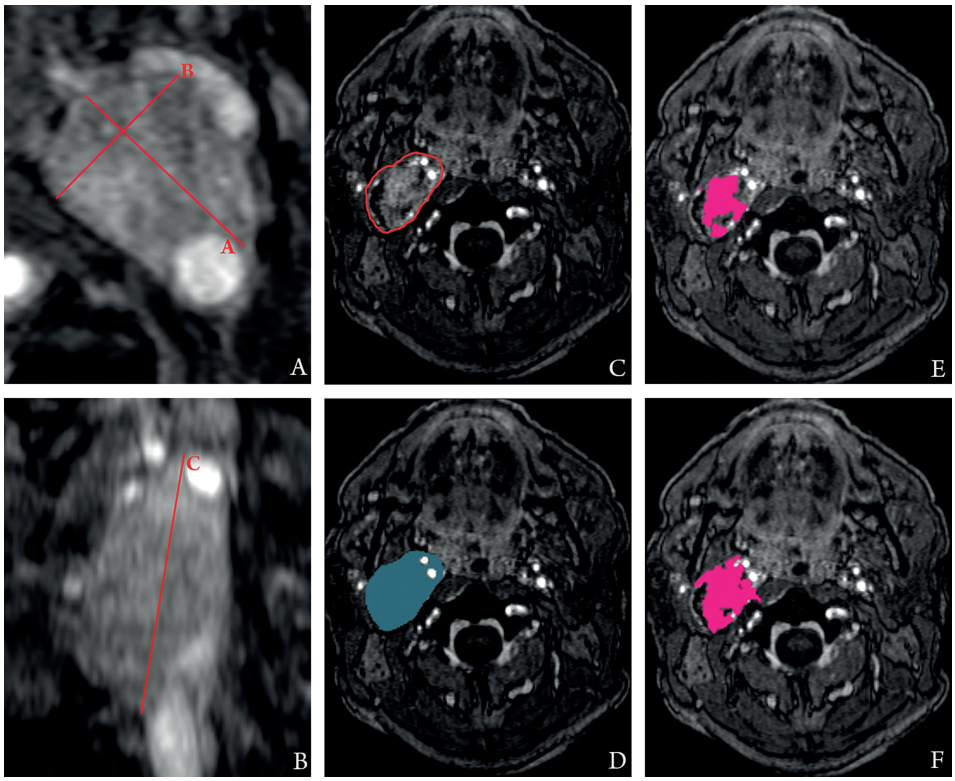

Figure 3.0.1:
Linear dimension measurements (a & b). To estimate volume based on linear dimensions, paragangliomas were considered to have an ellipsoid shape, and consequently, volume was calculated using equation 3.1. *A* is the largest diameter in the axial plane (a), *B* is the diameter perpendicular to *A*, and *C* is the largest craniocaudal diameter measured in the sagittal plane (b).
Manual area tracing method (c & d). As shown, the tumour was manually delineated in the axial plane excluding the main vessels.
Automatic segmentations technique (e & f). These are images of the same tumour as shown in c & d, it clearly illustrates the measurement error associated with the automatic segmentation technique.

Segmentation of the tumour was performed using two methods. Manual segmentation was performed using the computer-assisted free-sculpting tool (Vitrea, Vital Images, Minnetonka, Minnesota, USA). The tumour was manually delineated excluding the main vessels in axial slices using the free-sculpting tool (figure 3.0.1 c & d). Automatic segmentation was performed using a tool provided by Vitrea (Vital Images, Minnetonka, Minnesota, USA). With this tool, the tumour was automatically segmented by selecting a region of interest inside the tumour. Subsequently, the volume of the tumour was calculated based on both segmentation methods.

Statistics

IBM SPSS Statistics version 20.0 (IBM Corp.: Armonk, NY, USA) was used for statistical analysis. The Bland and Altman method was used to assess intra-observer agreement [16]. Relative differences (% differences) rather than absolute differences between two measurements were used, as a small absolute difference may still represent a large percentage of tumour volume in small paragangliomas. Relative differences were calculated as follows:

$$\frac{(measurement1 - measurement2)}{0.5 * (measurement1 + measurement2)} * 100 \tag{3.2}$$

The 95% limits of agreement: mean $\pm$ 1.96 $*$ SD of differences and the smallest detectable difference (SDD): 1.96 $*$ SD of differences were calculated [12, 16–18]. The linear dimension method was compared with the manual area tracing method using a linear mixed model and Wilcoxon signed-rank test. An independent t-test was used to compare the mean time necessary to take measurements. As sample sizes were small, a Shapiro-Wilk test was used to assess normality. A test statistic of $\leq$ 0.9 was considered to be the cut-off value. Finally, equality of variances was assessed by Levene's test of equality ($p < 0.05$). Continuous data are represented as mean $\pm$ SD, unless stated otherwise.

Results

Reproducibility

Intra-observer agreement was objectified for all measurement methods separately. The mean difference between consecutive measurements and the calculated limits of agree-

ment are displayed for carotid body, vagal body, jugulotympanic paragangliomas and conglomerates individually (figure 3.0.2). The Shapiro-Wilk test was used to assess normality of the relative differences of all measurement methods for all tumour categories individually. The test statistic was (approximately) 0.9 in all cases, indicating a normal distribution. The mean and SD of the relative differences were also approximately constant throughout the range of measurements (data not shown); therefore, the limits of agreement were considered to be constant. As shown by similar limits of agreement, the reproducibility of the linear dimension and manual area tracing method were comparable for vagal body and carotid body tumours, whereas the limits of agreement of the automatic segmentation method were wider, indicating an inferior reproducibility. This was also apparent from the calculated smallest detectable differences (SDD), which ranged from 8% to 75% depending on tumour location and measurement method (table 3.0.1). In addition, median tumour volumes of paragangliomas at different locations were estimated using each method; the results are displayed in table 3.0.1.

Technical notes

When calculating tumour volumes based on linear dimensions, paragangliomas were assumed to have an ellipsoid shape. Although this is broadly true for most carotid body tumours and many vagal body tumours, jugulotympanic tumours often do not have a clear geometrical shape. Consequently, conglomerates involving jugulotympanic tumours are often non-ellipsoid. Conglomerates of a carotid and vagal body paraganglioma are more likely to be ellipsoid or double ellipsoid in shape. In the latter case, the volume of both tumours can be measured separately. The linear dimension method was performed with a mean time of 4.27 ± 1.36 min.

The manual area tracing method involves separate review of each image in which the paraganglioma appears; therefore, any judgment errors only affect calculations for that particular image. In addition, this technique allows the inclusion or exclusion of each voxel and therefore provides an opportunity to exclude vessels even when they are surrounded by tumour tissue. However, with a mean time of 18.46 ± 10.67 min, the technique was the most time-consuming.

With a mean time of 2.19 ± 1.49 min, the automatic segmentation technique was the fastest measurement technique. However, as paragangliomas may contain necrotic por-

tions, the technique was (even after selecting several voxels inside the tumour with a different grey scale) frequently unable to select the entire paraganglioma. Furthermore, the provided tool often selected structures outside the tumour, leading to a calculated volume that did not correspond to the actual tumour size (figure 3.0.1 e & f). Because reproducibility was also poor, the technique was not further assessed.

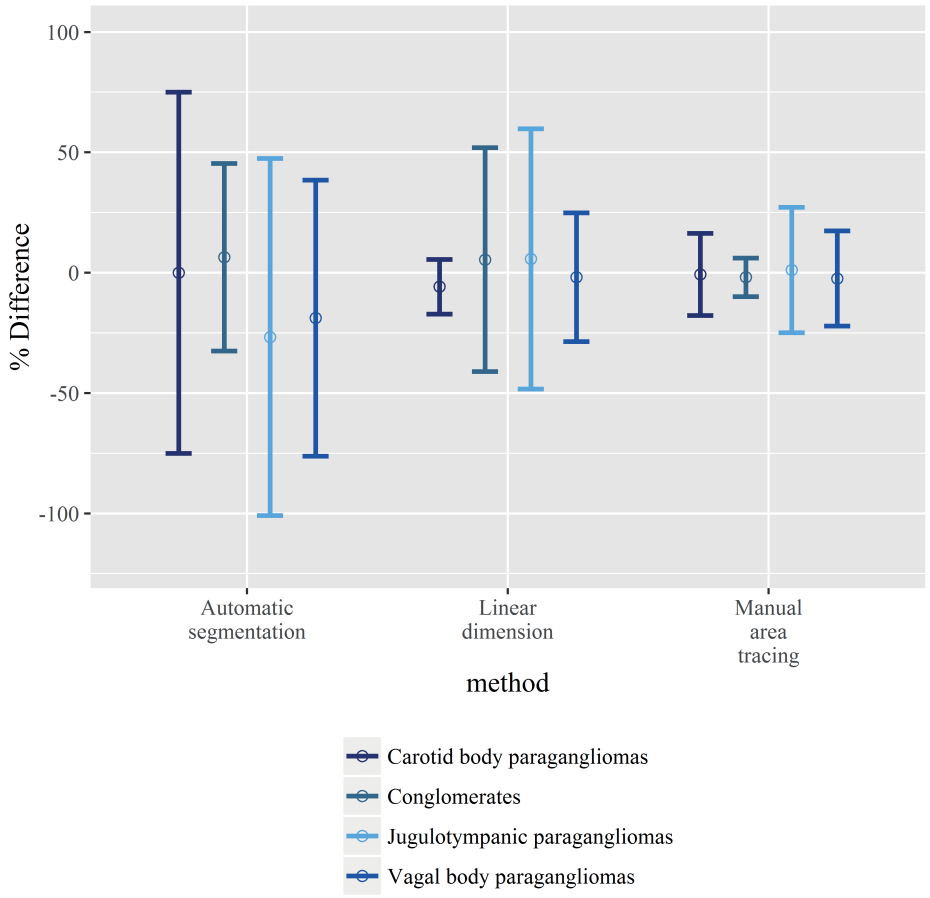

Figure 3.0.2: Reproducibility. Intra-observer agreement assessed by the Bland and Altman method: the mean difference and the 95% limits of agreement (mean $\pm$ 1.96 $*$ SD) are shown for each method. On the x-axis, the different measurement techniques are shown. The y-axis represents the % difference (equation 3.2).

Table 3.0.1: Median estimated volume (cm^3) and smallest detectable difference (SDD, 1.96 * SD of differences).

	Carotid body paragangliomas	Vagal body paragangliomas	Jugulotympanic paragangliomas	Conglomerates
Linear dimension method				
Median volume (cm^3), (range)	5.31 (1.28-27.86)	5.19 (1.88-34.34)	3.08 (0.70- 15.14)	33.97 (21.35-77.03)
Smallest detectable differences (%)	11.4	26.8	54.1	46.5
Manual area tracing method				
Median volume (cm^3), (range)	6.11 (0.81-25.49)	5.65 (2.29-31.96)	2.95 (0.64-13.16)	27.15 (18.37-83.20)
Smallest detectable differences (%)	17.0	19.8	26.0	8.0
Automatic segmentation method				
Median volume (cm^3), (range)	4.31 (0.74-20.85)	5.00 (1.28-23.10)	3.10 (1.22-10.18)	24.43 (15.53-68.72)
Smallest detectable differences (%)	75.0	57.3	74.2	39.0

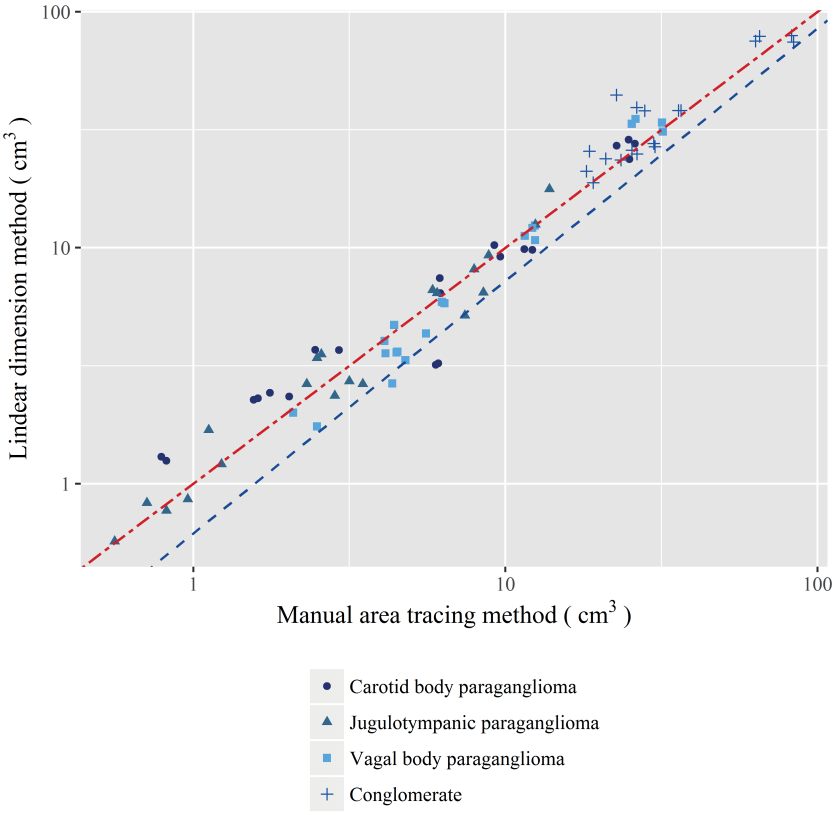

Figure 3.0.3: Linear dimension versus manual area tracing method. The values on the y-axis represent the measurements obtained by the linear dimension method, and the values on the x-axis represent the measurements obtained by the manual area tracing method. With the fitted regression line (blue line; $y = 1.07x - 0.21$) and the line of equality (red line; $y = x + 0$)

Linear dimension versus manual area tracing method

The linear dimension method was compared with the manual area tracing method using a linear mixed model, resulting in a fitted regression line with the following equation: $y = 1.07x - 0.21$. As the 95% confidence interval (CI) of the slope was -1.6-1.1 and the 95% CI of the intercept was 1.0-1.1, the fitted regression line resembled the line of equality ($y = x + 0$) (figure 3.0.3). Furthermore, there was no significant difference between the median volume estimated by the manual area tracing and linear dimension method, 7.68 (0.64-83.20) cm^3 and 6.93 (0.70-77.03) cm^3 (p = 0.332), respectively. A

significant difference was found in the variance of measurements ($p = 0.013$). However, if only carotid and vagal body tumours were analysed, the variance of measurement did not differ significantly ($p = 0.57$). With a mean time of 4.27 ± 1.36 min, the linear dimension method was significantly faster ($p < 0.001$).

Discussion

Since a "wait and scan" policy was first introduced in the early nineties as alternative management strategy for head and neck paragangliomas, it became more important with the increasing detection of very small paragangliomas following pre-symptomatic screening. Although tumour progression is not the only reason to treat these tumours, the decision to resort to surgery or radiotherapy of head and neck paragangliomas is often determined by tumour growth [10, 19, 20].

Understanding the practicability and reproducibility of measurement methods that estimate tumour volume is of great importance to evaluate growth. Although hardware and scanning techniques (e.g., slice thickness) can influence measurements, this influence is trivial compared to the impact of measurement methods and observer interpretation [21, 22]. In general, the more accurate the method used, the more time-consuming it is. For this study, we compared three methods with differing complexity: estimation of the volume using linear dimensions, manual area tracing and an automated segmentation technique.

Synopsis of key findings and comparison with other studies

The poor reproducibility of the automatic segmentation technique was a particularly disappointing finding. This poor performance was primarily attributable to inhomogeneous enhancement of tumours and to the close proximity of similarly enhancing large vessels. While new techniques and algorithms may be developed to improve (semi) automated methods, in the current setting, they are not (yet) useful in the evaluation of volume and growth of head and neck paragangliomas [23].

The manual area tracing method was the most robust of the three methods investigated, but was also the most time-consuming. For vagal body and carotid body tumours, volume estimates based on the linear dimensions of the tumour and the assumption that these

tumours have an ovoid shape produced intra-observer variability and tumour volumes comparable to manual area tracing but could be performed four times faster. These findings are in line with studies that measured glioblastomas and gliomas [24, 25].

Irregularly shaped tumours are difficult to consistently measure with any method. In the case of jugular paragangliomas, defining the tumour is further hampered by the intimate relationship of the tumour with the jugular bulb, and to a lesser extent, the internal carotid artery; including the jugular bulb in the measurement of tumour volume may reduce the variability but will overestimate tumour volume. For follow-up, this strategy is only useful when the vessel is already encompassed at the time of first imaging. When vessels are initially distinguishable but become gradually involved (as is often the case in head and neck paragangliomas), the inclusion of these vessels in subsequent measurements of tumour volume will result in an exaggerated growth rate. Studies comparing volumetric analysis and linear dimension methods for the measurement of irregularly shaped tumours such as vestibular schwannoma also concluded that volumetric analysis is the most accurate method to evaluate tumour growth [12–14]. These results are in line with our findings; jugular paragangliomas are most reliably measured using the manual area tracing method.

The tumour conglomerates included in this study consisted of vagal body tumours with jugular components. Linear dimension analysis was not suited to these generally dumbbell-shaped conglomerates, but circumferential tracing yielded good results. Linear dimension analysis was more suitable for conglomerates consisting of a carotid body and vagal body paraganglioma as these conglomerates are more likely to be ellipsoid or double ellipsoid in shape. In the latter case, it is often possible to separate the two tumour locations in a slightly arbitrary manner and then apply the linear dimension method.

Our experience is that growth of benign tumours of the head and neck, such as schwannomas, meningiomas and paragangliomas, is often measured in the axial plane only. This can provide a false sense of reassurance, especially as paragangliomas tend to expand in a craniocaudal direction. While the alternative approach of using volumetric measurement is often regarded as being excessively time-consuming, we have shown that measuring in three dimensions in paragangliomas in the neck is fast, reproducible and yields volume estimates similar to manual area tracing methods.

Clinical applicability

The smallest detectable differences of 11.4% for carotid body tumours and 26.8% for vagal body tumours can be used in practice to define the cut-off points to differentiate growth from measurement errors volume increases of 10% and 25%, respectively. Jugular paragangliomas are best measured using manual area tracing, which also shows a 25% error. It is important to realise that MRI images carry a substantial measurement error; therefore, the use of tumour growth as the sole indicator for surgery means that a longer observation period will be needed to confirm tumour progression. Consequently, growth can easily be overlooked if comparison is only made between subsequent MRI scans; therefore, the most recent image should also be compared with the first (digitally) available scan.

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