SYSTEMATIC REVIEW

Three-dimensional radiological evaluation of secondary alveolar bone grafting in cleft lip and palate patients: a systematic review

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Objectives: To systematically review the existing literature on the three-dimensional (3D) radiological evaluation of secondary alveolar bone grafting (SABG) in cleft lip and palate (CLP) patients, with specific interest in 3D imaging protocols and assessment methods.

Methods: A comprehensive literature search on PubMed, Embase and the Cochrane Library was conducted. Included publications concerned 3D imaging for evaluation of SABG in CLP patients while articles about primary or tertiary bone grafting or using of two-dimensional images only were excluded. Study quality was evaluated using the Methodological Index for Non-Randomized Studies or the Cochrane Collaboration tool for assessing risk of bias.

Results: The search yielded 1735 citations, of which 38 met the inclusion criteria. We noticed a large variability in imaging protocols and bone graft evaluation methods between studies. Most articles were observational studies with medium to low methodological quality, except for the one randomised clinical trial having a low risk of bias.

Conclusions: There is a lack of prospective, controlled trials based on a consistent imaging protocol with a sufficiently long follow-up period. A pressing need exists for the development of a consistent optimized imaging protocol for diagnosis and follow up of SABG in CLP patients. Although 3D evaluation methods seem to be more precise than two-dimensional methods, we should be careful when comparing the outcomes arising from different 3D measuring techniques.

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Introduction

Alveolar clefts, frequently present in patients with cleft lip and palate (CLP), may result in oronasal fistulae, failures in tooth development and a collapsed upper arch. Secondary alveolar bone grafting (SABG) has become a standard treatment in the management of patients with unilateral or bilateral CLP as a means of repairing the defect of the alveolar ridge. A successful surgical procedure (1) results in continuity and stabilization

of the maxillary arch, (2) eliminates oronasal fistulae hereby improving speech, (3) creates bony support for subsequent tooth eruption, (4) facilitates eruption of cleft-adjacent teeth and preserves their periodontal health, (5) enhances nasal base and facial appearance, (6) permits orthodontic tooth alignment and (7) allows placement of osseointegrated dental implants when indicated.^{1,2} Boyne and Sands³ introduced the idea of transplantation of cancellous autogenous bone harvested from the iliac crest for SABG. This surgical procedure has been established as clinical reference

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standard.² Other donor sites for harvesting autogenous bone include the mandible, ribs, tibia and calvarium.⁴ Recently, synthetic bone substitutes are upcoming as graft material.^{5,6}

One of the main objectives of SABG is the formation of a bone bridge, allowing tooth eruption and subsequent orthodontic tooth movement. SABG is typically performed prior to the eruption of the cleft-side canine to provide an osseous environment that encourages canine eruption. If the lateral incisor tends to erupt in the minor segment, an early SABG is indicated to allow proper tooth eruption.^{7,8} A sufficient bone volume must be available to accomplish that. Accurate radiological diagnosis and follow up of this area is, therefore, indicated, and in the last decades there has been a shift from two-dimensional (2D) to three-dimensional (3D) imaging for this purpose.

The aim of the current systematic review is to provide an overview of the existing literature concerning the 3D radiological evaluation of SABG in CLP patients. The main research questions are:

- (1) Which 3D imaging protocols are used in the radiological follow-up?
- (2) How is 3D imaging applied to assess the cleft site?

Additionally, we examined the clinically relevant outcome measures arising from the radiological assessment, with specific interest in the success and resorption rates after SABG and the applicability of promising alternative graft types.

Methods and materials

Protocol and registration

Both the analysis methods and inclusion criteria were specified *a priori* and registered as a protocol in the international prospective register of systematic reviews (PROSPERO, registration number CRD42016053151). Reporting was executed adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Eligibility criteria

P. Patients with CLP that underwent SABG; I. 3D imaging; C. 2D imaging or no comparison; O. Imaging protocol and radiological assessment of SABG.

Publications were considered eligible for inclusion when 3D imaging techniques were used for the evaluation of SABG in patients with CLP. Additional exclusion criteria were: primary or tertiary ABG and use of 2D imaging techniques only. The following study types were also rejected: animal studies, case reports, reviews, letters and expert opinions. Articles written in other languages than English and Dutch were excluded. No restrictions for publication date, patient demographics and publication status were imposed.

Information sources:

To identify the existing literature, an electronic search was conducted in three major databases: PubMed, EMBASE and the Cochrane Library, from inception till 2018 and with the last update on January 2018. Furthermore, unpublished literature was searched electronically at the GreyLit database (www.greylit.org). Reference lists of the included full text articles were also hand searched for relevant studies.

Search and study selection

An experienced librarian from the biomedical library of KU Leuven in Belgium specialized in health sciences contributed in the process of developing the search strategy. After an initial exploratory search, we found that when adding 3D imaging and cone beam CT to the search terms, a considerable number of relevant articles were omitted. Therefore, 3D imaging was used as a selection criterion when screening the articles for eligibility. A detailed description of the electronic search strategy in the selected databases is presented in [Table 1](#).

The list of publications from all databases were imported into a reference manager (www.mendeley.com). Duplicate records were then removed and the resulting collection of articles was screened based on title and abstract (and full text in case of unclear abstracts) by the first author. Subsequently, full texts of the selected articles were retrieved. Corresponding authors were contacted when publications were not accessible online. Disagreements regarding study inclusion were resolved by discussion with the second author to reach a final consensus.

Data extraction

Data extraction sheets from all included studies were developed, and data were extracted by the first author. The collected information included: first author, publication year, study design, study sample (sample size, mean age and age range), imaging modalities, type of radiographs used, graft type and study measures.

Table 1 Search strategy

<i>PubMed</i>	
("Cleft Lip"[Mesh] OR cleft lip*[tiab] OR harelip*[tiab] OR hare lip*[tiab] OR "Cleft Palate"[Mesh] OR cleft palate*[tiab]) AND (((("Bone Transplantation"[Mesh:NoExp] OR ((bone[tiab] OR bony[tiab] OR osseous[tiab] OR osteal[tiab]) AND (transplant*[tiab] OR graft*[tiab] OR repair*[tiab])) AND secondary[tiab])) OR "alveolar bone grafting"[MeSH] OR Alveolar bone Graft*[tiab] OR Alveolar Cleft Graft*[tiab])	
<i>Embase</i>	
cleft AND lip*:ab,ti	#1
harelip*:ab,ti	#2
hare AND lip*:ab,ti	#3
cleft AND palate*:ab,ti	#4
"cleft lip"/exp	#5
"cleft palate"/exp	#6
"bone transplantation"/mj	#7
bone:ab,ti	#8
bony:ab,ti	#9
osseous:ab,ti	#10
osteal:ab,ti	#11
transplant*:ab,ti	#12
graft*:ab,ti	#13
repair*:ab,ti	#14
secondary:ab,ti	#15
alveolar AND bone AND graft*:ab,ti	#16
alveolar AND cleft AND graft*:ab,ti	#17
"alveolar bone grafting"/exp	#18
#1 OR #2 OR #3 OR #4 OR #5 OR #6	#19
#8 OR #9 OR #10 OR #11	#20
#12 OR #13 OR #14	#21
#20 AND #21	#22
#7 OR #22	#23
#15 AND #23	#24
#16 OR #17 OR #18	#25
#19 AND (#24 OR #25)	#26
<i>Cochrane Library</i>	
cleft lip or harelip or hare lip or cleft palate	#1
MeSH descriptor:[Cleft Lip] explode all trees	#2
MeSH descriptor:[Cleft Palate] explode all trees	#3
MeSH descriptor:[Bone Transplantation] explode all trees	#4
bone or bony or osseous or osteal	#5
transplant or graft or repair	#6
Secondary	#7
alveolar bone graft or alveolar cleft graft	#8
MeSH descriptor:[Alveolar Bone Grafting] explode all trees	#9
#1 or #2 or #3	#10
#5 and #6	#11
#4 or #11	#12
#7 and #12	#13
#8 or #9	#14
#10 and (#13 or #14)	#15

Risk of bias in individual studies

For observational and non-randomized studies, we used the validated Methodological Index for Non-Randomized Studies developed by Slim *et al.*⁹ According to the scale, non-comparative and comparative studies were

scored separately. Eight methodological items had to be scored for all studies and assessment of four additional items were executed for comparative studies only (Table 2). Each item was scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The first author conducted the quality assessment and in case of doubt, the second author was consulted for discussion in order to reach a consensus. If necessary, a statistician was consulted for the evaluation of the statistical analysis used in the comparative studies. For Randomized Clinical Trials, the Cochrane Collaboration's tool for assessing risk of bias was used.¹⁰ The tool consisted of seven domains: sequence generation, allocation concealment, blinding of participants and investigators, incomplete outcome data, selective outcome reporting and other potential sources of bias. Studies were categorized into those having low risk of bias if all the criteria were met, unclear risk of bias if one or more criteria were partially met, or high risk of bias if one or more criteria were not met.

Results

Study selection

1735 articles were initially identified through electronic search, whereof 738 articles were retrieved from PubMed, 956 from EMBASE and 41 from Cochrane Library. No additional records were obtained through other sources. After removal of duplicate records, screening based on titles and abstracts of the remaining 1199 records was performed. 53 articles met the inclusion criteria and were assessed for eligibility. 15 studies were excluded because of not focusing on SABG, not including 3D imaging and being case series or congress abstracts. Finally, 38 studies were included in the qualitative synthesis of this systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process described above is shown in Figure 1.

Study characteristics

A summary of the key methodological data and study results is found in Table 3. Included articles were published between 1994 and 2017, with a considerable increase in the number of publications on this topic in function of time (Figure 2). Study design, sample size, mean age and age range showed a large variation between studies. The majority of the articles were observational studies ($n = 36$). There was one clinical trial and one randomized clinical trial. Almost two-thirds ($n = 22$) of the observational studies were prospective and more than one-third ($n = 14$) was retrospective. 6 articles were cross-sectional studies and 30 articles were cohort studies. Sample size ranged from 3 to 60 subjects, with an outlier of 308 in one study.²³ Unilateral and bilateral CLP patients were far more studied than unilateral and bilateral cleft lip and alveolus patients. Unilateral

Table 2 (a) Quality assessment according to MINORS⁹, (b) the Cochrane Collaboration tool for assessing risk of bias¹⁰

(a)													
First author, year	1	2	3	4	5	6	7	8	9	10	11	12	Score*
<i>Comparative studies</i>													
Herford, 2007 ¹¹	2	1	1	2	2	1	2	0	1	2	1	2	17
Van der Meij, 2001 ¹²	2	1	1	2	0	2	0	0	1	2	1	2	14
Kim, 2008 ¹³	2	1	2	2	0	2	2	0	1	2	1	2	17
Arctander, 2005 ¹⁴	2	2	1	2	0	0	0	0	1	2	2	2	14
Zhang, 2012 ²	2	2	2	2	0	2	2	0	1	2	1	2	18
Nagashima, 2014 ⁴	2	2	2	2	0	1	2	0	1	2	1	2	17
Dissaux, 2016 ¹⁵	2	2	1	2	0	2	2	0	1	2	2	2	18
Choi, 2012 ¹⁶	2	1	2	2	0	0	0	0	1	2	1	2	13
Kawakami, 2003 ¹⁷	2	2	2	2	0	2	2	0	1	2	1	2	18
Pradel, 2012 ⁵	2	1	2	2	0	2	2	0	2	2	1	0	16
Sakio, 2016 ¹⁸	2	1	2	2	0	2	0	0	1	2	1	2	15
<i>Non-comparative studies</i>													
Wangrimongkol, 2013 ¹⁹	2	2	2	2	0	0	0	0					8
Shirota, 2010 ²⁰	2	1	2	2	1	0	0	0					8
Feichtinger, 2007 ⁷	2	2	2	2	0	2	2	0					12
Honma, 1999 ²¹	2	1	2	2	0	2	2	0					11
Van der Meij, 1994 ²²	2	1	1	2	0	2	2	0					10
Hudak, 2014 ²³	2	2	1	2	0	2	1	0					10
Seike, 2012 ²⁴	2	2	1	2	0	1	2	0					10
Feichtinger, 2006 ²⁴	2	1	2	2	0	2	2	0					11
Linderup, 2016 ²⁵	2	2	1	2	0	2	2	0					11
de Ruiter, 2015 ⁶	2	1	2	2	0	2	1	0					10
Mikoya, 2010 ¹⁷	2	1	2	2	2	1	2	0					12
Yoshida, 2013 ²⁶	1	1	1	2	0	2	2	0					9
Reddy, 2015 ²⁷	2	1	2	2	0	2	2	0					11
Tai, 2000 ²⁸	2	2	2	2	2	2	2	0					14
Behnia, 2012 ²⁹	2	1	2	2	0	1	2	0					10
Feichtinger, 2008 ³⁰	2	1	2	2	0	2	2	0					11
Queresby, 2012 ³¹	2	1	1	2	2	0	0	0					8
Lee, 2013 ³²	2	1	2	2	0	1	2	0					10
Oberoi, 2009 ¹	2	2	2	2	0	2	2	0					12
Zhou, 2015 ³³	2	1	2	2	0	2	2	0					11
Zhang, 2015 ³⁴	2	2	2	2	0	2	0	0					10
Barbosa, 2016 ³⁵	2	1	1	2	0	0	0	0					6
Oh, 2016 ³⁶	2	1	1	2	0	2	0	0					8
Janssen, 2017 ³⁷	2	1	1	2	0	2	0	0					8
Watanabe, 2017 ³⁸	2	2	2	2	0	2	2	0					12
Han, 2017 ³⁹	2	1	1	2	0	2	0	0					8
(b)													
First author, year	Domains												
	Sequence generation	Allocation concealment	Blinding of participants and investigators	Incomplete outcome data	Selective outcome reporting	Other potential sources of bias	Interpretation risk of bias						
Movahedian Attar, 2017 ⁴⁰	Yes	Yes	Yes	Yes	Yes	Yes	Low						

Correspondence of the numbers on the first row (from Slim *et al*⁹): 1. a clearly stated aim; 2. inclusion of consecutive patients; 3. prospective collection of data; 4. end points appropriate to the aim of the study; 5. unbiased assessment of the study endpoint; 6. follow-up period appropriate to the aim of the study; 7. loss to follow up less than 5%; 8. prospective calculation of the study size; 9. an adequate control group; 10. contemporary groups; 11. baseline equivalence of groups; 12. adequate statistical analyses. The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). * The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

clefts were more often included than bilateral clefts and males more than females. These findings about cleft type and gender distribution followed the expected prevalence in cleft patients. Mean age of the included CLP patients varied between 6 years 11 months and 11 years 6 months in most studies. Arctander *et al*¹⁴ evaluated the 20 year postoperative outcome of SABG by performing 3D imaging in adult patients (mean age of 31 years). Zhang *et al*^{2,34} and Shirota *et al*²⁰ included patients with higher mean ages and notable wider ranges at the time of bone grafting. Dissaux *et al*¹⁵ included patients of younger age at the time of bone grafting as the success of early and late SABG was compared.

As depicted in [Figure 2](#), CT scans were the only 3D imaging modality used in all three publications between 1994 and 2000 to assess SABG. Between 2001 and 2010, cone beam CT (CBCT) was only used in 2 out of 11 studies, while from 2011 onwards it played a dominant

role. Therefore, [Table 3](#) was sorted by 3D imaging modality (CBCT or CT) and by publication year.

There was a large variability in the imaging protocol between studies. Because of the inclusion criteria, 3D images were taken in all studies. In a few other articles, 2D images such as dental, occlusal, and panoramic radiographs and a lateral cephalogram were taken as well.^{6,17,23,34,38,39,41} In one publication, a panoramic radiograph was reconstructed out of the CBCT scan.²⁵ Concerning the timing of these images, we observed that four studies^{16,20,35,42} took pre-operative 3D images only, mostly when the main objective was surgical planning. The majority of the articles aimed to describe the outcome and long-term success by longitudinal radiological follow up of the bone graft, which also varied significantly between studies. In most articles, a follow-up period of 6 months or 1 year post-operatively was reported, in 14 and 16 articles respectively. Only

Table 3 Data extraction sheet

First author, year	Design	Sample	Imaging modality				Graft type	Study measures				Other parameters			
			Pre-op		Post-op			Type	3D	R	L		S	R	
			N	Mean age [range]	3D	2D									
Movahedian Attar, 2017 ⁴⁰	RCT	20	9y 6m; 10y	X	1y	CBCT	MS + allograft+L-PRF; IC	X	VR						
Janssen, 2017 ³⁷	ORC	11	10y	1w	1y	CBCT	MS	X	VR						
Oh, 2016 ³⁶	ORC	40	9y 2m [6y 8m-12y 10m]	X	1y	CBCT	IC	X							Graft survival rate (%), classification bone resorption (Bergland), 8 risk factors
Disiaux, 2016 ¹⁵	ORC	28	5y 2m [4y-7y]; 10y [8y 6m-13y]	1d	1y	CBCT	IC	X	VR	X					
Linderup, 2016 ²⁵	ORC	32	9y 6m [8y 1m - 11y 11m]	1m	1y	CBCT	OPG ~ CBCT	X	BF						Root development of cleft-side canine, presence lateral incisor GAND classification
Barbosa, 2016 ³⁵	ORCS	33	8y [6y - 11y]	X		CBCT		X							
Zhou, 2015 ³³	OPC	12	10y 2m [8y - 12y]	X	1w	CBCT	IC	X							
Zhang, 2015 ³⁴	OPC	60	13y [9y - 27y]		3m, 6m	CBCT	IC								Bone Mineral Density, Bergland classification
de Ruiter, 2015 ⁶	OPC	7	11y 2m	X	1w, 6m	CBCT	OPG, Ceph, Occl	X	ms β-TCP	X					Cleft adjacent tooth eruption
Hudak, 2014 ²³	ORC	308	11y 6m [4y - 51y]	X	1y	CBCT	OPG	X	CB	X	BF				Clinical outcome parameters
Lee, 2013 ³²	OPC	7	11y 5m [8y 10m-14y 10m]	X	1m	CBCT		X							
Wangrimongkol, 2013 ¹⁹	OPCS	20	11y 6m [9y-17y]		3-6m	CBCT						X			Qualitative X-ray scores, questionnaire
Pradel, 2012 ⁵	CT	8	11y 2m [9y-16y]; 9y 6m [8y-11y]	X	6m	CBCT	TEB; IC	X	BF						
Behnia, 2012 ²⁹	OPC	3	10y [8y-13y]	X	3m	CBCT	Triade	X	BF						
Zhang, 2012 ²	OPC	19	15y 10m [9y 2m-26y 4m]		1m, 6m	CBCT	IC	X	RR	X		X			Cleft adjacent tooth eruption
Quereshy, 2012 ³¹	ORCS	14		X		CBCT		X							
Shirota, 2010 ²⁰	OPCS	13	22y 1m [8y-47y]	1m		CBCT	IC	X		X					
Obero, 2009 ¹	OPC	21	10y 7m [8y-12y]	X	1y	CBCT	IC	X	BF						Variables potentially influencing outcome

(Continued)

Table 3 (Continued)

First author, year	Design	Sample	Imaging modality				Graft type	Study measures				Other parameters			
			Pre-op		Post-op			Type	3D	2D					
			N	Mean age [range]	3D	2D	3D			2D	3D	2D	V	R	L
Watanabe, 2017 ³⁸	OPC	50	10y 5m [8y-16y]	X		1y	CT	PA	T	X					Classification of bone graft height, weight of transplanted bone Cleft adjacent tooth eruption
Reddy, 2013 ²⁷	OPC	10	10y [8y-12y]	X	1d, 6m		CT		IC	X					
Choi, 2012 ¹⁶	OPCS	47	9y 10m [8y-11y]	1m			CT		IC	X					
Mikoyva, 2010 ¹⁷	OPC	42	6y 11m [5y 1m-10y 1m]	X	6m	X	CT	PA	MMB			X	X		Bone formation, cleft adjacent tooth eruption +eruption stage, Chelsea scale Presence lateral incisor Cleft adjacent tooth eruption
Kim, 2008 ¹³	OPC	15	10y	1m	3m, 1y		CT		IC	X	RR	X			
Feichtinger, 2008 ³⁰	OPC	20	11y [9y-15y]	X	1y, 2y		CT		IC	X	VR				
Feichtinger, 2007 ⁷	OPC	24	10y 7m [8y 2m-15y 10m]	X	1y, 2y, 3y		CT		IC	X	VR				Locations of bone resorption, cleft adjacent tooth eruption
Herford, 2007 ¹¹	ORC	12	10y [9y-11y]; 8y [7y-10y]	X	4m		CT		IC + rhBMP-2X		VR				Cleft adjacent tooth eruption Scoring marginal bone level (Enemark), Residual Cortical Bone (RCB) ratio
Feichtinger, 2006 ²⁴	OPC	16	10y 6m [9y 2m-14y 11m]	X	1y		CT		IC	X	VR				
Kawakami, 2003 ⁴¹	OPC	17	10y 1m [8y 10m-12y 8m]	X	6w, 3m, 6m, 1y	1y	CT	PA	IC				X	X	
Van der Meij, 2001 ¹²	ORC	50			3d, 1y		CT		IC						Cleft adjacent tooth eruption, bone bridge quality
Tai, 2000 ³⁸	OPC	14	9y 1m [6y-16y]		1d, 1y		CT		IC	X		X			
Honma, 1999 ²¹	OPC	15	10y [8y-15y]	X	3m, 1y		CT		IC	X	VR				
Van der Meij, 1994 ²²	ORC	8	9y 5m [9y-10y 10m]		3d, 1y		CT		IC				X	X	Canine position and length Graft survival (Enemark)
Yoshida, 2013 ²⁶	ORC	12	9y 10m [8y-12y]	X	6m		hCT		IC	X	VR	X			
Han, 2017 ³⁹	ORC	27	9y [6y - 12y]		6y 6m	7y	MDCT	PA	CB			X			

(Continued)

Table 3 (Continued)

First author, year	Design	Sample	Imaging modality				Post-op	Type		Graft type	Study measures				Other parameters
			Pre-op		2D			3D	2D		3D	2D	3D	2D	
			N	Mean age [range]	3D	2D	3D	2D	3D	2D	V	R	L	S	R
Sakio, 2017 ¹⁸	OPC	29	[7y - 9y]	X		1m, 1y		MDCT	IC ± PRP	X	RR				
Nagashima, 2014 ⁴⁴	OPC	29	10y [8y - 14y]	X		1m, 6m		MDCT	IC	X	RR	X			
Seike, 2012 ⁴²	ORC	41	9y 10m [6y - 15y]			3m	3m	QCT, CT PA	IC			X		Scoring marginal bone level (Enemark), bone mineral density	
Arctander, 2005 ¹⁴	ORCS	18	31y [29y - 34y]			20y		sCT	IC				X		

2D, two-dimensional; 3D, three-dimensional; BF, bone fill ratio; CB, cranial bone; (L)CBCT, (Limited) cone beam CT; Ceph, cephalogram; CT, clinical trial; DBB, deproteinized bovine bone; DBM, demineralized bone matrix; hCT/sCT, helical/spiral CT; IC, iliac crest; L, Linear; L-PRF, leukocyte - and platelet-rich fibrin; MDCT, multidetector row CT; MMB, mandibular monocortical bone; MS, mandibular symphysis; ms β-TCP, microstructured beta-tricalciumphosphate; Occl, occlusal radiograph; OPC, observational prospective cohort study; OPCS, observational prospective cross-sectional study; OPG, orthopantomogram; ORC, observational retrospective cohort study; ORCS, observational retrospective cross-sectional study; PA, periapical radiograph; QCT, quantitative CT; R, ratios (%); RCT, randomized clinical trial; rhBMP-2, recombinant human bone morphogenetic protein Type 2; RR, resorption ratio; S, surface; T, tibia; TEB, tissue-engineered bone; Triade, scaffold, mesenchymalstem cells and platelet derived growth factors; V, Volume; VR, Volume Ratio; X, Present but no details were mentioned.

Figure 2 Number of studies published in function of publication period, with corresponding numbers of 3D imaging modalities used. 3D, three-dimensional; CBCT, cone beam CT; hCT/sCT, helical/spiral CT; MDCT, multi detector row CT; QCT, quantitative CT.

four studies evaluated the bone graft over a time span of more than 1 year.^{7,14,30,39} The longest longitudinal follow-up period was 3 years.⁷ The longest cross-sectional follow-up period was 20 years.¹⁴ The most frequently chosen donor region was cancellous bone from the iliac crest ($n = 25$). Four articles did not mention the graft type and six studies selected other autogenous donor sites such as the mandibular symphysis ($n = 3$), cranial bone ($n = 2$) and tibial bone ($n = 1$). Six studies reported on alternative bone substitutes as depicted in Table 3. Evaluation of the bone graft was executed in different ways in the included studies. Both 2D and 3D measurements were taken on the 3D images. 3D quantitative measurement parameters were volume ($n = 29$) and three ratios derived from the calculated volumes: volume ratio ($n = 9$), bone fill ratio ($n = 5$) and resorption ratio ($n = 4$). 2D quantitative measurement parameters were linear measurements (height, width and depth) ($n = 10$), surface calculations ($n = 4$) and ratios derived from those measurements ($n = 2$). Most articles ($n = 21$) assessed quantitative study measures only, while 16 studies assessed both quantitative and qualitative parameters. Wangsrimongkol et al²⁴ collected qualitative parameters only. Frequently assessed qualitative parameters either clinical or radiological were: cleft-adjacent tooth

eruption and condition, factors influencing outcome, locations of bone resorption and bone mineral density.

Methodological quality assessment revealed that most studies ($n = 26$) were non-comparative and only one-third ($n = 11$) were comparative with a median MINORS score of 10/16 (range 6–14) and 17/24 (range 13–18) respectively (Table 2). The methodological items with the lowest scores were “unbiased assessment of study endpoint” and “prospective calculation of study size” and the highest scores were given for the items “clearly stated aim” and “end points appropriate to the aim of the study” for both comparative and non-comparative studies. Additional criteria for comparative studies were almost always scored as “reported and adequate” for the items “contemporary groups” and “adequate statistical analyses” and as “reported but inadequate” for the items “adequate control group” and “baseline equivalence of groups”. The randomized clinical trial by Movahedian Attar *et al*⁴⁰ was scored by the Cochrane Collaboration’s tool for assessing risk of bias as having low risk of bias (Table 2).

Discussion

Optimal timing for SABG

Some terminological confusion exists in literature on the timing of SABG. In this systematic review, we held on to the aforementioned terminology used in the CLP team of our department. Some authors differentiated early and late SABG, meaning that it is executed before and after canine eruption respectively. Tertiary ABG is then defined as bone grafting in adulthood without taking the factor canine eruption into account. However, in our opinion late SABG should rather be considered as tertiary ABG since at this stage the permanent canine is erupted. Furthermore, it is also possible that a bone graft in an adult patient^{2,14,20,23,34} with an impacted canine has to be considered as SABG instead of tertiary ABG. This justifies the inclusion of some articles reporting on a study group with age ranges far beyond secondary repair ages.

Despite the terminological contradictions in literature, all articles in this systematic review agreed on the advantages of SABG and several studies reported a lower success rate of bone grafts executed after the eruption of the cleft-side canine. We can, therefore, conclude that the optimal timing to carry out SABG is dictated by canine development rather than by biological age. Although some authors state that the ideal timing for SABG is when the unerupted canine is located close to the cleft border and when the root is from half to two-thirds developed,^{3,14,36} there is no agreement in literature about the influence of root development stage on graft outcome. None of the articles mentioned the effect of completed canine root formation. In the study of Oberoi *et al*,¹ no significant difference in outcome was found between canine root development greater or less than 50%. These results corroborate those reported by

Linderup *et al*,²⁵ showing that the volumetric outcome was not affected by root development stage. As a consequence, we have to interpret those results with caution and regard them as a clinical guideline because we cannot firmly state that this factor has an impact on graft success.

Evolution from 2D towards 3D imaging

We noticed an increasing number of articles published over the last decades, revealing a growing interest on this topic. This finding can be explained by a shift in imaging modality used for the assessment of SABG since the introduction of 3D imaging in dentistry.

Traditionally, 2D radiographs have been used for bone graft evaluation and several scales based on those 2D images have been developed over the years for outcome determination of the bone transplant.⁷ However, the reliance on 2D radiographs is acknowledged to be problematic in the assessment of alveolar clefts because of the 3D nature of the cleft defect.⁴³ The main criterion to determine the success rate of the bone graft procedure was the postoperative marginal bone level of the cleft-adjacent teeth.⁷ These 2D outcome evaluation methods assessed bone resorption in relation to bone height. Long-term success rates of up to 95% for SABG were reported in literature for methods based on 2D images. Although detection of bone bridging is feasible on conventional X-rays, assessment of bone graft quantity or quality is impossible.²² The main drawback of graft evaluation methods based on 2D images is the inability to visualize the irregular shape of the cleft and to measure bone formation along the buccolingual axis, *i.e.* depth or buccopalatal thickness.³⁸ This loss of information is a consequence of trying to derive 3D information from a 2D image.

Because of this, in the last years there has been a trend toward the use of 3D imaging to evaluate the status of the bone graft. The information derived from those images is advantageous over the conventional approach by excluding many factors affecting image quality and reliability, such as enlargement, distortion, structural overlap, and positioning problems.^{1,41}

Earlier, CT scans were the most important 3D imaging modality. With 200 to 300 times the amount of radiation required for a panoramic radiograph, CT scans went far beyond the maximum risk threshold for radiation exposure. CBCT scans produce a narrow, collimated cone beam of radiation that is able to scan a limited field of the maxilla and is characterized by a shorter scanning time.⁴¹ This requires only two to eight times the amount of radiation generated in a panoramic radiograph and the effective radiation dose of a CBCT scan is 30 times less compared with a conventional spiral CT of the head.⁴⁰ The higher radiation load of CBCT compared with panoramic radiographs is justified because the 3D image provides crucial information about alveolar cleft repair.⁶ Its growing popularity for bone graft evaluation is confirmed by the fact that

CBCT scans play a dominant role in the articles of this systematic review from 2011 onwards, while the amount of CT scans diminished visibly (Figure 2).

Although 2D images of the cleft region become superfluous when a 3D image is available, we noticed that in some studies an additional 2D image was taken. Although taking redundant X-rays is not justified, it can be understandable that 2D images are taken to serve as a comparison for a new 3D evaluation technique.^{17,34,41} However, reconstructing those additional 2D images out of the existing CBCT scans can be a solution to reduce the cumulative dose for the patient, as proposed by Linderup *et al*.²⁵

3D imaging protocols

We observed that imaging protocols for radiological follow up of SABG differed significantly between studies. Mostly, one or two post-operative 3D scans were made, except in the publications of Feichtinger *et al*⁷ three scans were made with a time interval of 1 year between scans and in the article of Kawakami *et al*⁴⁰, four scans were made in a time span of 1 year. Both studies^{7,40} took conventional CT scans which elevates the radiation hazard even more. The latter⁴⁰ also combined those 3D scans with a periapical radiograph after 1 year. Even though successive 3D scans with lower radiation dose (CBCT) can be justified in CLP patients when a demand for information exists, it is important to emphasize that the cumulative dose of several CBCT scans together can reach high levels in the pediatric patient who is known to be more susceptible for radiation. Thus, there is a pressing need for the development of a consistent optimized imaging protocol for diagnosis and follow up of SABG in CLP patients.

3D assessment of SABG

Nowadays, the cleft site can be assessed by software analysis of a 3D image to enable evaluation of the alveolar defect pre- and post-operatively, enabling surgical planning and outcome assessment of the bone graft. Several studies based on (CB)CT scans emphasized the importance of the amount of bone in the buccopalatal direction, because a high amount of resorption is normally present in the horizontal plane as well and can be as high as that in the vertical dimension.²⁸ This information is crucial in treatment planning and follow up because it concerns the target area of canine eruption. Cleft-adjacent teeth can get lost due to excessive bone resorption. Therefore, post-operative evaluation of the amount of residual bone is vital to the process of subsequent orthodontic treatment.³⁴ 6 months post-operatively, Mikoya *et al*¹⁷ considered a bone bridge with a buccopalatal width of 9,6 mm at the middle level between the apical and coronal borders as a successful outcome. They based themselves on the theory of Bähr and Coulon⁴⁴ who recommended this width to be at least 9 mm to accommodate the permanent canine and

provide it with bone plates around the largest buccopalatal diameter (8 mm).

Literature is unanimous that 2D outcome evaluation methods tend to overestimate the extent of bony fill.^{23,34} The number of successful bone grafts has been reported to be overestimated in up to 17–25% of dental radiographs compared with CT scans.^{4,12,45} In these articles, significantly lower success rates of SABG were reported when 3D evaluation methods were performed.

Some studies only measured linear distances or surfaces of some selected slices of the cleft. In the articles of Van der Meij *et al*,^{12,22} bone graft evaluation was performed by surface measuring on three different axial levels. In our opinion, the limitation of this technique is the loss of accuracy because a cleft consists of several axial slices together. In this way, the exact shape of the cleft boundaries between the selected slices is unknown and as a consequence results based on this technique are less precise.

Bone graft resorption

We briefly summarized the found results about volumetric assessment of the cleft region, as it is a recurrent topic in the included articles and introduces the crucial clinical matter of bone graft resorption.

Volume was determined in different ways in the included articles by using several commercially available volume-rendering software and although tools were different, techniques were quite comparable. Segmentation was either performed manually or semi-automatically, guided by the most optimal pseudoHounsfield units.²⁵ The computer software calculated volume by integration, according to a particular formula.^{7,27,28} In unilateral CLP cases, the morphology of the corresponding area on the contralateral side often served as a template during segmentation of the cleft side through mirroring, which suggests that the limited number of bilateral CLP patients present in the studies is not only an epidemiological phenomenon but it's mostly related to methodological convenience.^{4,6,7,13,14,24–27,30–32,34–36} Outlining of the bone graft borders after successful integration was problematic for some authors^{22,28,34} while others were still capable of differentiating the bone density of the graft and the adjacent alveolar process.²⁴ A 3D reconstruction of the cleft defect could be generated after delimiting for the surgeon to have a better understanding of the bony architecture.³³

Volumetric measurements served to describe outcome in terms of bone graft resorption or bony fill of the cleft defect. The outcome was expressed in ratios that we were able to classify into three groups: “resorption ratio”, “volume ratio” and “bone fill ratio”. The two last are calculated in a different manner but they both compute the amount of post-operative volume of the restored bone bridge relative to the pre-operative volume of the cleft defect. The “resorption ratio” on the other hand does not take the pre-operative volume of the cleft into account but represents the amount of resorption of the

Table 4 (a) VR and RR for iliac crest bone graft, (b) VR, BF and RR for alternative types of bone graft

(a)					
First author	Follow-up period				
	3 months	4 months	6 months	1 year	3 years
Feichtinger ⁷				VR 49,5%	VR 52%
Honma ²¹	VR 115%			VR 99%	
Feichtinger ²⁴				VR 36%	
Oberoi ¹				VR 84%	
Pradel ⁵			VR 37%		
Herford ¹¹		VR 78%			
Zhang ²			RR 29%		
Nagashima ⁴			RR 47%		
Sakio ¹⁸				RR 45%	
Feichtinger ³⁰				VR 51%	VR 50%
Dissaux ¹⁵			VR 46%; 63%		
Movahedian Attar ⁴⁰				VR 74%	

First author	Graft type	Follow-up period		
		3 months	6 months	1 year
Hudak ²³	CB			BF 85%
Linderup ²⁵	MS			BF 87%
Behnia ²⁹	Triade	BF 51%		
Sakio ¹⁸	IC + PRP			RR 50%
Pradel ⁵	TEB		BF 41%	
Movahedian Attar ⁴⁰	MS + allograft+L- PRF			VR 70%
Janssen ³⁷	MS			VR 62%

BF, bone fill ratios; RR, resorption rates; VR, volume ratios.

post-operative graft material by comparing the post-operative volumes on two time points. The volume and resorption ratios for the iliac crest bone graft have been summarized in Table 4.

The study with the longest longitudinal follow-up period of 3 years was conducted by Feichtinger et al.⁷ The highest decrease in postoperative bone volume seems to take place in the first postoperative year, remaining stable on the following two. Histological findings reveal that the active remodeling of the bone bridge was more or less completed by 1 year.²¹ Because the first year after SABG is a period of intense bone graft remodeling, we then assume that a follow-up period of 6 months is not long enough to draw firm conclusions in terms of a successful outcome. Several studies noticed that the residual bone bridge volume increased after a longer period of time as a result of the osteogenic effect of the erupting canine into the graft.^{7,21,23} Therefore, it may be advisable to load the bone graft with a functioning tooth to prevent excessive bone resorption and regrafting due to a lack of physiological loading.

As results varied significantly between studies, caution should be taken when comparing the volume ratios and resorption rates between studies, because different measurement techniques and protocols may deliver different outcomes. Especially the segmentation method, slice thickness, and how the cleft margins are defined can be responsible for this variation.³⁹ To date, there is no standard criterion against which the validity of the volumetric measurements can be compared. Another factor in the variability of the measurements is the degree of filling of the cleft defect. An overfilled cleft defect contains a larger portion of graft material that is not functionally loaded and higher resorption rates can be expected. It is a misunderstanding that the alveolar defect should be restored completely. Some degree of bone graft resorption is compatible with a successful outcome, as long as it allows tooth eruption.⁶ Furthermore, it could be misleading to equate quantitative volume and success rate, since other qualitative factors such as a bony continuity of the alveolar ridge, status of the adjacent teeth, a normal bony architecture and the eruption path of the permanent canine should be taken into account as well to consider the procedure as clinically successful.³⁹

Types of bone graft

Particulate cancellous bone marrow from the iliac crest is still accepted as clinical reference standard, while other autogenous donor sites and artificial bone substitutes are introduced and thoroughly tested to bypass donor site morbidity. In our results, studies evaluating the outcome of synthetic bone substitutes are characterized by small study samples.^{5,6,29} Some graft types are promising and try to elucidate a path toward their clinical use in future practice,^{5,6,11,39} while other substitutes are far from being satisfactory.²⁹ A summary of these data has been added to, for the interested reader.

Conclusion and remarks for future research

The availability of 3D imaging has enabled quantitative evaluation of SABG, becoming a routine practice to overcome the drawbacks of 2D evaluation techniques. Although CBCT scans produce a lower radiation dose compared with CT scans, clinicians and researchers should carefully justify 3D imaging. Because a higher cumulative radiation dose in pediatric patients rises ethical questions, we expect that radiation efficiency of low-dose CBCT devices will further evolve in future research. Further optimization should include a reduced field of view to a limited part of the maxilla, and reconstruction of 2D images out of 3D ones to avoid double radiation. A pressing need exists for the development of a consistent optimized imaging protocol for diagnosis and follow up of SABG in CLP patients, since imaging protocols differed significantly between studies. If a CLP team would like to change the imaging protocol

of SABG, they should begin by evaluating the results of long-term follow up in large patient groups. Subsequently, clinical trials should be set up.

There was a large heterogeneity in the methodology of measurements. Although 3D evaluation methods seem to be more precise than 2D methods, we should be careful when comparing outcomes arising from different 3D measuring techniques. On the one hand, outcome comparison between studies with a different study set up (study sample, 3D imaging protocol, applied software and study measures) is problematic. On the other hand, the process of 3D image analysis and segmentation are observer-dependent and subjected to human errors thereby limiting measurements accuracy.

Although insight in the morphology and size of the preoperative cleft defect and the amount of subsequent bone graft resorption in 3D is of large clinical value,

we should avoid to equate success rates with quantitative volumetric measurements only. Future researchers should take the dynamic process of graft integration into account. Calculated resorption rates can vary significantly depending on local biological factors. The development of a cutoff score to decide whether the measured amount of bone resorption is normal or excessive could serve as a guideline to quantify the outcome of the bone graft in a standardized way.

There is a lack of prospective, controlled trials based on a consistent imaging protocol with a sufficiently long follow-up period. A follow-up period of at least 1 year is advisable to draw conclusions in terms of a successful outcome. To overcome the limitations of studies examining alternative bone grafts, future research should include larger sample sizes and continued long-term follow-up to determine the usefulness of the procedure.

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