RESEARCH ARTICLE

Image segmentation-based volume approximation—volume as a factor in the clinical management of osteolytic jaw lesions

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Objective: Size characterization of osteolytic jaw lesions (OJL), in particular of neoplastic nature, is heterogeneously performed and lacks standardization in the medical literature and clinical practice. An OJL's volume holds promise as a surrogate for treatment response and prognosis. We comparatively evaluate various methods for size characterization of odontogenic OJLs.

Methods: We retrospectively performed semiautomatic image segmentation of CBCT data sets for volume approximation of neoplastic (51) and non-neoplastic odontogenic OJLs (100). We assessed the three greatest orthogonal diameters and calculated the volume using the cuboid- and ellipsoid-formula. Image segmentation was carried out using ITK-SNAP. Image segmentation-based volume approximation served as reference. Intra- and inter-rater variability were evaluated at hand of Bland–Altman-Analysis and dice similarity coefficient (DSC).

Results: Concerning the intrarater variability, we found the DSC to be highest for image segmentation-based volume approximation, simultaneously showing the tightest limits of agreement and greatest reliability. The cuboid formula showed consistent overestimation of the lesion's volume with a percent mean difference of -52% (upper and lower limits of agreement $+8.57\%$ and -112.63% , respectively). In mean, the ellipsoid formula underestimated the lesion's volume by 10.1% (upper and lower limits of agreement $+76.8\%$ and -56.6% , respectively). Inter rater variability was higher for formula-based volume approximation. Volume and multilocularity ($p = 0.001$) correlate with aggressiveness and growth potential.

Conclusions: Segmentation-based volume approximation holds great promise for patient individualized treatment planning and clinical management. The data suggest that maximum tumour diameter-based size characterization, especially the cuboid-formula and the maximum diameter alone, should not be recommended.

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Introduction

Odontogenic cystic jaw lesions are epidemiologically and clinically relevant diseases of the oral and maxillofacial complex. Approximately, 20% of all bioptically evaluated oral pathologies have shown to be odontogenic tumours and odontogenic cysts.^{1–3} Therefore, craniomaxillofacial

(CMF) surgeons are frequently faced with management decisions concerning these entities of disease.

Radiological size delineation has its relevancy in the context of diagnostics and therapeutic management decisions. The size is frequently taken as a surrogate for the aggressiveness and respectively the growth potential of a lesion, thereby constituting an imaging biomarker.^{4–7} Importantly, in the context of pharmaceutically targeted

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therapy of neoplasms in general, radiological size delineation is important in order to quantify the therapeutic success as judged by neoplastic disease regression. Pharmacologically targeted therapy of ameloblastomas, the most prevalent neoplastic odontogenic tumour, with BRAF-inhibitors has made it to clinical trials.^{8,9} Hence, a reliable and accurate mean for size characterization and therefore, therapeutic success is indispensable.

Pre-operatively generated biomedical image data sets can be analyzed and exploited for radiographic phenotype analysis with the help of complex algorithms, e.g. for image segmentation purposes.¹⁰ *Image segmentation can be seen as the biomedical image data set processing equivalent of surgical dissection.*¹¹ Hence, with the help of such methods, the physician is provided with a powerful tool to radiologically separate pathological tissue (e.g. osteolytic jaw lesions, OJL) from healthy, unaffected bone tissue, ultimately allowing morphometric and volumetric analysis.^{10,12} This is particularly important for imaging of neoplastic diseases.

However, image segmentation-based size characterization of odontogenic lesions is widely neglected. Even most recent investigations evaluating the benefit of BRAF-targeted therapy of ameloblastomas employ the maximum tumour diameter or formula-based volume measurement to quantify therapeutic success.^{8,13} Nevertheless, investigations have shown that the maximum tumour diameter and formula-based volume measurements are less reliable and accurate for size characterization when compared to image segmentation-based volume approximation.¹⁴ Image segmentation for size characterization has shown to be promising and demonstrates an unparalleled intrinsic repeatability and reliability for volumetric size characterization in neuroimaging studies.^{10,12}

Hence, we intended to evaluate the reliability and feasibility of semi-automatic image segmentation for size delineation of potentially infiltrative odontogenic neoplasms and non-neoplastic jaw cysts of varying size categories. Therefore, we comparatively evaluate three methods for size characterization of odontogenic OJLs (maximum tumour diameter, formula- and image segmentation volume approximation) and discuss the importance and relevancy of image segmentation-based size characterization for oral research and patient individualized treatment planning.

Methods and materials

Patients

We included patients showing the most commonly surgically assessed benign odontogenic jaw lesions with radiologically visible osteolytic lesions of either uni- or multilocular configuration with or without an irregular outline. Hence, we considered patients who have been diagnosed with either one of the two most common odontogenic cysts (periapical and dentigerous) or with one of the three most common potentially infiltrative

odontogenic tumours [ameloblastoma, keratocystic odontogenic tumour, odontogenic myxoma (OM)] by histopathological, radiological and clinical means.^{4,5,7,15} Each individual received pre-operative diagnostics according to a standardized imaging protocol as well as therapeutic assessment between 2007 and 2017. Due to the retrospective nature of this study, it was granted an exemption in writing by the University Hospital IRB.

Preoperative CBCT imaging

CBCT scans were taken with the GALILEOS® CBCT device (Sirona, Bensheim, Germany). Reconstruction of the raw data yielded a matrix of 512³ isotropic voxels with a spatial resolution of 300 µm or 2.5 line pairs/mm. Consecutively, secondary reconstruction yielded multiplanar data sets allowing visualization of the pathologic process in axial, coronal and sagittal plane. In order to provide data for image segmentation, DICOM (Digital Imaging and Communications in Medicine) data sets were exported and anonymously saved for each individual.

Image segmentation

For segmentation of odontogenic jaw lesions, we used the open source software ITK-SNAP (Insight segmentation and registration toolkit-Snake automatic partitioning; Penn Image Computing and Science Laboratory, University of Pennsylvania, Philadelphia, Yushkevich et al. 2006).¹⁰ The CBCT DICOM data sets were imported into ITK-SNAP and were demonstrated in sagittal, coronal and axial slices. The intraosseous lesions were identified and delineated with the means of semi-automatic segmentation. Afterward, manual segmentation was performed to control and ensure correct segmentation (Figure 1). The volume of the lesions was computed automatically in cubic millimeters by the program. The open source medical imaging program ITK-SNAP is based upon geodesic active contour and region competition methods, and thus offers manual and semiautomatic tools to approximate the volumes of anatomical regions of interest.¹⁰ The program was initially validated for volumetric and morphometric analysis of the caudate nucleus of the brain.¹⁰ Multiple consecutive studies confirmed these results.^{4-7,16-20}

Maximum tumour diameter and formula-based volume approximation

With the help of ITK-SNAP, we manually measured the three maximum orthogonal tumour diameters in centimeters (cm) in anteroposterior, mediolateral and craniocaudal direction. The measurement was automatically indicated by the program in millimeters. The maximum tumour diameter was defined as the largest measurement either in anteroposterior, mediolateral or craniocaudal direction.

With the help of the three orthogonal diameters, we calculated the volume in cm³ (ml) based on two commonly used volume formulas. The formulas used were the

Figure 1 The interface of the program ITK-SNAP. One can see that the region of interest has been labelled (axial, coronal, sagittal planes displayed). Furthermore, the program allows three-dimensional visualization of the segmented region of interest (lower right-hand corner). ITK-SNAP, Insight segmentation and registration toolkit-snake automatic partitionin.

cuboid formula: $Vol = \frac{(x*y*z)}{1000}$
and the

ellipsoid formula: $Vol = \pi * \frac{(x*y*z)}{6}$.¹⁴

All measurements were repeated after 1 month (Investigator A) and additionally performed by a second investigator (Investigator B) without knowledge of the results gathered by the primary one.

Statistical analysis

General

Student's *t*-test was used to compare mean values. The association between categorical variables was assessed by χ^2 test. The significance level was set to $p < 0.05$. All statistical analyses were performed using SPSS Statistics 24.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, v. 24.0. Armonk, NY: IBM Corp). Volume in mm^3 was divided by 1000 in order to obtain results in cm^3

(ml). Image segmentation-based volume approximation was used as the reference volume for comparative analyses.

Overlap statistics

In order to quantify the similarity of two measurements, we used overlap statistics as described by Yushkevich et al in the context of image segmentation validation.¹⁰ The following formula describes the equation used for calculating the “dice similarity coefficient (DSC)” at the example of the overlap between both segmentation measurements conducted by investigator A:

$$DSC(SEG1, SEG2) = \frac{2VOL(S1 \cap S2)}{VOL(SEG1) + VOL(SEG2)}$$

The same equation was used to assess the overlap between other measurement groups (Table 1). The result is in the range of 0 to 1. The closer the value gets to 1, the greater is the overlap and thus the similarity between both measurements.

Table 1 Volumetric data for each method of volume approximation

	Mean (ml)	SD (ml)	Minimum (ml)	Maximum (ml)
Image Segmentation A1 (SEG A1)	7.70	8.17	0.31	53.34
Image Segmentation A2 (SEG A2)	7.69	8.36	0.31	55.67
Cuboid Formula A1 (Cuboid A1)	14.60	17.44	0.54	111.50
Cuboid Formula A2 (Cuboid A2)	14.72	17.46	0.42	113.87
Ellipsoid Formula A1 (Ellipsoid A1)	7.65	9.14	0.28	58.38
Ellipsoid Formula A2 (Ellipsoid A 2)	7.71	9.15	0.22	59.62
Image segmentation B (SEG B)	7.73	8.02	0.33	52.18
Cuboid Formula B (Cuboid B)	13.81	15.65	0.65	81.43
Ellipsoid Formula B (Ellipsoid B)	7.23	8.20	0.34	42.64

1, first measurement by investigator A; 2, second measurement by investigator A; A, first investigator; B, second investigator;

Bland Altman analysis

Bland–Altman analysis was used to assess the intra- and inter-rater variability as well as the agreement between primary (e.g. image segmentation-based volume approximation) and secondary quantitative measurements (e.g. formula-based volume approximation).²¹ The agreement is graphically demonstrated (Figure 2) and mathematically indicated by the mean difference of the two measurements as well as the upper and lower limits of

agreement (mean ± 1.96 SD).²¹ We tested for proportional bias with the help of linear regression. In the case of proportional bias, logarithmic transformation was performed as recommended by Bland and Altman.²²

Figure 2 Four Bland–Altman plots graphically demonstrating the agreement between image segmentation and formula based volume approximation (B, C) as well as the intra-rater variability for image segmentation and formula-based volume approximation (A, D). On the x-axis, the mean of both measurements is displayed after logarithmic transformation (log [ml]). The y-axis shows the percentage difference for each measurement. x-Axis parallels display the mean bias as well as the upper and lower limits of agreement.

Figure 3 On the y-axis, the volume (gathered by image segmentation) is plotted against the correlating tumour diameter (x-axis) for each individual patient. The focus is set on volumetrically small lesions that can be particularly overestimated by the maximum tumour diameter. Extremes have been highlighted (filled dots).

Results

Patients

The present patient sample consisted of 151 patients with a mean age of 46 (± 18) years. 35 patients showed involvement of the maxilla and 116 of the mandible. Patients showed either an unilocular (120) or multilocular (31) odontogenic OJL. 51 lesions were evaluated as an odontogenic neoplasm with potentially infiltrative capacities (5 odontogenic myxomas, 19 ameloblastomas, 27 keratocystic odontogenic tumours) and 100 individuals showed a non-neoplastic jaw cyst (48 dentigerous and 52 periapical cysts). Irregular outline (due to cortical perforation and/or inflammatory alteration) was radiologically present in 58 cases.

Volumetric data and general results

Results of each method for volume approximation (image segmentation-based- and formula-based approximation) are provided in Table 1. Mean maximum tumour diameter was calculated as 30.6 (± 12.1) mm with a median of 27.3 mm and a minimum and maximum of 9.2 and 63.3 mm, respectively. Mean segmentation-based volume for mandibular and maxillary lesions was 7.7 (± 7.9) and 7.7 (± 9.2) ml, respectively ($p = 0.958$). Student's *t*-test revealed that infiltrative odontogenic lesions showed in mean a significantly larger maximum tumour diameter

compared to odontogenic cysts ($p = 0.001$) with 38.5 (± 12.8) and 26.6 (± 9.6) cm, respectively. Image segmentation-based volume approximation confirmed that infiltrative odontogenic neoplasms were significantly larger than non-neoplastic jaw cysts ($p = 0.001$) with 12.7 (± 11.5) and 5.2 (± 3.8) ml, respectively.

Furthermore, multilocular lesions (mean 16 $\pm$ 13 ml) were significantly larger than unilocular ones (mean 5.6 $\pm$ 4.4 ml) with $p = 0.001$. Multilocularity was significantly associated with the diagnosis of an odontogenic neoplasm (χ^2 , $p = 0.001$).

Maximum tumour diameter and volumetric size characterization

Figure 3 illustrates the relationship between the maximum tumour diameter and the volumetric expansion (segmentation-based approximation) of the respective jaw lesion. The maximum orthogonal diameter seems to be prone to overestimate the size of smaller lesions. For example, one can observe that volumetrically small lesions (e.g., 2 ml) can show a great variety of corresponding maximum orthogonal tumour diameters (range from approximately 15–25 mm). Volumetrically small lesions (e.g. 2 ml), therefore, can display maximum tumour diameters that correspond to volumetrically much bigger lesions (e.g. 8 ml of volume and maximum tumour diameter of 25 mm).

Table 2 DSC for each comparison of interest

Category	DSC					
	Total	SD	Mandible	SD	Maxilla	SD
1. SEG1 vs SEG2 TOTAL	0.977	0.02	0.976	0.02	0.978	0.02
2. SEG1 vs SEG2 OT	0.976	0.02	0.977	0.02	0.970	0.02
3. SEG1 vs SEG2 CYSTS	0.978	0.02	0.977	0.02	0.980	0.17
4. SEG1 vs CUBOID1	0.730	0.13	0.719	0.14	0.761	0.11
5. SEG1 vs ELLIPSOID1	0.864	0.12	0.865	0.12	0.860	0.12
6. F1 vs F2 TOTAL	0.925	0.07	0.924	0.07	0.927	0.06
7. F1 vs F2 OT	0.938	0.05	0.938	0.05	0.939	0.05
8. F1 vs F2 CYSTS	0.918	0.07	0.920	0.08	0.923	0.07
9. SEG A vs SEG B TOTAL	0.962	0.04	0.962	0.03	0.960	0.04
10. SEG A vs SEG B OT	0.953	0.03	0.956	0.03	0.931	0.04
11. SEG A vs SEG B CYSTS	0.966	0.04	0.966	0.04	0.967	0.04
12. Formula A vs Formula B	0.860	0.11	0.852	0.10	0.870	0.13

1, first measurement by investigator A; 2, second measurement by investigator A; A, first investigator; B, second investigator; CYSTS, non-neoplastic jaw cysts; F, formula-based; OT, odontogenic tumour; SD, standard deviation; DSC, dice similarity coefficient;

Image segmentation and formula-based volume approximation—inter- and intra-rater variability

Image segmentation-based volume approximation showed a small intra-rater variability (Tables 1 and 2, Figure 2A). The DSC was smaller for odontogenic tumours when compared to non-neoplastic jaw cysts. The mean bias was calculated as -0.031% difference. Upper and lower limits of agreement were calculated as 12.25 and -12.31% , respectively.

Formula-based volume approximation (F1 and F2) showed a high overlap (DSC 0.925) overall (Table 2), and therefore a low intra-rater variability. The intra-rater variability was, however, much higher when compared to image segmentation (Figure 2D). We found a mean percentage difference of -1.75% with upper and lower limits of agreement of 38.5 and -42.03% , respectively.

Concerning the inter-rater variability, we found a high overlap between investigator A and B concerning image segmentation-based volume approximation (Tables 1 and 2, DSC 0.962). Non-neoplastic jaw cysts showed a slightly higher overlap when compared to odontogenic tumours. Mean percentage difference between investigator A and B was calculated as -0.9% with upper and lower limits of agreement of 19.6 and -21.4% , respectively. Formula-based volume approximation showed a relatively poor overlap with 0.860 DSC and a mean percentage difference of 0.04% with upper and lower limits of agreement of -48 and 49% , respectively.

Image segmentation vs formula-based volume approximation

Furthermore, we investigated the agreement and overlap between image segmentation- and formula-based volume approximation (Tables 1 and 2, Figure 2B,C).

Primarily, we found that the cuboid formula yielded volumetric approximations that were in mean 52.03% higher when compared to the values gathered by image segmentation (limits of agreement: -112.63 and $+8.57\%$,

Figure 2B). A DSC of 0.730 indicates a poor overlap. For mandibular lesions, the DSC dropped to 0.719 (maxillary 0.761). The mean values between segmentation and cuboid-formula based volume approximation were statistically significant from each other (Table 1; Student's *t*-test $p = 0.001$).

Secondly, the ellipsoid formula yielded volume approximations that were in mean 10.1% lower when compared to segmentation-based volume approximations (Figure 2(C)). Limits of agreement were calculated as -56.6 and 76.8% . The DSC was 0.864 with a strong numerical overlap. Mean volume approximations were not statistically significant from each other (Table 1; Student's *t*-test $p = 0.956$).

Discussion

Osseous integrity of the jaws, particularly of the tooth-bearing areas, is paramount to the functionality of the stomatognathic system. Therefore, odontogenic tumours and odontogenic jaw cysts constitute important entities of diseases. Above all, odontogenic tumours constitute a heterogenous entity of disease, showing potentially infiltrative variants. The three most commonly surgically treated odontogenic tumours are ameloblastoma, the keratocystic odontogenic tumour and OM.^{5,7,23}

For diagnostics and therapeutic planning, a method that reliably delineates the extent of an osteolytic jaw lesions and simultaneously allows for the relative visualization of surrounding healthy tissue is indispensable for guidance of the managing craniomaxillofacial surgeon. This is of utmost importance in the context of pre-surgical planning of osseous reconstructive procedures. Technological advancements have made it possible for physicians and related specialties to generate a vast amount of biomedical data for each patient ("big data"). In the fields of oral surgery, preoperative multidimensional imaging procedures constitute an important

foundation for management decisions. Thereby generated biomedical data can be extracted and saved (*e.g.* as a DICOM file), rendering the data available for image processing software and analysis. An intensively studied topic in the fields of biomedical data analysis is image segmentation.

Image segmentation is the biomedical image processing equivalent of surgical dissection, aiming to separate two radiologically visible entities.¹¹

The process involves labeling of voxels with different values, thereby clearly distinguishing the two entities (Figure 1), ultimately allowing morphometric and volumetric size characterization. However, in the fields of craniomaxillofacial surgery and oral medicine in general, there is so far no consensus about the optimal method for size delineation of osteolytic jaw lesions. Especially in the scientific literature, various methods are used. Importantly, the maximum tumour diameter and the cuboid formula (based on the three maximum orthogonal tumour diameters) are prominent methods, despite the widespread availability of three-dimensional image data sets.^{24,25} However, a large portion of an imaging data set's information is thereby neglected, failing to optimize individualized patient care. Considering the promising advent of quantitative radiographic phenotyping ("Radiomics") and the importance of image segmentation prior to feature extraction, it is of high relevance to propagate the usage of such fundamental methods, in order to improve therapeutic assessment of destructive jaw diseases (*e.g.* in the context of BRAF-targeted therapy of ameloblastomas).^{26,27}

In the fields of oral medicine, separable radiologically visible entities can be an OJL and the surrounding healthy bone of the respective jaw

Primarily, we sought to evaluate the value of the maximum tumour diameter for size characterization of osteolytic odontogenic jaw lesions. Both in daily routine and in the scientific community, this method is widely used, even to plan surgical interventions and decide between conservative and aggressive surgical approaches.²⁸ Our data suggest that the maximum tumour diameter should no longer be recommended. Jaw lesions are three-dimensional objects that cannot be accurately described by the maximum tumour diameter. This results in the fact that the relative size of volumetrically small lesions (*e.g.* 2 ml) can be overestimated by the maximum tumour diameter. For example, Figure 3 illustrates that small lesions can show the same maximum tumour diameter as a 10 ml lesion (Figure 3). Therefore, image segmentation-based volume approximation (based on voxel-specific size characterization) is more accurate and allows comparative analysis of jaw lesions. In fact, the maximum tumour diameter tends to mask the real size of an osteolytic jaw lesion. This fact is of high importance in the context of therapeutic management of odontogenic myxoma. The maximum tumour diameter has shown to be error-prone and

Figure 4 The volume was automatically approximated by the program and indicated as 8 ml. In red, one can see the three-dimensionally reconstructed osteolytic jaw lesion based on image segmentation. The lesion was amenable to a periapical cyst originating from the anterior mandible. In both pictures the issue of using formula based volume approximation is illustrated (A, cuboid formula; B, ellipsoid formula). The cuboid formula yielded a volume of 12.5 ml whereas the ellipsoid formula indicated a volume of 6.5 ml.

imprecise when wanting to decide between conservative and aggressive treatment approaches.⁵ The present investigation strongly suggests the association between the maximum tumour diameter and the real intraosseous extent (volume) is inconsistent and thus relative over- or even underestimation can be the result. Prospective investigations would be desirable to, *e.g.* evaluate image segmentation-based volume approximation in the context of therapeutic assessment of OM.

Secondly, we outline that formula-based volume approximation is error-prone when compared to image segmentation. In the context of volume approximation, image segmentation should constitute the gold-standard as it allows voxel-specific size characterization of a three-dimensional structure.^{10,12,14} As odontogenic jaw lesions rarely grow in the perfect shape of a cuboid or ellipsoid, both formulas are naturally error-prone (Figure 4). In particular, this applies to infiltrative odontogenic neoplasms, capable of arbitrary three-dimensional infiltration with budding and thus irregular three-dimensional configuration (Table 2).⁵ Both Bland–Altman analysis and DSC mathematically and graphically depict the great disparity between image segmentation- and formula-based volume approximation (Figures 2 and 4; Table 2). This fact applies foremost to the cuboid formula. Interestingly, the cuboid formula is preferably used to quantify neoplastic disease regression following pharmaceutically targeted therapy of ameloblastoma.⁸ Based on our results, the cuboid formula seems to be particularly error-prone, mainly overestimating the real volume of odontogenic jaw lesions. Hence, one must conclude that the cuboid formula is inaccurate for size characterization of osteolytic jaw lesions and does not allow for comparative size characterization in the context of clinical patient

management. Importantly, the ellipsoid formula showed volumes that were very similar to the ones based on image segmentation. In mean, a slight underestimation was noted (Figure 2, Table 1). Thus, for formula-based size characterization of osteolytic jaw lesions, one must recommend the ellipsoid formula.

ITK-SNAP is free to use and a user-friendly program for image segmentation of various modalities, including CT, MRI, and CBCT.¹⁰ We show that this program can be used for size characterization of odontogenic OJLs. It is recommendable, in order to scientifically standardize size characterization of jaw lesions, to use image segmentation-based volume approximation. Thereby, interinstitutional comparative analyses of the size distribution of odontogenic jaw lesions, such as ameloblastoma, would be feasible. Such a standardization is necessary in order to reliably evaluate the success of BRAF-Inhibitors as a treatment option for ameloblastomas. With the help of image segmentation, tumour regress could be precisely monitored and thus the success or failure could be documented in a detailed and reproducible way.

Image segmentation-based volume approximation could be helpful in clinical management decisions, e.g. in the case of odontogenic myxoma. Among the patients that were investigated within the present investigation, we were able to demonstrate that biologically

aggressive lesions (neoplasms) were significantly larger than non-neoplastic jaw cysts. Therefore volume, as delineated by image segmentation, could be considered an imaging biomarker of growth potential and aggressiveness in odontogenic jaw lesions. However, further investigations of larger cohorts must be conducted in order to elucidate the exact role of lesion size (volume), as well as, e.g. multilocularity, as imaging biomarkers of tumour aggressiveness and growth potential.

Conclusion

To conclude, the maximum tumour diameter, as well as formula-based volume approximation, for size characterization seem to be unreliable and imprecise for OJLs. Image segmentation-based volume approximation of odontogenic jaw lesions is feasible and reproducible as shown by a low intra- and inter-rater variability.

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