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ORIGINAL ARTICLE

Age estimation based on pulp cavity/chamber volume of 13 types of tooth from cone beam computed tomography images

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Abstract
Aim The aims of this study are to identify which type of tooth has the strong relationship between age and pulp cavity/chamber volume among 13 types of tooth from the same dentition and to determine whether the inclusion of multiple types of tooth may improve the accuracy of age estimation.
Materials and methods Cone beam computed tomography (CBCT) images from 115 females and 125 males aged between 16 and 63 years were analyzed. The DICOM data of all the images were imported into ITK-SNAP 2.4 for the calculation of pulp cavity/chamber volumes. Logarithmic regression analysis and multiple linear regression analysis were applied to establish the relationship between age and pulp cavity/chamber volumes.
Results Among the 13 types of tooth, maxillary second molars have the largest R^2 (0.491, 0.642, and 0.498) and the smallest SEE (8.119, 6.754, and 8.022) in male, female, and pooled gender samples, respectively. The multiple linear regression analysis for the combination of multi-types of tooth indicated that a larger R^2 (0.627, 0.701, and 0.631) and smaller SEE (7.100, 6.258, and 6.970) than the counterpart calculated from the logarithmic regression analysis of a single type of tooth in male, female, and pooled gender samples, respectively.
Conclusion The pulp chamber volume of the maxillary second molars has the largest correlation coefficient with age. Using multiple types of tooth may improve the accuracy of age estimation compared with only one type of tooth used.

Keywords Age estimation · Cone-beam CT · Pulp cavity volume · Secondary dentine

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Introduction

Age estimation is an important aspect of forensic science. Accurate age estimation method is required for an increasing number of situations such as unidentified body remains, corpses from massive disasters, refugees and asylum seekers without proof of identification, and people with question of a threshold age arises for legal reasons.

Due to the fact that tooth are highly resistant to mechanical, chemical, or physical impacts and time [1, 2] as well as that age-related changes of tooth are minimally influenced by the nutrition, environment, and living conditions that an individual is submitted to [3, 4], many age estimation methods based on teeth have been established.

Secondary dentine apposition is an age-associated process that begins after tooth root completely developed and continues through people's whole life. With age increases, secondary dentine lays on the walls of pulp cavity and decrease the size of pulp cavity [5–8]. With this principle in mind, many attempts have been done to correlate the pulp cavity size and chronological age by the use of two-dimensional radiographic images like panoramic or periapical radiographs for age estimation [9–12]. Despite the favorable results, the use of two-dimensional radiographic images is controversial because it does not represent the complete three-dimensional morphological changes of pulp cavity. Recently, with the wide use of three-dimensional images in practice, three-dimensional image datasets obtained from cone beam CT, CT, and micro-CT have been applied to investigating the potential relationship between age and volume ratio of pulp cavity to entire tooth using single-rooted teeth and concluded that pulp/tooth volume ratio is a useful indicator for age [13–24]. Meanwhile, an age estimation method from multi-rooted first molars was also established with reasonable precision and accuracy [25].

In the analysis of these studies, we found that the previous studies only focus on one or two specific types of tooth. Considering the fact that human tooth can be categorized into maxillary tooth and mandibular tooth, and each of them contains seven types of tooth, namely central incisors, lateral incisors, canines, first premolars, second premolars, first molars, and second molars, information carried by only one or two specific types of tooth is limited. Furthermore, the image quality from 3D images and the sample size demonstrated in the previous studies were not comparable. This makes it difficult to evaluate which type of tooth has a strong relationship between age and pulp cavity volume. The aims of the present study were thus (1) to assess which type of tooth has a strong relationship between age and pulp cavity volume among 13 types of tooth from the same dentition and (2) to investigate whether the inclusion of multiple types of tooth from the same dentition may improve the accuracy of age estimation.

Materials and methods

Subjects

Cone beam computed tomography (CBCT) images of 240 patients were retrospectively collected from the database in Peking University School and Hospital of Stomatology. The birth date of all subjects was confirmed in the hospital's patient information system. The age and gender distribution of the subjects are shown in Table 1. All the CBCT images were taken for diagnosis or treatment purpose; there was thus no unnecessary or additional radiation exposure to the patients.

Due to the complexity of root and canal system in maxillary first premolars, the maxillary first premolars were not included in the present study. Thus, a total of 13 types of tooth were finally included and subsequently divided into two categories: single-rooted tooth and multi-rooted tooth. The single-rooted tooth contains maxillary central and lateral incisors, maxillary canines, maxillary second premolars, mandibular central and lateral incisors, mandibular canines, and mandibular first and second premolars. The multi-rooted tooth contains maxillary first and second molars, mandibular first and second molars. The inclusion criteria of the tooth were no caries, no excessive tooth wear, no dental restorations, no artifacts due to metal restorative materials present in adjacent teeth, and no pulpal calcification. To specify the extent of "excessive tooth wear," we borrowed the Smith and Knight's tooth wear index (TWI) [26] and the results from the tooth wear epidemiological investigation in Chinese population [27]. The tooth with TWI $\leq$2 before 50 years and TWI $\leq$3 after 50 years was included. Only the images where all the 13 types of tooth met the inclusion criteria were chosen.

Table 1 Age and gender distribution of the patients

Age (year)	Male	Female	Total
16–20	19	24	43
21–30	41	36	77
31–40	33	32	65
41–50	20	13	33
51–63	12	10	22
Total	125	115	240

Image acquisition and segmentation

All the CBCT images were acquired with a CBCT unit NewTom VG (Quantitative Radiology, Verona, Italy). Exposure parameters for CBCT image were 110 kVp and 5.14–89.37 mAs in accordance with patient size and field of view. Selection of field of view (FOV) was based on clinical needs. The FOVs included 6 cm × 6 cm, 8 cm × 8 cm, 12 cm × 8 cm, 15 cm × 12 cm, or 15 cm × 15 cm.

Acquired images were subsequently reconstructed with a voxel size of 0.15 mm and exported as DICOM data sets. These data were then imported into a 3D image semiautomatic segmenting and voxel-counting software ITK-SNAP 2.4 (open source software, www.itksnap.org) for the calculation of pulp cavity/chamber volumes [28].

For single-rooted tooth, we calculated the full volume of tooth pulp cavity. For multi-rooted molars, we set the pulp chamber floor as the "cut plane" to cut off the roots and calculate the volume of tooth pulp chamber to avoid the influence of the complex root system [25]. The final segmented image of multi-rooted tooth pulp chamber is shown in Fig. 1. The final segmented image of all types of tooth pulp cavity/chamber is shown in Fig. 2.

Segmentation accuracy

To validate the measurement accuracy of image segmentation and volume calculation, images of ten extracted multi-rooted molars and five extracted single-rooted premolars were acquired with the CBCT unit NewTom VG and a high-resolution micro-CT unit (Inveon, Siemens, Germany). Projecting parameter of the micro-CT was 80 kV, 500 mA, and 8.82 μm effective pixel size. In order to simulate an in vivo environment, extracted teeth were mounted in a dry mandibular bone and a 20-mm-thick water phantom was placed

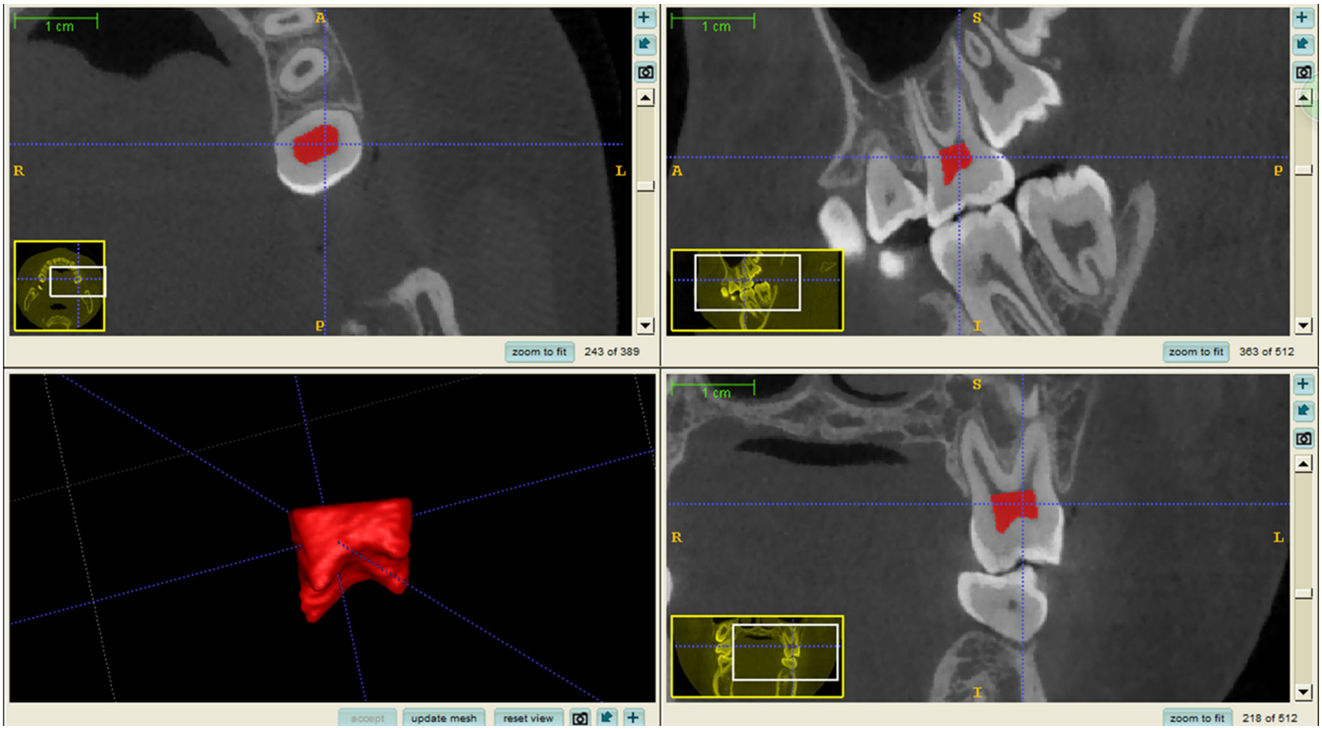

Fig. 1 The final segmented image of multi-rooted tooth pulp chamber

around the bone to simulate soft tissues during the CBCT exposures.

The images were then imported into the software ITK-SNAP 2.4 to calculate the pulp cavity/chamber volume. With the volume calculated from the micro-CT images as the reference standard, the volume calculated from the CBCT images was quantified for the accuracy of the volume calculation.

Inter-observer and intra-observer variability

All the measurements were carried out by the same examiner. To test intra-observer reproducibility, slice data of a random sample of 15 patients (13 teeth in each patients, totally 195 teeth) were reexamined after an interval of 3 weeks. At the same time, the same slice data of 15 patients were examined by another calibrated examiner to test the inter-observer reproducibility.

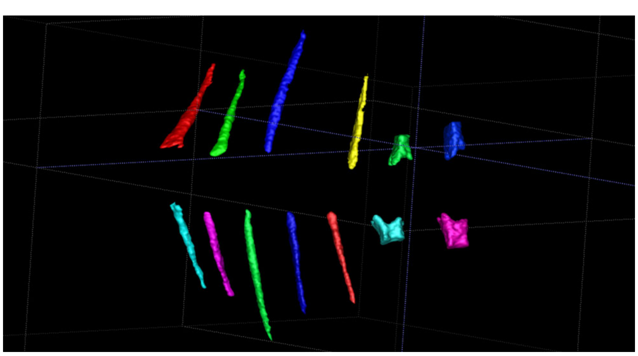

Fig. 2 The final segmented image of all types of tooth pulp cavity/chamber

Statistical analysis

Descriptive statistics for the volume of pulp cavity/chamber were calculated.

Paired *t* test was used to determine the statistical significance of inter-observer and intra-observer variability. A *p* value of 0.05 or less was considered significant.

Independent-sample *t* test was applied to comparing the difference of the pulp cavity/chamber volume between male and female. A *p* value of 0.05 or less was considered significant.

Logarithmic regression analysis was conducted with age as dependent variable and pulp cavity/chamber volume of each type of tooth as independent variable to establish mathematical models for the human age estimation.

Multiple linear regression analysis was conducted with age as dependent variable and logarithmic transformed (Log10) pulp cavity/chamber volume data of 13 types of tooth as independent variables to establish mathematical equations. To determine the most significant variables and optimize the models, the 13 independent variables were screened by backward method. The one with the biggest *p* value ($p > 0.1$) in the equation would be weeded out one by one until all the remained independent variables have a *p* value less than 0.1 which means that the regression equation was statistically significant.

The coefficient of determination (R^2) from the regression analyses was calculated to evaluate the relationship between chronological age and pulp cavity/chamber volume. The standard errors of the estimate (SEE) calculated from the regression analyses were used to determine the accuracy of the mathematical models.

All statistical analyses were performed using SPSS Statistics 19.0 (SPSS, Inc., Chicago, IL).

Results

Descriptive statistics of the pulp cavity/chamber volume for the 13 types of tooth in the pooled gender samples are shown in Table 2.

Except for the mandibular first molars ($p = 0.102$), the difference in volume between genders was statistically significant for other 12 types of tooth ($p = 0.000$ for maxillary lateral incisor, maxillary canines, maxillary second premolars, mandibular canines, mandibular first premolars, mandibular second premolars, and maxillary second molars, $p = 0.001$ for mandibular lateral incisors, $p = 0.003$ for mandibular second molars, $p = 0.006$ for mandibular central incisors, $p = 0.019$ for maxillary central incisors, and $p = 0.045$ for maxillary first molars).

The average difference of the pulp volumes obtained from micro-CT and CBCT image was 4 % for the multi-rooted molars and 6 % for the single-rooted premolars.

The R^2 and SEE of each type of tooth from logarithmic regression analysis for male, female, and the pooled gender samples are shown in Table 3.

The R^2 and SEE for the remained types of tooth screened by backward method from the multiple linear regression analysis for male, female, and the pooled gender samples are shown in Table 4. Table 4 demonstrates that for male, the combination of multi-type tooth of maxillary central incisors, maxillary lateral incisors, maxillary canines, maxillary first molars, mandibular first premolars, and mandibular second molars had a relatively large R^2 value of 0.627 and a small SEE value of 7.100. Similarly, the combination of maxillary central incisors, maxillary canines, maxillary second molars, and mandibular second molars for female and the combination of maxillary central incisors, maxillary lateral incisors, maxillary canines, maxillary second premolars, maxillary first molars, maxillary second molars, and mandibular second molars for the pooled gender samples also had a relatively large value of R^2 (0.701 for female, 0.631 for the pooled gender) and small value of SEE (6.258 for female, 6.970 for the pooled gender).

Sample scatter diagram is shown in Fig. 3, in which the relationship between the volumes of pulp chamber and ages for the maxillary second molars in the pooled gender samples was illustrated.

No significant differences were found for inter-observer ($p = 0.864$) and intra-observer ($p = 0.426$) variances for all teeth and separately for each of the 13 types of tooth (p values range from 0.057 to 0.924 for inter-observer variances, and p values range from 0.152 to 0.997 for intra-observer variances).

Discussion

Age estimation from radiographic assessment of pulp cavity/chamber volume is of particular value due to the feature of secondary dentine apposition. It is not only for living

Table 2 Descriptive statistics of the pulp cavity/chamber volume for the 13 types of tooth in the pooled gender samples

	Tooth position	Number	Minimum (mm^3)	Maximum (mm^3)	Mean (mm^3)	Std. deviation
Single-rooted tooth	U1	240	6.496	41.865	20.531	6.479
	U2	240	3.102	27.342	13.125	4.640
	U3	240	11.968	50.283	24.915	7.628
	U5	240	8.765	40.232	18.656	5.660
	L1	240	3.365	19.133	8.573	2.541
	L2	240	4.705	25.011	11.213	3.468
	L3	240	9.883	54.393	22.502	6.800
	L4	240	7.884	31.964	16.125	4.168
	L5	240	7.240	35.615	15.748	4.661
Multi-rooted tooth	U6	240	8.242	67.288	24.408	8.779
	L6	240	8.023	51.684	21.826	7.276
	U7	240	9.049	64.445	25.492	9.431
	L7	240	8.330	57.081	26.153	9.075

U upper jaw, *L* lower jaw, *1* central incisor, *2* lateral incisor, *3* canine, *4* first premolar, *5* second premolar, *6* first molar, *7* second molar

Table 3 The R^2 and SEE of each type of tooth from logarithmic regression for male, female, and the pooled gender samples

	Tooth position	Pooled gender		Male		Female	
		R^2	SEE	R^2	SEE	R^2	SEE
Single-rooted tooth	U1	0.323	9.322	0.391	8.884	0.290	9.512
	U2	0.311	9.402	0.406	8.777	0.285	9.547
	U3	0.108	10.698	0.198	10.195	0.117	10.607
	U5	0.305	9.440	0.323	9.364	0.386	8.844
	L1	0.253	9.787	0.334	9.292	0.206	10.061
	L2	0.201	10.120	0.284	9.630	0.162	10.334
	L3	0.167	10.337	0.252	9.845	0.269	9.655
	L4	0.330	9.267	0.413	8.725	0.351	9.098
	L5	0.344	9.173	0.404	8.791	0.393	8.795
Multi-rooted tooth	U6	0.489	8.093	0.481	8.199	0.554	7.538
	L6	0.434	8.522	0.457	8.392	0.458	8.310
	U7	0.498	8.022	0.491	8.119	0.642	6.754
	L7	0.487	8.111	0.458	8.380	0.614	7.011

U upper jaw, *L* lower jaw, *1* central incisor, *2* lateral incisor, *3* canine, *4* first premolar, *5* second premolar, *6* first molar, *7* second molar

individuals with tooth but also for adults whose age is difficult to be determined by the methods basing on changes from organic evolution. After a search of literatures, it is indicated that studies in this field are still in the beginning and worth of being analyzed in depth.

The present study shows that among the 13 types of tooth, the maxillary second molars show the largest value of R^2 in the male, female, and pooled gender samples. Maxillary canines show the smallest correlation coefficient between the pulp cavity volume and age in male, female, and pooled gender samples. So, the maxillary second molar was the most suitable type of tooth for age estimation based on pulp chamber/cavity volume, and the maxillary canine was the least. The possible reasons may include the following. First, the main function of molars is to grind food and canines are used to tear food. From the clinical function point of view, more dentition apposition may lay down on the pulpal cavity walls of molars than of other types of tooth, especially canines. Second, canines locate at the turning point of dental arch. After reconstruction, the 3D images at a turning point maybe not as clear and accurate as those obtained at a planar field, such as the back part of denture where molars locate. This may affect the segmentation precision and accuracy for pulp cavity and pulp chamber. Third, the pulp chamber of molars is wider than the pulp cavity of other tooth. This makes it easier to delineate the borders of pulp chamber from 3D images for segmentation purposes for molars than for other tooth.

To determine the variables that significantly influence the age estimation, a backward regression procedure which did not exclude variables with any significant contribution to the

Table 4 The R^2 and SEE for the remained types of tooth screened by backward method from the multiple linear regression analysis for male, female, and the pooled gender samples

	Remained tooth	R^2	SEE
Male	U1 + U2 + U3 + U6 + L4 + L7	0.627	7.100
Female	U1 + U3 + U7 + L7	0.701	6.258
Pooled gender	U1 + U2 + U3 + U5 + U6 + U7 + L7	0.631	6.970

U upper jaw, *L* lower jaw, *1* central incisor, *2* lateral incisor, *3* canine, *4* first premolar, *5* second premolar, *6* first molar, *7* second molar

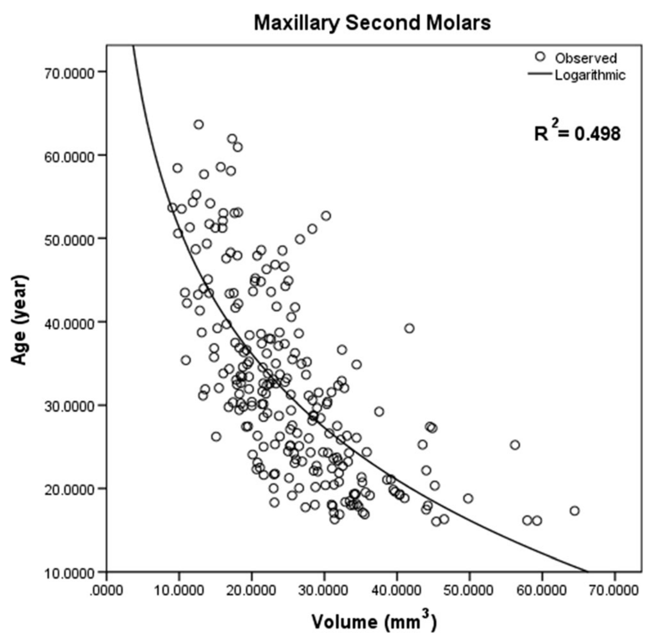

Fig. 3 Scatter diagram shows the relationship between the volumes of pulp chamber and age for the maxillary second molars in the pooled gender samples

regression was applied with an inclusion level at $p < 0.1$. After analysis, only the variables from maxillary central incisors, maxillary lateral incisors, maxillary canines, maxillary second premolars, maxillary first molars, maxillary second molars, and mandibular second molars were chosen as independent variables for the pooled gender samples. For the male samples, maxillary central incisors, maxillary lateral incisors, maxillary canines, maxillary first molars, mandibular first premolars, and mandibular second molars were chosen as independent variables, and for the female samples, the maxillary central incisors, maxillary canines, maxillary second molars, and mandibular second molars were selected as independent variables. From the multiple linear regression analysis, we find a larger value of R^2 and a smaller value of SEE than the counterpart calculated from the logarithmic regression analysis of a single type of tooth in male, female, and pooled gender samples (Tables 3 and 4). This indicates that using multiple types of tooth may improve the accuracy of age estimation compared with only one type of tooth used. Thus, the combination of the abovementioned multiple types of tooth were recommended when using the pulp chamber/cavity volume to estimate age for people with unknown sex, males and females, respectively.

To determine the measurement accuracy, the volume calculated from micro-CT images was used as the reference standard. Micro-CT provides accurate and precise assessment of internal dental structures including root canal morphology [29, 30] and has been considered as a reference standard in dental liner and volumetric measurements [31, 32]. In some studies focusing on the relationship between age and volume ratio of pulp cavity to entire tooth, the usefulness of micro-CT images has also been identified [21–24]. In the present study, an average difference of only 4 % for multi-rooted molars and an average difference of 6 % for single-rooted premolars between the pulp volumes obtained from micro-CT and CBCT image were found. The average difference is relatively small when compared them to the differences reported in previous studies [13, 14, 16]. The measurement difference may be due to the fact that micro-CT images provide much higher spatial resolution than does a CBCT unit and hence a much more accurate measurement.

Independent sample *t* test in the present study showed that difference in pulp volume between genders was statistically significant for the 12 types of tooth except for mandibular first molars. The observed relation between the volume of pulp cavity/chamber and age was stronger for female than for male in the maxillary second premolars, maxillary first molars, maxillary second molars, mandibular canines, mandibular first molars, and mandibular second molars. The relation between the volume of pulp cavity and age was stronger for male than for female in maxillary central incisors, maxillary lateral incisors, maxillary canines, mandibular central incisors, mandibular lateral incisors, mandibular first premolars, and mandibular second premolars. Thus, the use of gender-specific age estimation equations is recommended when using dental pulp cavity/chamber volume for age estimation. This recommendation is in agreement with the previous studies [23, 33].

In the studies dealing with the relationship of dental pulp and chronological age, the R^2 is often used to indicate the association between chronological age and pulp cavity/chamber volume or the relationship between chronological age and pulp to tooth volume ratio. To get a rough comparison of the R^2 values from the previous studies, a summary of R^2s with related study parameters is presented in Table 5. From Table 5, we can see that the study objects, such as tooth type, sample size, age distribution range, imaging system, and population source, are diverse in different studies. These differences subsequently affect the value of R^2. The R^2 values from the present study are very comparable with those in the studies in which CBCT was used as a 3D imaging media. On the other hand, the R^2s from a CBCT study are generally smaller than those R^2 values from a micro-CT study. This is also true for the present study. The reason just as what we have discussed above, i.e., micro-CT image provides much higher spatial resolution than does a CBCT unit and hence a much more accurate segmentation and measurement.

Contrast to other studies in which pulp cavity to tooth volume ratio was used as an indicator for estimating human age, the volume of pulp cavity/chamber was employed in the present study. The reasons why we chose pulp cavity/chamber volume as the indicator are as follows. First, the decrease of pulp cavity/chamber volume is directly related to the age-related formation of secondary dentine, while the volume of the tooth hard tissues can be increased by the dentine apposition and decreased by the attrition of enamel. Thus, a pulp cavity to tooth volume ratio may not reflect the real change from secondary dentine apposition [22]. Second, the pulp cavity volume calculation was more accurate than the volume calculation of whole tooth because of high image contrast between dentine and pulp chamber [14].

Maxillary first premolar was not included in the present study because it has been reported that the root and canal systems of maxillary first premolars were variable and complex. The prevalence of one-rooted tooth and two-rooted tooth of maxillary first premolars differs in different populations [34, 35]. In Chinese population, a study shows that the frequency of one-rooted teeth of maxillary first premolars was 66 % and two-rooted teeth was 33 % [35]. Besides, in the same study, it shows that amongst the two-rooted teeth, 41 % bifurcated from the pulp chamber floor, forming two independent roots, while the remaining 59 % bifurcated at different levels in the apical third of the roots. Thus, there was no uniformly cut plane to cut tooth root for the calculation of the pulp chamber volume like molars in the present study.

Table 5 Summary of the studies investigating the relationship between age and the pulp to tooth volume ratio/pulp chamber volume by the use of 3D images

Authors	Published year	Tooth position	Number	Age distribution	R^2	Imaging system	Population	Machine brand
Yang et al. [13]	2006	Single-rooted teeth	28	23–70	0.29	CBCT	Belgian	3D Accuitomo
Star et al. [14]	2011	1 and 2 3	64 32	10–65	0.41 0.07	CBCT	Belgian	Scanora 3D
		4 and 5	15		0.23			
Jagannathan et al. [15]	2011	Lower 3	140	10–70	0.397	CBCT	Indian	3D Accuitomo
Pinchi et al.[16]	2015	Left upper 1	148	10–80	0.58	CBCT	Italian	Scanora 3D
Porto et al. [33]	2015	Upper 1	118 (total) 58 (M)	22–70	0.21 0.152	CBCT	Brazilian	i-CAT Next Generation
			60 (F)		0.297			
Ge et al. [25]	2015	Upper 6 Lower 6	373 372	12–69	0.66 0.604	CBCT	Chinese	NewTom VG
De Angelis et al. [17]	2015	Right upper 3	91 (total) 42 (M)	17–80	0.389 0.263	CBCT	Italian	i-CAT Next Generation
			49 (F)		0.485			
Tardivo et al. [18]	2011	3	101	14–74	0.38	CT	French	Non-provided
Tardivo et al. [19]	2014	3	840	15–85	0.915–0.964	CT	French	Siemens Sensation
Sakuma et al. [20]	2013	Lower 4	136 (total) 105 (M)	14–79 14–79	0.571 0.596	MDCT	Japanese	ECLOS
			31 (F)	19–78	0.186			
Vandevoort et al. [21]	2004	Single-rooted teeth	43	24–66	0.31	Micro-CT	Belgian	SkyScan bvba
Someda et al. [22]	2009	Lower 1	76 (M) 79 (F)	12–79	0.65 0.77	Micro-CT	Japanese	HMX225 ACTIS4
Agematsu et al. [23]	2010	Lower 1	73 (M) 75 (F)	20–79	0.67 0.75	Micro-CT	Japanese	HMX225 ACTIS4
		Lower 5	56 (M)		0.56			
			54 (F)		0.58			
Aboshi et al. [24]	2010	Lower 4 Lower 5	50 50	20–78	0.635 0.703	Micro-CT	Japanese	SMX-130CT-SV

M male, *F* female, *1* central incisor, *2* lateral incisor, *3* canine, *4* first premolar, *5* second premolar, *6* first molar

In the present study, cone beam CT was used to acquire three-dimensional datasets. Compared with micro-CT, CBCT can provide a relatively large scanning area, while micro-CT only has a confined scan area in which one extracted tooth can be scanned at a time. Meanwhile, extracting teeth for age estimation purpose is not acceptable for a live person. CT imaging can be acquired for a live person, but it needs relatively high cost and radiation dose compared with CBCT [36]. Another advantage by the use of CBCT is that with the wide use of CBCT in dental practice, 3D volume information of teeth on living individuals can be easily accessed.

Systemic diseases status of the patients was not investigated in the present study because the basic principle for age estimation by the use of pulp cavity is that teeth are less susceptible to nutritional, hormonal, and systemic pathological changes after completion of permanent dentition development. Although some systemic disease may cause pulpal calcification according to the literatures [8], tooth with pulpal calcification have been excluded in the present study. Other influence on the volume of pulp cavity from systemic diseases has not been certainly confirmed [7, 37].

One limitation of the present study is that the sample population is less homogeneous. This is caused by the small number of old people who are more prone to teeth loss and thus is difficult to meet the inclusion criteria employed in the study. This may affect the age estimation for old people.

Conclusion

The present study investigated the relationship between age and pulp cavity/chamber volume of 13 types of tooth from the same dentition. Gender difference exists in the volume of pulp cavity/chamber volume for most types of tooth. Therefore, the use of gender-specific age estimation equations is recommended when using the pulp cavity/chamber volume for the age estimation. Among the 13 types of tooth, pulp chamber volume of maxillary second molars has the largest correlation coefficient with age in male, female, and pooled gender samples. Using multiple types of tooth can improve the accuracy of age estimation compared with only one type of tooth used. The study of pulp cavity/chamber volume from multiple types of tooth for age estimation is promising and is worth of being analyzed by a larger data sample with a homogeneous age distribution.

Compliance with ethical standards

Conflict of interest The authors have no relevant conflicts of interest to declare.

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