Factors Contributing to Canine Impaction in Patients with Unilateral Cleft Lip and Palate (UCLP) Undergoing Alveolar Bone Grafts (ABG)

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Abstract

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Background:
Patients with unilateral cleft lip palate (UCLP) undergo alveolar bone grafting (ABG) to unite the maxillary bony segments and allow for proper eruption of the permanent canine. The aim of this study was to assess the incidence of canine impaction in the UCLP patient population and identify pre-graft and surgical factors as well as dental anomalies that are associated with impaction.

Materials and Methods:
This study included 257 patients with UCLP who received alveolar bone grafting at Seattle Children's Hospital. Electronic health records were reviewed to obtain data on cleft information, pre-graft procedures, and surgical details. Dental anomalies were identified through panoramic/cephalometric radiographs and intraoral photo taken before ABG and up to 2 years after ABG. T-tests, chi-square tests and logistic regression analysis were used to evaluate incidence of canine impaction and test for associations with pre-graft factors, surgical factors, and non-cleft factors.

Results:
Of the 257 patients included in the study, 56% were male with a mean age of 9.2 years old at the time of ABG. Left-sided clefts (63%) were more common than right-sided clefts (37%). The incidence rate of canine impaction in this cohort of patients was 27% (N=257). Clefts extending to the secondary palate were more likely to have impacted canines (30% vs 12%, $p = 0.017$). Patients with a hypodivergent facial pattern also had a higher incidence of canine impaction (low angle: 46%; high angle: 29% versus 22% normal angle, $p = 0.042$). Logistic regression indicated canine impaction was more likely in females than males (adjusted odds ratio [OR] = 2.1, $p = 0.015$), root development of less than 1/3 expected total length at time of of graft (OR= 3.36, $p = 0.024$), extraction of primary canine (OR = 2.3, $p=0.009$) and greater permanent canine angulation (OR = 1.1, $p <0.0001$). No associations between canine impaction and pre-graft orthodontic expansion nor re-grafting were detected.

Conclusion:
There is a substantially higher incidence of canine impaction in cleft populations compared to non-cleft populations. Multiple factors including pre-graft extraction of the primary canine and increased canine angulation were associated with permanent canine impaction and should be considered when managing patients with UCLP.

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Introduction

Cleft lip and cleft palate are congenital defects in which there is lack of fusion of tissues in the upper lip, palate, or both. Collaborative multidisciplinary care is recommended for patients with orofacial clefting from birth to adulthood. The American Cleft Palate-Craniofacial Association (ACPA) specifies that an orthodontist must be a member of all ACPA-approved teams, highlighting the key role of orthodontic treatment in the care of these patients (*Standards for Approval of Cleft Palate and Craniofacial Teams*, 2019).

Patients with an alveolar cleft commonly require an alveolar bone graft (ABG) to unite the maxillary bony segments and provide support for tooth eruption, orthodontic movement of teeth adjacent to the cleft and, if necessary, tooth replacement. Without surgical reconstruction of the alveolar cleft, patients face multiple challenges including oronasal fistula, fluid reflux, speech difficulties, ectopic tooth eruption, malocclusion, periodontal disease, and maxillary and facial asymmetry that can give rise to self-esteem issues (Uzel et al., 2019).

An impacted tooth is defined as an unerupted tooth that exhibits a nearly complete or fully developed root and has an eruption process impeded by one of several etiologies including insufficient space, failure of resorption of deciduous roots, abnormal eruptive path, soft tissue pathology or a disturbance in the eruption mechanism of the tooth (Becker, 2012). In non-cleft populations, maxillary third molars are the most frequently impacted, followed by the mandibular third molars, maxillary canines and mandibular premolars (Al-Zoubi et al., 2017). The frequency of maxillary canine impaction reported in non-cleft populations is 0.9% to 2.2% (Bishara, 1992; Ericson & Kurol, 1987; Oberoi et al., 2010). Maxillary canine impaction in the noncleft population has been genetically associated with several dental anomalies including tooth agenesis and microdontia (Bishara, 1992).

In contrast, reports of the incidence of maxillary canine impaction in patients with CLP range from 4.4% to 35% (Alqerban, 2019; Enemark et al., 2001; Matsui et al., 2005; Tortora et al., 2008; Westerlund et al., 2014). This wide range indicates the need for further studies to understand the etiology of maxillary canine impaction in patients with CLP. It is unclear whether canine impaction in patients with CLP is due to the same genetic factors as noncleft populations, cleft anatomy, surgical management of the cleft, or a combination of factors (Hereman et al., 2018; Simões Holz et al., 2018). Literature specific to this topic is limited by small sample sizes.

Background

Definition and Prevalence of Cleft Lip and Palate

Unilateral cleft lip and palate (UCLP) is a congenital defect characterized by asymmetric division of the alveolus into a greater segment and a lesser segment. UCLP is one of the most common congenital birth defects and can occur either in isolation or in association with genetic syndromes. According to the Centers for Disease Control and Prevention, approximately 1 in 1,600 babies are born with cleft lip and palate (CLP) in the United States (Mai et al., 2019). Clefts may be complete (including lip, alveolar process, hard palate and soft palate) or incomplete (including lip and alveolar process). In existing studies, up to 75.8% of patients with UCLP have complete clefts over incomplete clefts (Enemark et al., 1987; Jamilian et al., 2015).

Management of Unilateral Cleft Lip and Palate (UCLP)

Infants with UCLP undergo a surgical lip repair between three to six months of age. In the United States, those with complete clefts have surgery to close the palate by 18 months old. Timing of alveolar bone graft surgery (ABG) is controversial and varies between craniofacial teams. At the hospital hosting

this study, patients are managed with secondary alveolar bone grafting, done when most patients are between 8-12 years old and root development of the permanent maxillary canine is 1/4 - 1/2 of its projected length (Proffit et al., 2018). The alveolar bone graft serves to close the oronasal communication and creates bone union of the greater and lesser segments (Boyne and Sands, 1976; Kleinpoort et al., 2017). At other institutions, there is a trend towards earlier secondary alveolar bone grafting when the patient is 5 to 7 years old (Kleinpoort et al., 2017).

Prior to ABG surgery, some patients have orthodontic maxillary expansion. Maxillary arch constriction in UCLP patients results from the inward rotation of the lesser segment toward the cleft (Boyne & Sands, 1976). Palatal expansion appliances including W-arch, quad-helix, or rapid maxillary expander with differential opening are used for segment repositioning prior to ABG surgery in selected patients with UCLP. The expansion also helps to align the segments and facilitate the surgeon's access for placement of the graft during surgery (Uzel et al., 2019) (Figure 1).

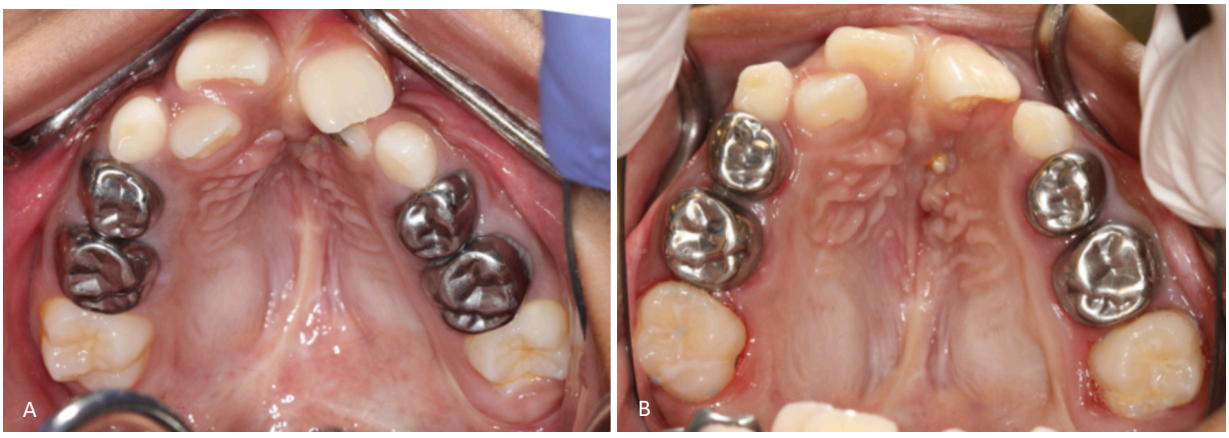

Figure 1. 1A depicts initial presentation of a 7-year old patient with a complete unilateral cleft lip palate. The lesser left posterior segment is rotated medially. 1B depicts the same patient following extraction of a tooth in the cleft site and pre-alveolar bone graft expansion to align alveolar segments (Preston et al., 2022).

At least one author has recommended extraction of the primary canine proximal to the cleft margin one month or more in advance of ABG to reduce the rate of wound dehiscence and improve the survival of the graft (Lilja et al., 1987). In noncleft populations, a systematic review found that extraction

of the primary canine can facilitate eruption of palatally displaced canines; it is hypothesized that extraction of the primary canine creates an eruption path for the permanent canine (Almasoud, 2017). It is unclear whether primary canine extraction in cleft populations promotes eruption of permanent canines or conversely contributes to impaction by inducing scarring or site trauma.

Patients with UCLP with persisting oronasal fistulas may suffer from periodontal disease due to chronic inflammation from oral nasal reflux (Coots, 2012). At the time of ABG, if an oronasal fistula is identified, closure of the soft tissue fistula is attempted (Miranda et al., 2020). During ABG surgery, a permanent lateral incisor erupted into the cleft may be extracted due to severe malformation of the tooth, ectopic position, and/or risk of impaired healing of the graft (Bergland et al., 1986). There is little evidence for whether surgical factors such as extraction of teeth during ABG, visibility of the permanent canine during the surgery, or lack of closure of the soft tissue fistula may contribute to canine impaction.

Not all alveolar bone graft surgeries are successful with a single attempt. One or more augmentation/revision surgeries are required if the alveolar bone has insufficient volume to allow for tooth movement and retention. A single center review of 103 patients with UCLP found that 18% required re-grafting revision surgeries (Goudy et al., 2009). It is unknown whether a higher frequency of revision surgeries may alter the cleft environment as well as influence the incidence of canine impaction.

Associated Dental Anomalies

In noncleft populations, impacted canines have been associated with microdontia or agenesis of the lateral incisor, ectopic eruption of the maxillary first permanent molar, infraocclusion of primary molars, and female sex (Baccetti, 1998; Mercuri et al., 2013). Association between canine malposition and female sex, hypodivergent vertical skeletal relationships, and size defect in the lateral incisor have

been reported (Sacerdoti & Baccetti, 2004). For cleft populations, limited studies have been carried out to identify the correlation of these specific characteristics with impacted canines. A study of 201 cleft patients reported that 64.1% had hypodontia but there was no association between incidence of hypodontia and gender (Jamilian et al., 2015). Another study of 87 patients with UCLP reported congenital absence of the permanent lateral incisor on the cleft side in 48.8% of patients (Tortora et al., 2008). Canine angulation has also been noted as an indicator for canine impaction risk, with one study reporting a higher risk for permanent canines angled greater than 30 degrees from the long axis of the lateral incisor in noncleft populations (Shin et al., 2022). A recent study evaluating a cohort of males with UCLP found a higher incidence of canine impaction in patients with missing laterals and canine angulations greater than 25 degrees relative to the midsagittal plane (Hong et al., 2022).

Treatment of impacted canines often requires specific surgery to expose the canine followed by orthodontic traction, which increases costs and extends orthodontic treatment time. Criteria for surgical exposure of canines include complete root development of canine, canine malposition, and eruption of the contralateral canine. In a study of 18 patients with UCLP, 56% required surgical exposure of cleft-associated canines following ABG (Hinrichs et al., 1984). In a study of 190 patients with UCLP, 18.9% underwent surgical exposure of permanent canines (Matsui et al., 2005). A study of 53 patients found a 20-fold increased risk for canine impaction in the cleft population compared with the general population (Russell & McLeod, 2008). The variation in rates of surgical exposure may be attributed to differences between study groups, clinical protocols, and research designs.

Understanding the etiology of canine impaction in UCLP patients as well as the relationship with timing of the ABG, interceptive orthodontics, and surgical factors will help establish a base of evidence to create science-based guidelines for optimal cleft care. Early identification of the risk of canine impaction may help the clinician to develop and sequence a treatment plan that optimizes outcomes and minimizes treatment time.

Research Design and Methods

Research Questions

1. What is the incidence of maxillary canine impaction in patients with UCLP managed with secondary alveolar bone grafting (defined as root development of canine is 1/4 to 2/3 of its final length at the time of grafting)?
2. Is there an association between the following pre-surgical procedures and incidence of canine impaction in patients with UCLP?
    a. Pre-surgical orthodontic treatment (expansion, uprighting teeth with fixed appliances)
    b. Extraction of primary canine 6-8 weeks prior to ABG
3. Is there an association between the incidence of canine impaction and the following surgical factors?
    a. Canine root development at time of ABG
    b. Extraction of teeth at the time of ABG
    c. Visibility of the canine during ABG
    d. Closure of the soft tissue fistula
    e. Multiple grafts
4. For each of the factors that have been associated with a higher incidence of canine impaction in the non-cleft population, is there an association with canine impaction in patients with UCLP?

Research Design to Accomplish Specific Aims

This retrospective single center cross-sectional study was conducted using patient records from the Seattle Children's Hospital. Available records of patients with UCLP including electronic health

records, panoramic radiographs, lateral cephalograms, and intra-oral photographs were obtained. Records taken before orthodontic treatment and ABG surgery, after pre-ABG surgery orthodontic treatment if done, and following ABG surgery were analyzed.

Methods

Sample

Patients were identified through institutional reports including billing codes for ABG and for exposure and bonding or extraction of unerupted maxillary canines. The qualifying criteria for patients with UCLP included indication for alveolar bone graft, availability of diagnostic records at time points of interest, and ABG surgery was performed at SCH. The projected study population included 293 patients with UCLP undergoing alveolar bone graft surgery between 2005 and 2019 at SCH.

Inclusion Criteria

Eligible patients met these criteria:

- Patients with unilateral cleft lip and palate indicated for alveolar bone grafting
- Electronic health records and diagnostic quality radiographic and photographic records at time points of interest: at initial orthodontic assessment for ABG readiness, following pre-ABG orthodontic treatment with expansion or fixed appliances, post-ABG surgery, and follow-up until canine eruption or procedure for canine exposure.
- ABG surgery completed at SCH between 2005 – 2019
- Contralateral canine unerupted at time of ABG

Exclusion Criteria

- Patients with bilateral cleft lip and palate, non-cleft conditions, and craniofacial syndromes
- Patients with nondiagnostic or incomplete records
- Patients with congenitally missing canines

Research Procedures

Electronic health records for each patient were reviewed for the following data (described in Table 1) and entered into a REDCap database with de-identification of patients.

Table 1. Data Collected from Medical Records

Patient Information	
Gender	Male or Female
Date of Birth	*Used to calculate Age*
Cleft Lip Palate Information	
Extent of Cleft	Alveolus only Alveolus and Palate
Cleft Type	Unilateral Left Unilateral Right Bilateral
Segment Displacement	Yes/No
Alveolar Bone Graft	
Date of Graft 1	*Used to calculate Age at First Graft*
Primary Canine Absent at time of ABG	Yes/No
Canine Development at Graft	
Success of Graft 1	Yes/No *If no, collected date of subsequent grafts and canine development.*
Canine Impaction (If Applicable)	
Position Relative to Cleft	Ipsilateral Contralateral Bilateral
Alveolar Position	Palatal Buccal Mid-alveolar
Canine Treatment	Expose and Bond Extraction (due to non-retrievability) Extraction (due to other reasons) Referred for treatment but not yet done

Expose and Bond Date	*Used to Calculate Age at Expose and Bond*
Pre-Graft Orthodontics	
Expansion	Yes/No
Type of Expander	W Arch Quad Helix Fan Expander Hyrax Expander Other
Uprighting of teeth adjacent to cleft with fixed appliances (braces)	Yes No
Surgical Factors	
Extractions at time of graft	Yes/No
Extraction Proximity to Cleft	Within Cleft Proximal to Cleft Remote extraction
Permanent lateral extracted	Yes/No
Canine visible within cleft at time of surgery	Yes/No
Soft Tissue Fistula Present/closed during surgery	Yes/No

Intraoral photographs and models were assessed for initial segment displacement and pre-ABG segment alignment. Canine impaction at the cleft site was characterized as malposition of the fully developed canine with full eruption into occlusion of the contralateral canine.

Patient panoramic and cephalometric radiographs were evaluated for: (1) lateral incisor agenesis and microdontia, (2) agenesis of premolars, (3) ectopic eruption of first molar on cleft side, (4) mandibular plane angle, (5) infraoccluded primary molars, and (6) permanent canine angulation within 1 year of ABG. Radiographic variables are defined in Table 2. Cephalograms were traced to determine mandibular plane angle (MPA). Landmarks were identified on Dolphin ImagingPlus™ software to measure mandibular plane angle: Sella, Nasion, Gonion, Menton. MPA was considered high or low if measurements were greater than 1 standard deviation from the established norm. Permanent canine angle measurements were conducted on Universal Viewer™ (Figure 3). Landmarks and measurements were identified by a single examiner trained in identification.

Table 2. Radiographic Data

Variable	Definition	Image Used
Canine Impaction	Failure to erupt when the contralateral canine has fully eruption into occlusion	Panoramic
Agenesis of premolars and/or laterals	Radiographic absence of tooth buds	Panoramic
Lateral incisor microdontia	Severe crown size reduction with possible narrowing of the diameter from the cervix to the incisal edge	Panoramic and intraoral photographs
Ectopic eruption of maxillary 1st molars	Malposition of the 1st molar resulting in resorption of the distal root of the adjacent primary molar (Figure 2A)	Panoramic
Infraocclusion of maxillary or mandibular primary molars	Distance between the occlusal surface of primary molars and the occlusal plane was greater than or equal to 1mm (Figure 2B)	Panoramic
Mandibular Plane Angle	Intersection of the mandibular plane and Sella-Nasion (Figure 2C)	Cephalometric, Angular Measure
Permanent Canine Angulation	Angle between the sagittal plane (perpendicular to occlusal plane) and long axis of permanent canine on cleft side (Figure 3).	Panoramic, Angular Measure

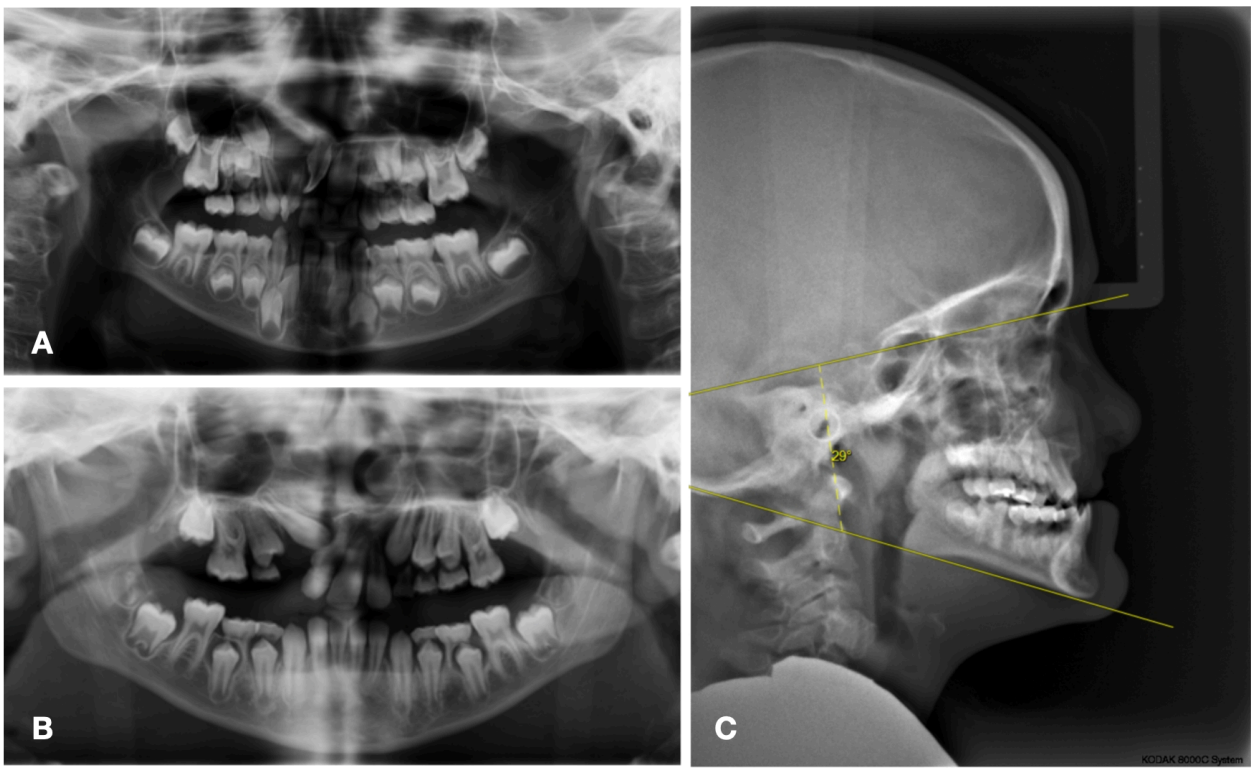

Figure 2A shows ectopic eruption of maxillary 1st molars in a subject. Figure 2B depicts a radiographic example of infraocclusion of primary molars. Figure 2C demonstrates cephalometric measurement of mandibular plane angle (SN-MP).

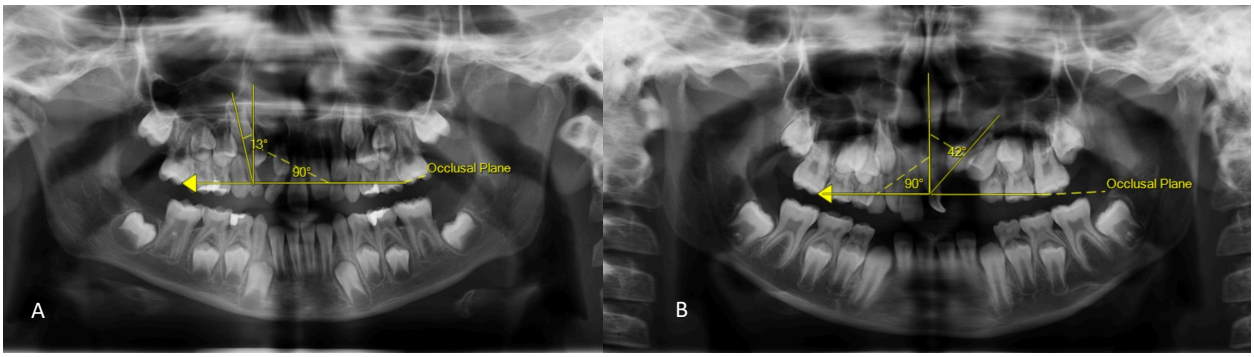

Figure 3. Permanent canine angle measurement. The occlusal plane was measured as a horizontal line between the mesial buccal cusps of the maxillary first molars. The canine angle was measured between the sagittal plane perpendicular to the occlusal plane and the long axis of permanent canine on the cleft side. Figure 3A depicts a measurement less than 25°, and Figure 3B shows a measurement greater than 25°.

Records for canine eruption follow-up were taken at least two years after alveolar bone grafting. For data collection purposes, canine impaction was determined according to the date of the surgery request for exposure and bonding or extraction due to impaction.

Data Analysis

Given the sample size, categorical variables and discrete variables with little variation were grouped into binary variables. Variables indicated whether segments are aligned or not aligned, whether patients received maxillary orthodontic expansion prior to grafting, and whether patients had a single ABG surgery or multiple surgeries. The incidence of canine impaction and 95% confidence interval were calculated based on all patients.

Logistic regression analysis was used to compare incidence of canine impaction by pre-orthodontic expansion, number of ABG surgical attempts, extraction of primary canine, and surgical factors. Logistic regression was also used to assess for an association with canine impaction for factors that have been shown to be associated with canine impaction in the non-cleft population and to test if any of these factors modify the association of segment alignment, pre-orthodontic expansion, number of ABG surgical attempts, primary canine extraction, noncleft associative factors, and surgical variables with canine impaction. All analyses were done using R statistical software (Version 4.2.0) (R Core Team, 2022).

Sample Size Calculation

Preliminary screening of hospital records identified 293 potential patients. The incidence of canine impaction was initially expected to be 20 to 25% on the cleft side. Based on the ½ width of a 95% confidence interval for the incidence of canine impaction, a sample size of 200 to 250 patients provided precision of at least $\pm$5.5% to estimate the incidence of canine impaction and 80% power to

demonstrate an odds ratio for canine impaction of 2.4 or larger for risk factors with a prevalence of 20% to 50%. demonstrate that the incidence rate was higher than compared to the non-cleft population (0.9% to 2.2%) (Appendix A).

Results

Two hundred and ninety-three patients received ABG between 2005 to 2019. In total, 257 eligible patients were included in the study. Reasons for exclusion were: 28 due to inadequate imaging, five received ABGs after the contralateral canine had erupted, and three had congenitally missing canines. Follow-up extended up to two years after time of ABG.

A majority of patients were male (56.8%). Most clefts were complete (83.6%) and 62.6% of clefts were on the left side. At the time of initial assessment, 126 patients (49%) had segment displacement. Of 126 patients with displaced segments, 117 were expanded prior to ABG. Nearly two-thirds of patients (160 patients, 62.3%) had absence of the primary canine at the time of ABG (most often due to prescribed extraction six weeks prior to ABG). The mean age at the time of first ABG was 9.2 years old and ranged from 6.5 years old to 14.5 years old (Table 3). One hundred fifty-four patients (59.9%) underwent alveolar bone grafting when 1/3 – 2/3 of the canine root was developed.

Table 3. Sample Descriptive Statistics

Characteristic	N = 257
Gender	
Male	146 (56.8%)
Female	111 (43.2%)
Extent of Cleft	
Alveolus only	42 (16.4%)
Alveolus and Palate	215 (83.7%)
Cleft Position	

Unilateral Left	161 (62.6%)
Unilateral Right	96 (37.4%)
Segment Displacement	
Yes	126 (49.0%)
No	131 (51.0%)
Canine Impaction	
Yes	69 (26.8%)
No	188 (73.2%)
Age at 1st Graft in Years	
Mean (SD)	9.2 (1.2)
Median (IQR)	9.2 (8.4, 9.9)
Range	6.5, 14.5

Nearly all patients (89.9%) had soft tissue fistula closure at the time of ABG. Twenty-seven patients (10%) had extractions at the time of graft.

At timepoint two, at least two years after alveolar bone graft surgery, 69 patients (26.8%) had an impacted canine; 56 (81.2%) of impacted canines were ipsilateral to the cleft side; 6 (8.7%) were contralateral to the cleft side; 7 (10.1%) were bilateral. Alveolar positions of the impacted canines were palatal in 53 (77.9%, N=69); mid-alveolar in 9 (13.2%); buccal in 6 (8.8%). Alveolar position could not be confirmed for one patient. Frequency of canine impaction was significantly higher in patients with clefts extending into the secondary palate (29.9%) versus clefts limited to the primary palate (11.9%), (p=0.016). There was no association between canine impaction and cleft location (Table 4).

Table 4. Cleft type and location by canine impaction

Characteristic	N = 257	Canines Impacted	95% CI	p-value
Cleft Type				0.017
Alveolus only	42 (16.4%)	5 (11.9%)	4.5%, 26%	
Alveolus and Palate	215 (83.7%)	64 (29.9%)	24%, 36%	
Cleft Location				0.95
Unilateral Left	161 (62.6%)	43 (26.7%)	20%, 34%	
Unilateral Right	96 (37.4%)	26 (27.1%)	19%, 37%	

[1]n (%)
[2]CI = Confidence Interval
[3]Pearson's Chi-squared test

59.9% of patients underwent alveolar bone grafting when 1/3 – 2/3 of the canine root was developed. There was no significant difference in frequency of canine impaction by stage of root development (Table 5). There was also no association between age at first graft and incidence of canine impaction (p = 0.51, Table 6).

Table 5. First graft success, canine development and canine presence by canine impaction

Characteristic	N=257	Canine Impacted	95% CI	p-value
Success of Graft 1				0.59
Yes	228 (88.7%)	60 (26.3%)	21%, 33%	
No	29 (11.3%)	9 (31.0%)	16%, 51%	
Canine development at first graft				0.066
<1/3 Root Development	72 (28%)	25 (34.7%)	24%, 47%	
1/3 - 2/3 Root Development	154 (59.9%)	38 (24.7%)	18%, 32%	
2/3 - Full Root Development	31 (12.1%)	6 (19.4%)	8.1%, 38%	
Primary Canine Presence at Time of ABG				0.020
Yes	97 (37.7%)	18 (18.6%)	12%, 28%	
No	160 (62.3%)	51 (31.9%)	25%, 40%	

[1]n (%)
[2]CI = Confidence Interval
[3]Pearson's Chi-squared test

Table 6. Age at first graft by canine impaction

Characteristic	Overall (N = 257)	Canine Impacted (N=69)	p-value
Age at Graft 1, y			0.51
Mean (SD)	9.2 (1.2)	9.1 (1.3)	
Median (IQR)	9.2 (8.4, 9.9)	9.1 (7.9, 9.8)	
Range	6.5, 14.5	6.6, 14.5	

[1]Welch Two Sample t-test

The primary canine on the cleft side had been extracted in advance of the bone graft for 160 patients (62.3%). There was a significant difference in incidence of canine impaction between patients without primary canines and those with retained primary canines at the time of graft (p = 0.02). Figure 4 displays the locally estimated scatterplot smooth (LOESS) of the trends over time for permanent canine impaction and primary canine extraction (Alpaydin, 2014). There was an increased trend in permanent

canine impactions from 2005 to 2020. Between 2012-2018, there were more pre-graft extractions of the primary canine that corresponded with a slight increase in permanent canine impaction frequency.

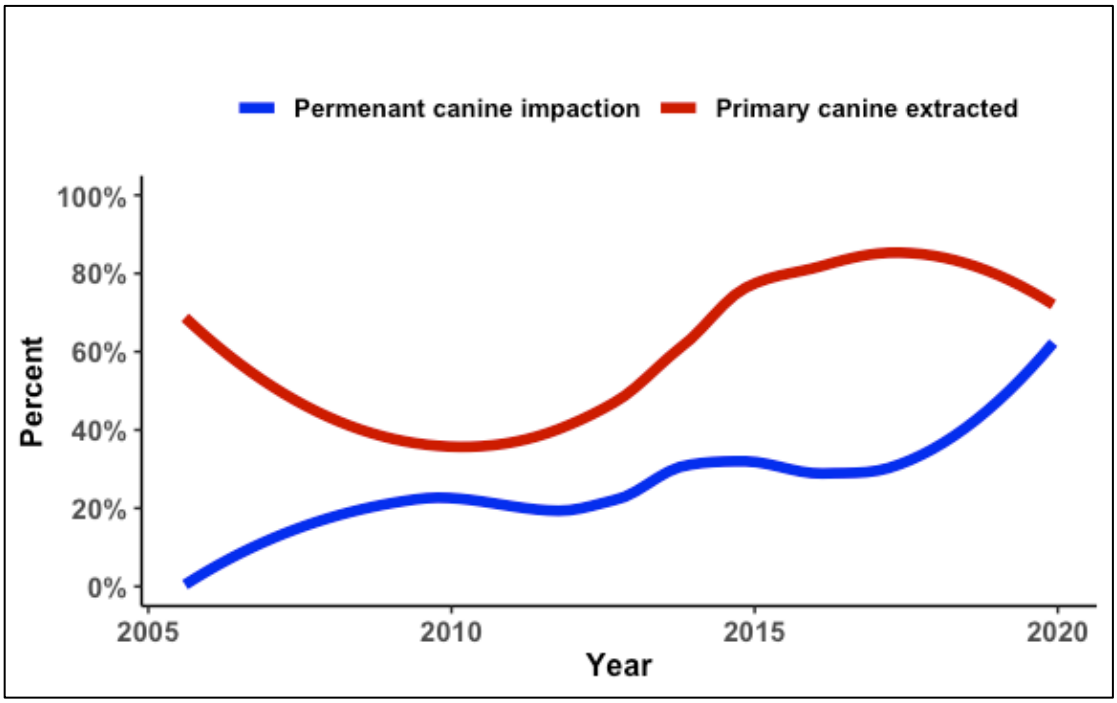

Figure 4. Loess smooth of percentage of permanent canine impaction and primary canine extractions by year

Out of 126 patients with displaced segments, 117 were expanded whereas 9 were not expanded due to behavioral challenges or prioritizing immediate scheduling of the ABG surgery. Of those who received expansion, 74 (28.8%) had a W-Arch; 4 (1.6%) had a quad helix; 1 (0.4%) received a fan expander; 26 (10.1%) had a Hyrax expander; and 12 (4.7%) had other types of expanders. No association with canine impaction was found for expansion, segment displacement, and partial bonding of fixed appliances (Figure 7).

Table 7. Segment displacement and expansion pre-graft by permanent canine impaction

Characteristic	N = 257	Canine Impacted	95% CI	p-value
Expansion				0.063
Yes	117 (45.5%)	38 (32.5%)	24%, 42%	
No	140 (54.5%)	31 (22.1%)	16%, 30%	
Segment Displacement				0.15
Yes	126 (49.0%)	39 (31.0%)	23%, 40%	
No	131 (51.0%)	30 (22.9%)	16%, 31%	
Fixed uprighting adjacent to cleft				0.55
Yes	22 (8.7%)	7 (31.8%)	15%, 55%	
No	231 (89.9%)	60 (26.0%)	21%, 32%	
Unknown	4	2		

[1]n (%)
[2]CI = Confidence Interval
[3]Pearson's Chi-squared test

59.1% of subjects had a congenitally missing lateral; 41.6% had microdontia of a lateral, 8.2% had an ectopic 1st molar; 27.6% had a congenitally missing premolar; 8.2% had infraoccluded premolars or primary molars. No significant association was detected with congenitally missing laterals, microdontia of laterals, ectopic 1st molars, congenitally missing premolars, or infraoccluded primary molars. For mandibular plane angle measurement, 9.3% of subjects had a low MPA, 59.5% had a normal MPA, and 29.2% had a high MPA. An association between canine impaction and low mandibular plane angle was found to be significant (p = 0.042) (Table 8).

Table 8. Other non-cleft population risk factors by canine impaction

Characteristic	N=257	Canines Impacted	95% CI	p-value
Gender				0.078
Male	146 (56.8%)	33 (22.6%)	16%, 30%	
Female	111 (43.2%)	36 (32.4%)	24%, 42%	
Congenitally missing lateral(s)				0.53
Yes	152 (59.1%)	43 (28.3%)	21%, 36%	
No	105 (40.9%)	26 (24.8%)	17%, 34%	
Microdontia of laterals				0.13
Yes	107 (41.6%)	34 (31.8%)	23%, 42%	
No	150 (58.4%)	35 (23.3%)	17%, 31%	
Ectopic 1st molars				0.48
Yes	21 (8.2%)	7 (33.3%)	15%, 57%	
No	236 (91.8%)	62 (26.3%)	21%, 32%	
Mandibular Plane Angle				0.042
Low	24 (9.3%)	11 (45.8%)	26%, 67%	
Normal	153 (59.5%)	34 (22.2%)	16%, 30%	
High	75 (29.2%)	22 (29.3%)	20%, 41%	
Unknown	5 (1.9%)	2		
Congenitally missing premolars				0.74
Yes	71 (27.6%)	18 (25.4%)	16%, 37%	
No	186 (72.4%)	51 (27.4%)	21%, 35%	
Infraoccluded Primary Molars				0.084
Yes	21 (8.2%)	9 (42.9%)	23%, 66%	
No	236 (91.8%)	60 (25.4%)	20%, 32%	

[1]n (%)
[2]CI = Confidence Interval
[3]Pearson's Chi-squared test

Of 257 subjects, 198 subjects had adequate records to measure permanent canine angulation relative to the sagittal plane. The mean canine angulation was 29° with a standard deviation of 13.2°. Canine angulations ranged from 1° to 85°. Greater permanent canine angulations were significantly associated with a higher incidence of canine impaction ($p < 0.001$) (Table 9).

Table 9. Permanent canine angulation by permanent canine impaction

		Canines Impacted		Non-Impacted Canines		
Characteristic	N	N = 55	95% CI	N = 143	95% CI	p-value
Permanent Canine Angulation (°)	198	33 (27, 42)	31, 39	27 (19, 35)	25, 29	<0.001

[1]Median (IQR)
[2]CI = Confidence Interval
[3]Welch Two Sample t-test

55.6% (N=27) of extractions at the time of grafting were within the cleft; 25.9% were proximal to the cleft; 11.1% had both extractions within and proximal to the cleft; and 7.4% had remote extractions. No association with canine impaction was detected for any of the surgical characteristics evaluated (Table 10).

Table 10. Surgical characteristics by permanent canine impaction

Characteristic	N=257	Canines Impacted	95% CI	p-value
Soft Tissue Fistula Present/Closed during surgery				0.16
Yes	231 (89.9%)	59 (25.5%)	20%, 32%	
No	26 (10.1%)	10 (38.5%)	21%, 59%	
Extractions at time of graft				0.42
Yes	27 (10.5%)	9 (33.3%)	17%, 54%	
No	230 (89.5%)	60 (26.1%)	21%, 32%	
Permanent lateral extracted				0.45
Yes	12 (44.4%)	5 (41.7%)	16%, 71%	
No	15 (55.6%)	4 (26.7%)	8.9%, 55%	
Unknown	230	60		
Canine visible within cleft at time of surgery				>0.99
Yes	4 (1.6%)	1 (25.0%)	1.3%, 78%	
No	253 (98.4%)	68 (26.9%)	22%, 33%	

[1]n (%)
[2]CI = Confidence Interval
[3]Pearson's Chi-squared test; Fisher's exact test

Of the 257 patients who received an alveolar bone graft, 29 (11.3%) required another graft. No significant difference in incidence of canine impaction was found between patients with a successful first graft and patients in need of multiple grafts (Table 5). There was no association between canine

root development and success of the first graft. The presence or absence of the primary canine ipsilateral to the cleft did not affect ABG success (Table 11).

Table 11. Permanent Canine development and primary canine presence by success of first graft

Characteristic	N=257	Successful 1st Graft	95% CI	p-value
Permanent Canine development at first graft				0.71
<1/3 Root Development		63 (87.5%)	77%, 94%	
1/3 - 2/3 Root Development		138 (89.6%)	83%, 94%	
2/3 - Full Root Development		27 (87.1%)	69%, 96%	
Primary Canine Presence at Time of ABG				0.67
Yes		85 (87.6%)	79%, 93%	
No		143 (89.4%)	83%, 94%	

[1]n (%)
[2]CI = Confidence Interval
[3]Fisher's exact test; Pearson's Chi-squared test

Univariate and multivariable logistic regression were used to adjust for potential confounders and assess for interactions (Table 12). The multivariable logistic regression adjusted for sex, age at first graft, multiple grafts, and canine development at the first graft, and early loss of the primary canine. After potential confounders were controlled for early loss of primary canine was associated with a higher risk of canine impaction (OR = 2.26; p=0.009). Also, females were more likely than males to have canine impaction (OR = 2.14; p=0.015) and less canine development was associated with an increased risk of canine impaction (p=0.024) (Table 12).

Table 12. Univariate and multivariable logistic regression model for canine impaction

	Univariate Log Regression		Multivariate Log Regression	
Characteristic, N =257	OR[1] [95% CI[1]]	p-value	OR[1] 95% CI[1]	p-value
Gender		0.079		0.015
Male	1.00		-	
Female	1.64 [0.94, 2.87]		2.14 [1.16, 4.01]	
Age at Graft 1, y	0.92 [0.72, 1.16]	0.48	1.07 [0.80, 1.43]	0.64
Canine development		0.068[2]		0.024[2]
2/3 - Full Root Development	1.00		-	
1/3 - 2/3 Root Development	1.36 [0.55, 3.90]		1.66 [0.64, 4.88]	
<1/3 Root Development	2.22 [0.84, 6.60]		3.36 [1.09, 11.5]	
Multiple grafts		0.59		0.55
No	1.00		-	
Yes	1.26 [0.52, 2.85]		1.31 [0.52, 3.13]	
Primary canine extracted		0.017		0.009
No	1.00		-	
Yes	2.05 [1.13, 3.86]		2.26 [1.22, 4.36]	

[1]OR = Odds Ratio,
CI = Confidence Interval
[2]Trend test for odds ratio

Due to a smaller sample size available for measuring canine angulation, separate univariate and multivariate regressions were conducted to include canine angulation in Table 13. In these models, females were more likely than males to have canine impaction (OR = 2.36; p = 0.021), and higher canine angulation was associated with canine impaction ($p < 0.001$). The association with primary canine extraction and early canine development is weaker compared to the model in Table 12, suggesting that canine angulation is a more powerful predictor of canine impaction.

Table 13. Univariate and Multivariable logistic regression including canine angulation

	Univariate Log Regression		Multivariate Log Regression	
Characteristic, N=198	OR[1] [95% CI[1]]	p-value	OR[1] [95% CI[1]]	p-value
Gender		0.077		0.021
Male	1.00		-	
Female	1.76 [0.94, 3.31]		2.36 [1.14, 5.00]	
Age at Graft 1, y	0.89 [0.68, 1.17]	0.41	1.05 [0.74, 1.46]	0.79
Canine development		0.23[2]		0.072[2]
2/3 - Full Root Development	1.00		-	
1/3 - 2/3 Root Development	1.15 [0.44, 3.39]		1.72 [0.59, 5.69]	
<1/3 Root Development	1.99 [0.72, 6.11]		3.92 [1.09, 15.6]	
Multiple grafts		0.27		0.6
No	1.00		-	
Yes	1.67 [0.66, 4.02]		1.30 [0.47, 3.36]	
Canine angle, degree	1.05 [.02, 1.08]	<0.001	1.05 [1.02, 1.09]	<0.001
Primary canine extracted		0.12		0.13
No	1.00		-	
Yes	1.72 [0.88, 3.55]		1.78 [0.85, 3.87]	

[1]OR = Odds Ratio,
CI = Confidence Interval
[2]Trend test for odds ratio

Discussion

This single center sample size of 257 patients with unilateral cleft lip and palate is comparable to studies done at other craniofacial centers. Out of 257 UCLP patients: 56.8% of patients were male; 83.6% of patients had complete clefts; 62.6% of clefts were on the left; and the mean age at time of ABG was 9.2 years. These sample characteristics were similar to those of other studies that were also predominantly male and between 8.9-10.5 years old (Enemark et al., 1987; Goudy et al., 2009; Hereman et al., 2018; Hinrichs et al., 1984; Jamilian et al., 2015; Matsui et al., 2005; Westerlund et al., 2014).

Patients with unilateral cleft lip and palate face a host of dental anomalies. Fifty-nine percent of patients in this study had congenitally missing laterals, comparable to reports by others with missing laterals in 48.8% - 88% of patients (Oberoi et al., 2010; Tortora et al., 2008; Westerlund et al., 2014). Our

sample had a higher incidence (41.6%) of malformed or undersized lateral incisors compared to the 24.8%-31.7% reported by others (Enemark et al., 2001; Tortora et al., 2008). Agenesis of mandibular second premolars (27.6%) was notably higher than the 7.3% incidence rate previously reported (Tortora et al., 2008).

Our findings add to the evidence that patients with unilateral cleft lip and palate have a substantially greater risk of canine impaction; this sample had a 26.8% incidence of canine impaction, which is over 10 times the incidence in noncleft populations. This finding was consistent with other studies of similar sample sizes that detected a canine impaction rate of 18.9% - 20.6%, with one study reporting as high as a 20-fold increased risk for canine impaction (Matsui et al., 2005; Russell & McLeod, 2008; Tortora et al., 2008; Westerlund et al., 2014). We found the incidence of impacted canines was higher in patients with clefts extending to the secondary palate compared to clefts limited to the primary palate, consistent with reports from another center (Jamilian et al., 2015).

In a survey of craniofacial teams, 35.5% respondents reported that they conducted pre-graft expansion to align the cleft segments (Preston et al., 2022). All patients with incomplete segments had well-aligned segments, yet surprisingly, pre-graft expansion to align alveolar segments did not affect the likelihood of canine impaction. This finding can help practitioners weigh the costs and benefits of pre-graft expansion in complex patients depending on the urgency of utilizing unfused sutures to correct posterior crossbites.

At the study hospital, the surgeons requested a shift towards extraction of primary canines as part of pre-graft preparation in 2012. Drivers of this decision were improved surgical access during grafting, minimizing oral hygiene challenges post-operatively, and reducing wound healing complications (Almasri, 2012). Extraction of the primary canine also allows the surgeon to design surgical flaps to optimize the amount of attached gingiva for the erupting permanent canine (personal communication S. Susarla, 2023). Prior to 2012, primary canines had been maintained unless

encroaching into the surgery site or had caries. Interestingly, our study found that presence or absence of the primary canine did not impact integration of the alveolar bone graft. This practice may not always be necessary but can be considered on an individual basis if the graft site is compromised or surgical access is nonideal.

In the noncleft population, extraction of the primary canine to encourage self-correction of mesioangulated maxillary permanent canines is a well-established practice (Ericson & Kurol, 1987). If the unerupted permanent canine crown overlaps less than 50% of the permanent lateral incisor root, extraction of the primary canine improves the odds for permanent canine eruption into the occlusal plane. Extraction of maxillary primary canines prior to alveolar bone grafting was significantly associated with higher incidence of impacted permanent canines in this study. At this craniofacial center, pre-surgical extraction of the primary canine was conducted 6 to 8 weeks before alveolar bone grafting. Removal of the primary canine increases exposure to inflammation and induces alveolar remodeling that may influence permanent canine eruption. Whereas noncleft patients do not undergo a follow-up surgery after extraction of the primary canine, cleft patients receive two surgical procedures that induce trauma to the site where the permanent canine attempts to erupt.

Among craniofacial teams, there is a current trend towards earlier alveolar bone grafting. A study of patients with UCLP found that early alveolar bone grafting did not significantly impact the risk of canine retention at age 10 years (Kleinpoort et al., 2017). In contrast, this study found that impacted permanent canines were more commonly associated with permanent canine development rather than chronological age at the time of ABG. After adjusting for confounders, grafting when permanent canines had less than one-third root development meant a higher risk of impaction in this sample. Additional studies with long-term follow-up are needed to assess this relationship.

Previous studies of noncleft populations have suggested a genetic association between impacted canines, missing or undersized laterals, infraoccluded primary molars, and ectopic first molars

(Baccetti, 1998). Despite having a 59.1% incidence of lateral incisor agenesis, 41.6% incidence of lateral microdontia, 8.2% frequency of infraoccluded primary molars, and 8.2% incidence of ectopic 1st molars our study did not find significant associations between these anomalies and impacted canines. Our findings were comparable to other studies of UCLP population reporting a 48.8-52.9% incidence rate of lateral incisor agenesis (Matsui et al., 2005; Tortora et al., 2008; Yezioro-Rubinsky et al., 2020).

Like the noncleft population, female sex and a low mandibular plane angle were associated with a higher incidence of permanent canine impaction. Other studies of the noncleft populations have reported that females were 2.5 to 3 times more likely to have at least one impacted canine compared to males (Bishara, 1992; Mercuri et al., 2013; Sacerdoti & Baccetti, 2004). There are limited reports of an association between hypodivergent craniofacial growth and canine impaction in noncleft populations (al Balbeesi et al., 2020; Sacerdoti & Baccetti, 2004). On the other hand, one other study did not detect an association between hypodivergence and canine impaction (Uribe et al., 2017). More studies evaluating the relationship between hypodivergence and canine impaction are needed.

This cohort exhibited a higher incidence of canine impaction for permanent canines with greater angulations within one year of alveolar bone grafting. Although statistically significant, the difference in average canine angulations of impacted canines and non-impacted canines was approximately 6° which may not be clinically significant. Other studies of cleft populations detected similar associations between canine impaction and higher canine angulation values ranging from 14.7° to 30° (Hong et al., 2022; Kadi et al., 2021; Shin et al., 2022; Westerlund et al., 2014). This finding suggests that monitoring for canine angulation on periodic panoramic radiographs leading up to alveolar bone grafting can guide clinicians to assess the risk of canine impaction and inform patients of the possibility of an additional surgical procedure to expose and bond.

Similar to reports from other centers, 11.3% required additional ABG (Goudy et al., 2009; Westerlund et al., 2014). Surprisingly, patients with 2 or more grafts did not have increased risk for

permanent canine impaction. Although this result contrasts the findings of another study that detected an association between impacted canines and reoperation of the transplant, our study likely did not have sufficient subjects undergoing revision surgeries to detect a significant difference (Westerlund et al., 2014). Further studies are necessary to clarify the influence of multiple grafts on canine impaction.

Limitations

Although our sample included patients with complete records between 2005 – 2019, fewer patients between 2005-2010 had complete records to be included. This could lead to an impression that there was a significant increase in canine impactions following 2010 when there were fewer records available prior to 2010. Furthermore, a decline in canine impactions after 2018 could also be due to fewer included records since not all patients had fully erupted contralateral canines by the time of this study. Not all subjects had sufficient records to measure canine angulation within one year of alveolar bone grafting.

Because clinical and operation report notes were the source of data on surgical factors and pre-graft orthodontics, one limitation of this study is the variation of notes between practitioners. Only a few instances of canine visibility at the time of graft were recorded in the operation note. It is possible that there were more incidences of extractions or use of the surgical handpiece at the time of graft that were not reported. This data presents preliminary evidence for lack of association between surgical factors and incidence of canine impaction. This study, however, did not evaluate differences in surgical technique or graft material which may vary between surgeons and influence outcomes.

Another limitation of this study was the subjective assessment of root development from panoramic radiographs. Buccopalatal angulation of the permanent canine and patient positioning may have influenced the accuracy of determining root length by foreshortening the appearance of the root.

The radiograph used for evaluation was usually taken within 3 months of ABG but for radiographs taken between 3 to 6 months before ABG, root lengths at the time of ABG were extrapolated. Two-dimensional imaging may not be the most accurate measure of teeth that are located outside the focal trough. This study also did not consider the 3D morphology of the cleft site which may independently influence the outcome of canine impaction. Standardizing protocols for radiographs prior to alveolar bone grafting and use of 3D CBCT imaging would increase accuracy in root length and angle assessments.

Conclusion

Monitoring eruption of permanent canines is critical in patients with UCLP due to the higher incidence of canine impaction in cleft populations compared to noncleft populations. With canine impaction occurring in 1 in 4 cleft patients, surgeons must prepare and counsel patients on the possible need for an additional procedure to bring in an impacted canine. Our results also detected a significant association between the following factors and risk of canine impaction in patients with unilateral cleft lip palate:

- Complete clefts that extend into the secondary palate
- Pre-graft extraction of the primary canine
- Alveolar bone grafting when the canine root is less than 1/3 developed
- Female gender
- Hypodivergent facial growth pattern
- Greater permanent canine angulation

Of these factors, there are some that cannot be controlled; therefore, counseling patients early in the treatment process will set patient expectations. Possible modifications to practice include case-

by-case discrete assessment of indication(s) for extracting the proximal primary canine prior to alveolar bone grafting. For example, evidence suggests that a female patient with a hypodivergent facial pattern and microdontic lateral incisors could be at higher risk for canine impaction when compared to a male patient with a hyperdivergent facial pattern and no missing teeth. Extraction of a primary tooth minimally requires local anesthesia administration and an additional dental visit; sedation or general anesthesia may be necessary for other patients. Furthermore, primary canine extraction may place the patient at higher risk of an impacted canine and therefore a need for surgical exposure, another intensive procedure. If surgical access is deemed to be sufficient with the primary canine in place, minimizing pre-surgical extraction of the primary canine would eliminate an unhappy experience from young patient and may reduce the risk of developing impaction of the maxillary permanent canine on the cleft side.

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Appendix A – Power Analysis

Table X1. Precision of incidence estimates based on a ½ width of a 95% confidence interval with 200 and 250 patients for incidence of canine impaction of 5% to 25%.

Incidence of canine impaction	Precision with 200 patients	Precision with 250 patients
5%	±3.1%	±2.8%
10%	±4.2%	±3.8%
15%	±5.0%	±4.5%
20%	±5.7%	±5.1%
25%	±6.1%	±5.5%

Based on a logistic regression using a two-sided 0.05 significance level and a sample size of 200 to 250 patients the power is 80% to detect an odds ratio of 2.4 to 2.9 (or equivalently, an incidence rate ratio of 1.9 to 2.2) for risk factors with a prevalence of 20% to 50% and an incidence of canine impaction of 20% to 25% (REFA, B) (Table X2). It is expected that 40-50% of patients will have not aligned segments, about 20% will have more than 1 surgery, 40-50% will have orthodontic expansion appliance use and about 30% will have surgical complications.

Table X2. Detectable odds ratio with 80% power at 0.05 significance level for risk factors with a prevalence of 20% to 50% and canine impaction incidence of 20% to 25%.

Prevalence of risk factor	Detectable odds ratio with 200 patients	Detectable odds ratio with 250 patients
20%	2.9	2.6
30%	2.7	2.5
40%	2.6	2.4
50%	2.5	2.4

REFA: Demidenko, E. (2007). Sample size determination for logistic regression revisited. Statistics in medicine, 26(18), 3385-3397.
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