SYSTEMATIC REVIEW

Three-dimensional imaging methods to quantify soft and hard tissues change after cleft-related treatment during growth in patients with cleft lip and/or cleft palate: a systematic review

¹Bennaree Awarun, ¹Jorden Blok, ^{1,2,3}Ruben Pauwels, ¹Constantinus Politis and ^{1,4}Reinhilde Jacobs

¹Department of Imaging and Pathology, KU Leuven and Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium; ²Department of Radiology, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand; ³Department of Mechanical Engineering, KU Leuven, Leuven, Belgium; ⁴Department Dental Medicine, Karolinska Institutet, Stockholm, Sweden

Objectives: To assess the use of three-dimensional (3D) imaging methods to quantify the changes in soft- and hard-tissues in cleft patients after cleft-related treatment during growth.

Methods: PubMed, EMBASE, Web of Science and the Cochrane Library were searched up to 1 June 2018. Included publications were those using 3D imaging to quantify soft- and hard-tissue changes after cleft-related treatments in patients with any type of cleft, during growth. Data extraction and qualitative analysis were performed by two reviewers. The methodological quality of each study was reviewed using the QUADAS-2 tool.

Results: From 4 databases, 2315 articles were found. Full texts of 422 articles were analyzed and finally 12 articles were included for qualitative analysis. CT was performed in the majority of studies for hard-tissue quantification. Stereophotogrammetry, Laser scanner and 3D digitizer were identified as viable methods to quantify both soft- and hard-tissue changes, depending on whether the scan was made of the facial surface or the cast surface. Most studies conducted imaging analysis without registration between multitemporal images, which is the reason why they did not fulfil the inclusion criteria.

Conclusions: Although several imaging modalities have the potential to quantify cleft-related treatment follow-up, there is an urgent need to assess the imaging methods and related analyses allowing to standardise a 3D imaging protocol to quantify hard- and soft-tissue treatment follow-up.

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Keywords: cleft lip; cleft palate; three-dimensional imaging; longitudinal study; growth

Introduction

Clefts of lip and/or palate (CL/P) are among the most common congenital anomalies worldwide, affecting one in 700 children.¹ There are many well-established treatments for these defects that vary in technique and timing.² Therapy aims to reach normal aesthetics and function for both skeletal and soft-tissue structures.³

Each technique has both advantages and drawbacks in terms of achieving both aesthetic and functional goals. Because maxillofacial and dental arch development in cleft patients differs from normal growth,⁴ one of the difficulties during treatment and follow-up is differentiation between the changes due to intervention and the changes due to the natural growth process that continues until 16 or 18 years of age for boys and girls, respectively.⁵ It is essential to find an objective tool to

Correspondence to: Prof Reinhilde Jacobs, E-mail: reinhilde.jacobs@uzleuven.be

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measure the outcomes following treatment and to identify residual deformities.⁶

The introduction of three-dimensional (3D) dento-maxillofacial assessment brings advantages compared to traditionally used direct anthropometric and indirect two-dimensional measurements.^{7,8} Different 3D imaging methods have been used to quantify treatment outcomes, including laser surface scanning, stereophotogrammetry (SP), CT, cone-beam CT (CBCT) and MRI. A rising number of studies are being published regarding the use of 3D methods to evaluate growth and treatment outcomes in cleft patients. Both the Americleft and Eurocleft guidelines are based on two-dimensional evaluation; no standardized protocol is yet available for 3D assessment.^{9,10}

There has been no prior publication of a systematic review to assess available 3D imaging methods which are clinically used and able to reliably quantify the long-term outcome of treatment in cleft patients. Therefore, the objective of this systematic review is to identify the 3D imaging methods that have been used to quantify changes in soft- and hard-tissues during treatment and follow up of orofacial cleft patients. This review aims to answer the following research questions:

- Which 3D imaging methods are used to quantify the changes of soft/hard tissue around the orofacial-cleft area after cleft-related treatment of patient during growth?
- What is the quantification technique used to observe the changes after treatment?
- Is it possible to synthesize the protocol in 3D imaging taken in cleft patient from identified studies?

Methods and Materials

Protocol and registration

Methods and general information regarding this review, including review question and quality assessment, were identified and registered as a systematic review protocol on PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>). The PROSPERO data set and summary guidance document of May 2016 was followed to conduct this review. The registration number on PROSPERO is: CRD42017057206.

Eligibility criteria

Publications aiming to evaluate cleft-related treatment outcome to quantify soft- and hard-tissue changes during growth using 3D imaging methods were included, provided that they met the following criteria: (1) subjects had any type of orofacial cleft, (2) subjects still had potential to grow (girls ≤ 16 years, boys ≤ 18 years), (3) subjects had a history of at least one cleft-related treatment, (4) 3D imaging records of at least two time points were available for each subject (before and after treatment), (5) publications included 3D quantitative assessment, and (6) registration of multitemporal

3D images was conducted for imaging analysis. Exclusion criteria were animal studies, reviews, expert opinions, letters and case reports. There was no restriction in terms of sample size. Publications for which the full text was available in English were included.

Information resources

Electronic databases used to perform the search were: (1) Cochrane Library, (2) PubMed (1965–2018), (3) EMBASE (1980–2017) and (4) Web of Science (1955–2017). The last search was performed on 1 June 2018. All identified publications were transferred for preliminary screening by titles and abstracts. Full texts of studies that agreed with eligibility criteria were then retrieved from licensed electronic databases. Authors of the studies that were unavailable digitally were contacted in order to request a copy of the full text. Cross-referencing from included studies was used to identify further articles for assessment.

Search strategy

A search string was developed, based on different concepts extracted from the research question and expected outcomes, through consultation with a university librarian. The main concepts of the search string were (1) cleft lip and/or palate (2) age of subject (3) 3D imaging techniques (4) longitudinal study. Synonyms were derived from each concept using Medical Subject Headings (MeSH) in PubMed for guidance. Concepts and their synonyms were combined and adapted for four databases. MeSH terms and words in title and abstract were searched in PubMed (Supplementary material 1).

Study records

Two authors (BA and JB) screened the studies by title, abstract and keywords independently and selected studies that fitted the eligibility criteria, in order to retrieve the full text. Full texts were retrieved where there was no abstract available and when there was any doubt over inclusion in the study. Disagreement was solved by discussion. Full texts of selected studies were retrieved and reviewed for final inclusion and exclusion. In case of disagreement in final study selection between the two aforementioned authors, consensus was made by discussion or consultation with a third author (RP).

Risk of bias and applicability assessment

According to the QUADAS-2 protocol, review-specific signalling questions were tailored as shown in Table 1 and consulted by two authors (BA and JB) independently to assess the risk of bias and applicability of the included studies.¹¹ To judge the risk of bias, three domains were used (patient selection, index test, flow and timing), due to the lack of a reference standard for 3D imaging techniques in the evaluation of cleft treatment. For the same reason, two domains were used to judge the applicability of studies: patient selection and index test. The process for tailoring QUADAS-2 was

Table 1 Tailored signalling questions used as QAUDAS-2 protocol

Domain 1: patient selection	
A. Risk of bias	• Were selection criteria clearly described?
	• Was a consecutive or random sample of patients enrolled?
B. Applicability	• Did the study avoid inappropriate exclusion?
	• Is there concern that the included patients do not match the review question?
Domain 2: index test	
A. Risk of bias	• Was the execution of the index text described sufficiently to permit the replication of the test?
	• Was the same index test used at different time points on the same patient?
B. Applicability	• Is there concern that the index test, its conduct or interpretation differ from the review question?
Domain 3: flow and timing	
A. Risk of bias	• Was there an appropriate interval between the index text at different time points, which allows enough time for the changes of treatment to be observed?
	• Were all patients included in the analysis?

followed and signalling questions were developed. A consensus was reached through discussion or consultation with a third author (RP) in case of disagreement.

Data extraction

Essential information of each study was extracted as below;

- (1) Study information: authors, year of publication.
- (2) Methods: study design, samples size, sample characteristics (age, race, type of cleft and treatment), sample selection (randomized, consecutive).
- (3) Intervention characteristics: 3D imaging modalities, interval between images, 3D imaging analysis methods.
- (4) Outcomes: type of measurements, intra- and interrater reliability and research conclusion.

Studies were categorized according to the identified 3D imaging modalities because some of these were used to quantify both soft and hard tissues.

Statistical analysis

Cohen's κ statistic was used to assess the interobserver reliability of the selection of articles based on full text.

Results

Study selection

From four databases, 2315 articles were identified. Additionally, 25 articles were identified through hand-search. There were 422 studies included for full-text review. However, the full text of five articles could not be retrieved, even though an attempt to contact the authors was made. A PRISMA flow chart showing the

Figure 1 Flow diagram of the study (Prisma 2009 format).

process of record selection and reason for article exclusion is provided in [Figure 1](#). The interobserver κ for the reliability of study selection based on the full text was 0.96. A total of 49 studies fulfilled the first five criteria but did not conduct image registration. A total of 12 studies fulfilled all criteria and were assessed for risk of bias and applicability.

Risk of bias and applicability assessment

Results of qualitative analysis using the QAUDAS-2 tool for each study are demonstrated in [Table 2](#). In general, the majority of studies were considered as low risk of bias concerning flow and timing, and all studies were at high risk for the index test due to the insufficiently described methods to allow for replication, while only three studies with low risk of bias were found concerning patient selection. There was no concern of applicability of all studies for patient selection owing to our strict criteria for patient groups, while half of the studies raised potential concerns in terms of applicability for the index test, especially studies with images taken from casts.

Study characteristics

An overview of study characteristics is shown in [Table 3](#). A randomised-control trial was found in one article, whereas others conducted either a retrospective or prospective longitudinal study. Intra- and interrater reliability were reported in four studies whereas the number of raters for most studies was one. 3D imaging modalities included CT,¹²⁻¹⁷ SP,¹⁸ 3D digitizer,^{19,20} and laser scanner.²¹⁻²³

Table 2 Risk of bias assessment using the QUADAS-2 tool

Authors (year)	Risk of bias			Applicability concerns	
	Patient selection	Index test	Flow and timing	Patient selection	Index test
a. CT					
Van der Meij et al. (1993) ¹²	–	–	+	+	+
Van der Meij et al. (2001) ¹³	+	–	+	+	–
Ozawa et al. (2007) ¹⁴	–	–	+	+	+
Nagashima et al. (2014) ¹⁵	–	–	+	+	+
Tong et al. (2015) ¹⁶	+	–	–	+	+
Takemaru et al. (2016) ¹⁷	–	–	+	+	+
b. Stereophotogrammetry					
Sander et al. (2011) ¹⁸	+	–	+	+	–
c. 3D digitizer					
Mishima et al. (1997) ¹⁹	–	–	+	+	–
Braumann et al. (2003) ²⁰	–	–	–	+	–
d. Laser scanner					
Baek et al. (2006) ²¹	–	–	+	+	–
Schwenzer-Zimmerer et al. (2009) ²²	–	–	–	+	+
Fuchigami et al. (2014) ²³	–	–	+	+	–

+ = low risk; – = high risk; ? = unclear risk; CT = computed tomography

Computed tomography (CT) ($n = 6$): A synthesis of imaging analysis of CT is shown in Table 4. Most studies used CT scanning to observe the outcome of secondary alveolar bone grafting by comparing pre-operative with post-operative scans at different follow-up times; 1 month to 1 year after operation. Only one study observed midfacial skeletal changes as an outcome of trans-sutural distraction osteogenesis without Le Fort osteotomy.

Unilateral cleft type was mostly observed due to the cleft characteristic allowing a split-face study design. A mirror image from the pre-operative image on the non-cleft side could be formed, which later -on was superimposed on the cleft side so the cleft volume could be calculated from subtraction. This process is, however, limited to one-sided clefts; bilateral clefts were recruited in three studies using the immediate post-operative image as a reference image instead for superimposition. With this cleft type, however, there is still no method available to know the cleft defect volume pre-operatively.

In three studies, thresholding was used to segment skeletal morphology from soft tissue.

All included studies conducted registration on multi-temporal images using landmark-based registration. Hard-tissue changes were quantified through best-fit method or Procrustes analysis and the differences were shown in root mean square difference (RMS). Identified anatomical landmarks reported were dorsal part of cranial base, shape of maxilla, first permanent maxillary molar, bilateral infraorbital foramina, magnum foramen, anterior and posterior nasal spine. None of the landmarks above were reported to be validated prior to the study as to observe their reliability and stability through growth. CT studies are heading toward

volumetric quantification, scans with smaller slice thickness and automatic registration to decrease man-made error.

A variety of imaging software and technique were found through all studies from 1994 to 2016, which means that a standardized guideline of CT scanning to measure outcome of cleft treatment is yet to be further developed. Meta-analysis could not be performed because of different study design and the lack of a report on reliability in most studies.

An overview of synthesis of non-radiographic method below can be consulted in Table 5.

Stereophotogrammetry (SP) ($n = 1$): Throughout full-text screening, abundant studies using SP were found owing to the advancement of commercial software and imaging analysis. SP is currently widely used in research and the number of studies is rising due to its non-invasive and non-ionizing characteristics. Nevertheless, most articles, typically longitudinal studies with up to 1 year postoperative follow-up, did not register images from different time points.

Image acquisition of casts retrieved from nasolabial impressions before and after bone grafting were carried out by Sander et al. (2011). Surface-based registrations and Procrustes analysis between pre- and post-operative images were performed to assess nasal asymmetry. The facial impression technique was validated, indicating that the casts were highly representative of the real-time soft tissue images (mean difference = 0.084 mm.). Reproducibility analysis of the registration method showed an intraclass correlation coefficient of 0.994. This is the only study we found that concerns the camouflage effect of changes from growth and

Table 3 Characteristics of included studies according to identified 3D imaging methods ($n = 12$)

3D imaging method	First author, year	Sample characteristics			Intervention characteristics				Outcome Characteristics
		Sample size	Age	Type of cleft	Assessment		Time of imaging		
					Tissue type	Treatment	Pre-operative	Post-operative	
CT	Van der Meij, 1993 ¹²	8	9 y 5 m	UCLP	H	2° bone graft	X	3 d, 1 y	remaining bone at graft site
	Van der Meij, 2001 ¹³	50	9–12 y	UCLP, BCLP	H	2° bone graft	X	3 d, 1 y	remaining bone at graft site
	Ozawa, 2007 ¹⁴	35	6.8 y	UCL, BCL	H	2° bone graft	X	im, 6 m	bone graft resorption and influence of germ of lateral incisor on bone graft resorption
	Nagashima, 2014 ¹⁵	20	10 y	UCL, UCLP	H	2° bone graft	√	1m, 6m	remaining bone at graft site
	Tong, 2015 ¹⁶	70	11.3 y	UCLP, BCLP	H	midfacial osteogenesis	√	im	direction and magnitude of midfacial distraction osteogenesis
SP	Takemaru, 2016 ¹⁷	15	8.3 y	UCL	H	2° bone graft	√	1m, 6m, 12m	blood loss, number of intravenous analgesic drug pushing and remaining bone at graft site
	Sander, 2011 ¹⁸	39	10.5 y	UCLP	S	2° bone graft	√	6m	asymmetry score and morphology of nose
	Mishima, 1997 ¹⁹	10	4 m	BCLP	H	maxillary arch expansion	X	every 2m	direction and magnitude changes of palatal configuration
3D digitizer	Braumann, 2003 ²⁰	21	1–2 d	UCLP	H	maxillary arch expansion and 1° lip repair	√	1w, 3m, 6m, 12m	morphologic and volumetric changes of maxillary arch and visual analysis compare incomplete and complete unilateral cleft lip and palate
Laser scanner	Baek, 2006 ²¹	16	1 m	UCLP	H	maxillary arch expansion	√	3m, 5m	morphological changes of maxillary arch in linear and area measurement
	Schwenzer-Zimmerer, 2009 ²²	5	3 m	UCL, UCLP, BCLP	S	1° lip repair	√	im, 7d	accuracy of T-scan to observe cleft lip morphology
	Fuchigami, 2014 ²³	60	4.8 m	UCLP	H	1° lip repair	√	1y	maxillary arch form changes in curvature radius, collapse rate, direction and magnitude

3D, three dimensional; d, day; w, week; m, month; y, year; im, immediately after operation; UCL(P), unilateral cleft lip(palate); BCL(P), bilateral cleft lip (palate); S, soft-tissue; H, hard-tissue; X, not mentioned; CT, computed tomography; SP, stereophotogrammetry.

treatment. The authors commented on the RMS value when comparing cleft side and non-cleft side on registered images, stating that the observed changes were likely to be due to treatment rather than growth when the RMS value on the cleft side is greater than on the non-cleft side. Longer follow-up time should be used in the future to confirm this finding. This technique is limited to unilateral cleft type, so that the patients can serve as their own controls. We found that there are many software tools which compliment SP imaging systems to help with 3D analysis.

3D-digitizer ($n = 2$): 3D-digitizer methods consist of non-contact-type (i.e. optical laser scanner) and contact-type. They can be used to evaluate maxillary morphology by scanning of cast surface. The system can generate a dense cloud of co-ordinates across the surface (mesh form) which later on can be transformed into a 3D image. Superimposition of this model is possible with a best-fit algorithm. Mishima et al. (1997) used a mesh framework to register directly between each time-series, while Braumann et al. (2003) transformed a

Table 4 Synthesis of 3D imaging analysis of studies using radiographic imaging (n = 6)

3D imaging method	First author, year	Quantification			Slice characteristics			Reliability test				
		Unit of measurement	Volumetric	Boundary of slices	Slice selection	No. of slices	Slice thickness (mm)	No. of observers	Segmentation	Registration	Intravater reliability	Inter vater reliability
CT	Van der Meij, 1993 ¹²	Residual graft (%)	X	Max. occlusal to nasal cavity	Center of graft	3	1.5	X	M	X	X	X
	Van der Meij, 2001 ¹³	Residual graft (%)	X	Max. occlusal to nasal cavity	Center of graft	3	1.5	X	M	X	✓	X
	Ozawa, 2007 ¹⁴	Residual graft (ml, %)	✓	Max. occlusal to nasal cavity	All	All	1	X	M	X	X	X
		Cleft width (mm) cleft volume (cm ³)										
	Nagashima, 2014 ¹⁵	graft volume (cm ³)	✓	Orbital roof to mandible	All	All	0.5	✓	S	X	X	X
		Direction and magnitude of midfacial osteogenesis (mm)	X	X	All	All	0.5	✓	S	X	✓	✓
	Takemaru, 2016 ¹⁷	Cleft volume (ml)	✓	Orbital roof to mandible	All	All	0.5	✓	S	X	X	X

3D, three-dimensional;
X = not mentioned or not conducted; M = manual; S = semi-automatic; max. = maxillary; CT = computed tomography.

Table 5 Synthesis of 3D imaging analysis of studies using non-radiographic imaging ($n = 6$)

3D imaging method	First author, year Scanned object	Registration				Reliability test		
		Technique	Landmarks (no.)	Placement of landmarks	Landmark specifications	Superimposition of multitemporal images	No. of observers	Inter-rater reliability
SP	Sander, 2011 ¹⁸	Surface	–	S	Polygons area on intercanthal line and long axis of nose	Procrustes technique, RMS values between surfaces	1	X
	Mishima, 1997 ¹⁹	Landmarks (mesh form)	700	A	Dense co-ordinates formed mesh image	Best-fit method (colour-map)	X	X
	Braumann, 2003 ²⁰	Landmarks	2	A	Distal edge of canine segment of non-cleft side	Best-fit method (colour-map)	X	X
3D digitizer	Baek, 2006 ²¹	Landmarks	1	M	Point selected from arbitrary manual landmarks (around middle of the palate)	Superimposition	2	✓
	Schwenzer-Zimmerer, 2009 ²²	X	X	X	X	Best-fit method (colour-map)	1	✓
	Fuchigami, 2014 ²³	Landmarks	1	M	Point selected from arbitrary manual landmarks (around middle of the palate)	Superimposition	1	X

3D, three dimension; X, not mentioned or not conducted; M, manual; S, semi-automatic; A, automatic; RMS, Root mean square distances; –, not applicable; SP, stereophotogrammetry;

mesh framework to 3D images and then superimposed those images between time-series.

3D image of casts in Braumann *et al.* (2003) were segmented into four parts, so that they could observe the changes in each part of the maxillary arch specifically. This article pointed out that the morphological changes were due to the growth of the maxilla after superimposition. In fact, passive arch expansion and lip repair were conducted on their subjects during follow-up; thus, these could be also the cause of changes.

Since a dental cast is obtained for analysis, a clear description of impression acquisition in the studies is vital. Soft-tissue distortion can be expected when acquiring a stone cast. Hence, validation of impression taking and cast fabrication must be done in order to test the reproducibility of the method, which these two studies did not mention.

Laser scanner ($n=3$): Laser scanner was used to scan casts and generate surface images in Baek *et al.* (2006) and Fuchigami *et al.* (2014). Manually identified reference points and lines on the digitized model were used to superimpose between series of images. Baek reported an excellent intraclass correlation for landmark placing; however, this method relies on observers and errors tend to occur. This technique represents the majority of studies found while screening full texts. The study of Schwenzer-Zimmerer *et al.* (2007) on the other hand, used a handheld laser scanner on the patient's face and the resulting image was depicted on a screen in real-time. The accuracy of this method was in the submillimeter range even though the scanning time was longer than that of SP (SP = <1.5 ms and laser scanner = 10–15 s). Young patients are required to be static while scanning to avoid motion artefacts, which is a drawback of this method.

Discussion

Despite the rising number of medical 3D imaging studies, we finally included 12 studies mostly because others failed to conduct registration of time-series images. Whenever these images need to be compared, registration is essentially required, except when the time interval is extremely short, and the same imaging equipment is used. Furthermore, patient motion should be compensated, and differences in patient position, gantry position and scan plane selection should be minimized. The accuracy of outcome could be much different without registration.^{24,25} Therefore, it became a strict criterion for this review.

One of the obstacles to synthesize imaging technique and analysis from most studies is that they are not clearly defined, and that reproducibility is not reported. This also hampers the development of standardized imaging methods for any modalities.^{26,27}

Studies using CT are heading toward volumetric assessment. We are, nevertheless, doubting the accuracy

of this technique to extract cleft volume and bone volume by subtracting between reconstructed mirror images and original images. Segmentation of cleft volume should further be promoted and standardized as seen in the study of El and Palomo²⁸ Weissheimer et al²⁹ Linderup et al.^{26,27} This can create the possibility to extract the cleft volume in bilateral cleft patients. Variability of landmarks used in the registration process was observed. We propose that the choice of landmarks should be validated and based on anatomical structures that have no or very subtle change during growth. Registration based on the whole surface of the cranial base was proposed by Cevitanes et al. (2009, 2010) using a CBCT machine with a 30 cm field of view.^{30,31} None of the included studies in this review used CBCT due to the fact that there is still a lack of proper study design and imaging analysis applied to this modality for quantifying true tissue changes, and because most studies did not conduct registration. On the other hand, we see that all CT studies suffer from an undistinguishable boundary between the residual bone graft and the adjacent alveolar bone 1 year postoperatively. Moreover, pediatric cleft palate patients showed a 3- to 5-fold increase in cumulative radiation exposure from dental radiology (including CBCT and CT) compared with an age- and gender-matched population, suggesting that clear guidelines need to be developed.³² CT is not routinely applied in clinical diagnosis especially in children and, therefore, may not be the method of choice in this group of patients when CBCT is available.

SP and laser scanning were found to be viable methods to quantify soft tissue changes such as nasal, facial and lip asymmetry relying on different soft-tissue landmarks. SP seems to be a method of choice nowadays with the advancements of accompanying software. Wu et al. (2014) developed an automated 3D imaging process from mesh data on SP images, including facial recognition, Procrustes analysis, final noise removal and image normalization.³³ High accuracy was reported in their work. High reproducibility and low random error of soft-tissue landmark definition were observed in some studies³⁴; however, problems with soft-tissue landmarks or “best-fit” methods complicate the ability to observe changes in time-series images as mentioned before.

3D digitizers consist of various types of imaging systems. Optical scanning is one of the most interesting methods, because its accuracy has been validated^{35,36} and it is able to identify landmarks semi-automatically. Random errors of less than 0.5 mm were reported.²⁰ It was applied mostly in casts which has many drawbacks, *i.e.* soft-tissue distortion during impression taking, and inability to segment soft-tissue out of maxillary arch. Intraoral scanning can be a potential alternative approach to produce a digital impression and increase accuracy.^{37–39}

From this review, we can conclude that no standardized guidelines are available yet for 3D imaging in cleft children, who possibly go through many treatments and radiation exposure using different imaging modalities in

their first 20 years of life. Accuracy of methods to quantify changes has yet to be increased through the development of automated computer-based imaging analysis, including segmentation and registration. Once accurate and reliable methods are standardized, routine clinical application needs to be tested.

Limitations of the study

Regarding the characteristics of the studies included based on eligibility criteria, a difficulty in conducting randomized control trials was observed. This occurred for several reasons. Firstly, due to the ethical concerns that different types of cleft require particular treatment, randomization of treatment or of imaging method is in some cases impossible. Secondly, because ionizing radiation is involved in some experimental studies, the inclusion of healthy children as a control group is difficult to achieve without proper justification.

Most studies observed were using a split-face study design, which is only applicable to unilateral cleft patients. Research in the area of 3D image analysis in bilateral cleft types still needs to be conducted.

There was a limitation in the comparison between different publications using the same modality because detailed information on hardware, software and imaging parameters was often lacking. Furthermore, image analysis was not always described clearly, which hampered comparative interpretation, proper discussion and drawing conclusions regarding the suitability of the imaging method. This also hindered a meta-analytic approach.

Different planes, boundaries and landmarks were used in all studies. This variety shows that standardization in planes, boundaries and landmark selection needs to be developed in the future before a comparison can be made and a dedicated protocol can be established.

Conclusion

Skeletal morphology, including maxillary arch expansion and alveolar bone graft, are best quantified in terms of volume or area with either CT, if clinician can justify its benefit. Automatic segmentation and registration methods should be further developed in quantitative experimental studies related to the cleft area. SP and laser scanner are a promising modality to quantify soft-tissue surface morphology after treatment such as lip repair and nasal moulding. However, there is still more work to be done toward the volumetric quantification of soft tissue using this modality as well as the development of software tools to carry out this task. Although several imaging modalities have the potential to quantify cleft-related treatment follow-up, it can be concluded that there is an urgent need to assess the imaging methods and related analyses allowing to standardise a 3D imaging protocol to quantify hard- and soft tissue treatment follow-up.

References

- Kadir A, Mossey PA, Blencowe H, Moorthie S, Lawn JE, Mastroiacovo P, et al. Systematic review and meta-analysis of the birth prevalence of orofacial clefts in low- and middle-income countries. *Cleft Palate Craniofac J* 2017; **54**: 571–81. doi: <https://doi.org/10.1597/15-221>
- Millard DR. *Cleftcraft: the evolution of its surgery*. 2nd edn. Philadelphia: PA: Lippincott Williams and Wilkins; 1976.
- Schwenzer-Zimmerer K, Chaitidis D, Berg-Boerner I, Krol Z, Kovacs L, Schwenzer NF, et al. Quantitative 3D soft tissue analysis of symmetry prior to and after unilateral cleft lip repair compared with non-cleft persons (performed in Cambodia). *J Craniomaxillofac Surg* 2008; **36**: 431–8. doi: <https://doi.org/10.1016/j.jcms.2008.05.003>
- Shi B, Losee JE. The impact of cleft lip and palate repair on maxillofacial growth. *Int J Oral Sci* 2015; **7**: 14–17. doi: <https://doi.org/10.1038/ijos.2014.59>
- Malina RM, Bouchard C, Bar-Or O. Growth, maturation and physical activity. In: *Human Kinetics*. 2nd edn. **712**. Champaign: IL; 2004.
- Trotman CA, Faraway JJ, Essick GK. Three-dimensional nasolabial displacement during movement in repaired cleft lip and palate patients. *Plast Reconstr Surg* 2000; **105**: 1273–83.
- Waitzman AA, Posnick JC, Armstrong DC, Pron GE. Craniofacial skeletal measurements based on computed tomography: Part I. Accuracy and reproducibility. *Cleft Palate Craniofac J* 1992; **29**: 112–7. doi: [https://doi.org/10.1597/1545-1569\(1992\)029<0112:CSMBOC>2.3.CO;2](https://doi.org/10.1597/1545-1569(1992)029<0112:CSMBOC>2.3.CO;2)
- Waitzman AA, Posnick JC, Armstrong DC, Pron GE. Craniofacial skeletal measurements based on computed tomography: Part II. Normal values and growth trends. *Cleft Palate Craniofac J* 1992; **29**: 118–28. doi: [https://doi.org/10.1597/1545-1569\(1992\)029<0118:CSMBOC>2.3.CO;2](https://doi.org/10.1597/1545-1569(1992)029<0118:CSMBOC>2.3.CO;2)
- The Americleft Project: Experiences and recommendations for establishing successful inter-center collaborative outcome study. 2018; Chapel Hill, NC, USA: American Cleft Palate-Craniofacial Association. Available from: https://acpa-cpf.org/wp-content/uploads/2017/06/americleft-study-guide_1_.pdf [cited 2018 Aug 4].
- Shaw WC, Semb G, Nelson P, Brattström V, Mølsted K, Prah-Andersen B, et al. The eurocleft project 1996-2000: overview. *J Craniomaxillofac Surg* 2001; **29**: 131–40. doi: <https://doi.org/10.1054/jcms.2001.0217>
- Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, et al. QUADAS-2 Group QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529–36. doi: <https://doi.org/10.7326/0003-4819-155-8-201110180-00009>
- van der Meij AJ, Baart JA, Prah-Andersen B, Valk J, Kostense PJ, Tuinzing DB. Computed tomography in evaluation of early secondary bone grafting. *Int J Oral Maxillofac Surg* 1994; **23**: 132–6. doi: [https://doi.org/10.1016/S0901-5027\(05\)80286-3](https://doi.org/10.1016/S0901-5027(05)80286-3)
- Van der Meij AJ, Baart JA, Prah-Andersen B, Valk J, Kostense PJ, Tuinzing DB. Bone volume after secondary bone grafting in unilateral and bilateral clefts determined by computed tomography scans. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 136–41. doi: <https://doi.org/10.1067/moe.2001.115274>
- Ozawa T, Omura S, Fukuyama E, Matsui Y, Torikai K, Fujita K. Factors influencing secondary alveolar bone grafting in cleft lip and palate patients: prospective analysis using CT image analyzer. *Cleft Palate Craniofac J* 2007; **44**: 286–91. doi: <https://doi.org/10.1597/06-054>
- Nagashima H, Sakamoto Y, Ogata H, Miyamoto J, Yazawa M, Kishi K. Evaluation of bone volume after secondary bone grafting in unilateral alveolar cleft using computer-aided engineering. *Cleft Palate Craniofac J* 2014; **51**: 665–8. doi: <https://doi.org/10.1597/13-045>
- Tong H, Wang X, Song T, Gao F, Yin J, Li H, et al. Trans-sutural distraction osteogenesis for midfacial hypoplasia in growing patients with cleft lip and palate: clinical outcomes and analysis of skeletal changes. *Plast Reconstr Surg* 2015; **136**: 144–55. doi: <https://doi.org/10.1097/PRS.0000000000001375>
- Takemaru M, Sakamoto Y, Sakamoto T, Kishi K. Assessment of bioabsorbable hydroxyapatite for secondary bone grafting in unilateral alveolar cleft. *J Plast Reconstr Aesthet Surg* 2016; **69**: 493–6. doi: <https://doi.org/10.1016/j.bjps.2015.10.040>
- Sander M, Daskalogiannakis J, Tompson B, Forrest C. Effect of alveolar bone grafting on nasal morphology, symmetry, and nostril shape of patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J* 2011; **48**: 20–7. doi: <https://doi.org/10.1597/09-007>
- Mishima K, Sugahara T, Mori Y, Sakuda M. Palatal configuration in complete bilateral cleft lip and palate infants before and after cheiloplasty. *Cleft Palate Craniofac J* 1997; **34**: 475–82. doi: [https://doi.org/10.1597/1545-1569\(1997\)034<0475:PCICB-C>2.3.CO;2](https://doi.org/10.1597/1545-1569(1997)034<0475:PCICB-C>2.3.CO;2)
- Braumann B, Keilig L, Stellzig-Eisenhauer A, Bourauel C, Bergé S, Jäger A. Patterns of maxillary alveolar arch growth changes of infants with unilateral cleft lip and palate: preliminary findings. *Cleft Palate Craniofac J* 2003; **40**: 363–72. doi: [https://doi.org/10.1597/1545-1569\(2003\)040<0363:POMAA-G>2.0.CO;2](https://doi.org/10.1597/1545-1569(2003)040<0363:POMAA-G>2.0.CO;2)
- Baek SH, Son WS. Difference in alveolar molding effect and growth in the cleft segments: 3-dimensional analysis of unilateral cleft lip and palate patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 160–8. doi: <https://doi.org/10.1016/j.tripleo.2005.09.009>
- Schwenzer-Zimmerer K, Boerner BI, Schwenzer NF, Müller AA, Juergens P, Ringenbach A, et al. Facial acquisition by dynamic optical tracked laser imaging: a new approach. *J Plast Reconstr Aesthet Surg* 2009; **62**: 1181–6. doi: <https://doi.org/10.1016/j.bjps.2007.11.080>
- Fuchigami T, Nakamura N, Nishihara K, Matsunaga K, Hasegawa H. Short-term molding effects on the upper alveolar arch following unilateral cleft lip repair with/without nasal vestibular expansion. *Cleft Palate Craniofac J* 2014; **51**: 557–68. doi: <https://doi.org/10.1597/12-317>
- Maintz JBA, Viergever VMA. Utrecht University Repository. In: *An overview of medical image registration methods*; 1998.
- El-Gamal FE-ZA, Elmogly M, Atwan A. Current trends in medical image registration and fusion. *Egyptian Informatics Journal* 2016; **17**: 99–124. doi: <https://doi.org/10.1016/j.eij.2015.09.002>
- Linderup BW, Küsel A, Jensen J, Cattaneo PM. A novel semiautomatic technique for volumetric assessment of the alveolar bone defect using cone beam computed tomography. *Cleft Palate Craniofac J* 2015; **52**: 47–55. doi: <https://doi.org/10.1597/13-287>
- Linderup BW, Cattaneo PM, Jensen J, Küsel A. Mandibular symphyseal bone graft for reconstruction of alveolar cleft defects: volumetric assessment with cone beam computed tomography 1-year postsurgery. *Cleft Palate Craniofac J* 2016; **53**: 64–72. doi: <https://doi.org/10.1597/14-143>
- El H, Palomo JM. Measuring the airway in 3 dimensions: a reliability and accuracy study. *Am J Orthod Dentofacial Orthop* 2010; **137**(4 Suppl): S50.e1–S50.e9. doi: <https://doi.org/10.1016/j.ajodo.2009.11.010>
- Weissheimer A, Menezes LM, Sameshima GT, Enciso R, Pham J, Grauer D. Imaging software accuracy for 3-dimensional analysis of the upper airway. *Am J Orthod Dentofacial Orthop* 2012; **142**: 801–13. doi: <https://doi.org/10.1016/j.ajodo.2012.07.015>
- Cevdanes LH, Heymann G, Cornelis MA, DeClerck HJ, Tulloch JF. Superimposition of 3-dimensional cone-beam computed tomography models of growing patients. *Am J Orthod Dentofacial Orthop* 2009; **136**: 94–9. doi: <https://doi.org/10.1016/j.ajodo.2009.01.018>
- Cevdanes LHC, Styner M, Proffit WR, Nanda R, ed. *Three-dimensional superimposition for quantification of treatment outcomes*. Current therapy in orthodontics. Maryland Heights: Mosby Elsevier; 2010. pp. 36–44.

32. Jacobs R, Pauwels R, Scarfe WC, De Cock C, Dula K, Willems G, et al. Pediatric cleft palate patients show a 3- to 5-fold increase in cumulative radiation exposure from dental radiology compared with an age- and gender-matched population: a retrospective cohort study. *Clin Oral Investig* 2018; **22**: 1783-1793-. doi: <https://doi.org/10.1007/s00784-017-2274-0>
33. Wu J, Tse R, Shapiro LG. Automated face extraction and normalization of 3D mesh data. *Conf Proc IEEE Eng Med Biol Soc* 2014; **2014**: 750-3. doi: <https://doi.org/10.1109/EMBC.2014.6943699>
34. de Menezes M, Rosati R, Ferrario VF, Sforza C. Accuracy and reproducibility of a 3-dimensional stereophotogrammetric imaging system. *J Oral Maxillofac Surg* 2010; **68**: 2129-35. doi: <https://doi.org/10.1016/j.joms.2009.09.036>
35. Yamada T, Mori Y, Minami K, Mishima K, Sugahara T, Sakuda M. Computer aided three-dimensional analysis of nostril forms: application in normal and operated cleft lip patients. *J Craniomaxillofac Surg* 1999; **27**: 345-53. doi: <https://doi.org/10.1054/jcms.1999.0097>
36. Yamada T, Mori Y, Minami K, Mishima K, Tsukamoto Y. Surgical results of primary lip repair using the triangular flap method for the treatment of complete unilateral cleft lip and palate: a three-dimensional study in infants to four-year-old children. *Cleft Palate Craniofac J* 2002; **39**: 497-502. doi: [https://doi.org/10.1597/1545-1569\(2002\)039<0497:SR0PL-R>2.0.CO;2](https://doi.org/10.1597/1545-1569(2002)039<0497:SR0PL-R>2.0.CO;2)
37. Kim JE, Amelya A, Shin Y, Shim JS. Accuracy of intraoral digital impressions using an artificial landmark. *J Prosthet Dent* 2017; **117**: 755-61. doi: <https://doi.org/10.1016/j.prosdent.2016.09.016>
38. Zhang F, Suh KJ, Lee KM. Validity of intraoral scans compared with plaster models: an in-vivo comparison of dental measurements and 3D surface analysis. *PLoS One* 2016; **11**: e0157713. doi: <https://doi.org/10.1371/journal.pone.0157713>
39. Camardella LT, Breuning H, de Vasconcellos Vilella O. Accuracy and reproducibility of measurements on plaster models and digital models created using an intraoral scanner. *J Orofac Orthop* 2017; **78**: 211-20. doi: <https://doi.org/10.1007/s00056-016-0070-0>