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GRADUATION PROJECT

Degree in Dentistry

Orthodontic approach to the treatment of lateral incisor agenesis

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Identification number: 146

RESUMEN

Introducción: La agenesia de incisivo lateral es una condición bastante común en la práctica clínica. El tratamiento requiere un abordaje multidisciplinar para tratar aspectos funcionales, periodontales y estéticos en el que el tratamiento ortodóntico desempeñaba un papel clave e importante para el resultado final. Los dos principales enfoques ortodóncicos implicados son el cierre de espacio con camuflaje canino y la apertura de espacio para futura rehabilitación protésicas: implantes o Puente Maryland. La elección ideal dependerá de: oclusión y función, estética general, salud periodontal, forma/tamaño/color de los dientes, así como la edad y expectativas del paciente.

Objetivos: Comparación tratamientos ortodóntica en agenesia del incisivo lateral superior: apertura vs cierre de espacios.

Material y métodos: Esta revisión sistemática se ha centrado en artículos de los últimos 10-11 años, utilizando Medline, PubMed, Cochrane, Google Scholars y Dentistry and Oral Science Sources.

Resultados: Aplicando los criterios establecidos de inclusión y exclusión, se estudiaron 8 artículos: dos opciones tienen en cuenta todos estos factores. Cierre del espacio ortodóntico, caninos maxilares camuflados: enameloplastia, coloreado dental o medidas restauradoras eran a menudo necesarias para mejorar un resultado estético global óptimo al sustituir los dientes. Por lo demás, la apertura de espacio buscaba crear un espacio adecuado para la sustitución protésica, como implantes dentales o Puente Maryland.

Conclusiones: En conclusión, ambos tipos de abordajes ortodóncicos son igualmente importantes y cada uno debe considerarse según cada caso y criterios del paciente, como el tipo de maloclusión, el diseño de la sonrisa, la salud periodontal y la edad del paciente.

PALABRAS CLAVE

Odontología, Agenesia incisivo lateral, Tratamientos ortodóncica de agenesia, Tratamientos de agenesia del incisivo lateral, Características ortodóncica de la agenesia.

ABSTRACT

Introduction: Maxillary lateral incisor agenesis was a common and significant dental condition in dentistry practices. Treatment might require multi-interdisciplinary approach to treat functional, periodontal and esthetic obstacles in which orthodontics treatment played a key and important role for the final outcome. The two mains orthodontic approach involved are space closure with canine camouflage and space opening for future prosthetic replacement: implants or Maryland Bridge. The selection for the ideal treatment will depend on numerous factors: occlusion and functional, general aesthetic, periodontal health, teeth shape/size/color, and patient's age and expectations.

Objective: Compare differences treatments options in maxillary lateral incisor agenesis patient's: open space-prosthodontic rehabilitation or closing space-canine camouflage.

Material and Methods: This systematic review had been concentrating on articles in the past 10-11years. We used mainly: Medline, PubMed, Cochrane, Google scholars and Dentistry and Oral Science Sources for our study.

Results: Applying the established inclusion and exclusion criteria, 8 articles were studied: two options were taking into account considering all these factors. Orthodontic space closure, with maxillary canines camouflaged into maxillary lateral incisor: enameloplasty, tooth coloring, or restorative measures were often necessary to improve and ensured an optimal overall esthetic outcome as replaced teeth. Otherwise, space opening aimed to produce an adequate space for prosthetic replacement, such as dental implants or Maryland Bridge.

Conclusions: In conclusion, both types of orthodontic approaches are equally important and each has to be considered depends on each case and patient criteria's, such as type of malocclusion, smile design, periodontal health and patient age.

KEYWORDS

Dentistry, Lateral incisor agenesis, Orthodontic agenesis treatments, Lateral incisor agenesis treatments, Orthodontic agenesis characteristics.

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1. INTRODUCTION

1.1. Definition:

Tooth agenesis, is known as missing teeth in the oral cavity. It represents one of the most frequent dental issues. It is defined as a “failure teeth development” at birth, recognized to be missing when it’s not erupted and not noticeable in the oral cavity and in the radiography (1).

1.2. Diagnosis and prevalence:

Diagnosing an agenesis start by understanding the sequence of eruption. Universally and in general,it follow this sequence: “M1-CI-LI-PM1-PM2-C-M2 for the maxilla and M1-CI-LI-C-PM1-PM2-M2 for the mandible” (2). This sequence is the one for permanents teeth’s eruption, and it is considered an active factor for children, beginning at age of 6 years old till 12/13 years old.

Starting by an anamnesis, asking questions and checking the medical and dental history of the patient, history of trauma, going to an intraoral examination where a missing tooth is noticed based on the chronology and the sequence of permanent teeth eruption, complementary examinations should be achieved. Confirmation of missing tooth usually happens through radiographic imaging such as panoramic x-ray or CBCT known as Cone-beam computed tomography. Based on clinical and radiographical exams, we can diagnose an agenesis. Open spaces, crowding, dental malposition, rotations, ankylosis teeth, gingiva bumps from teeth eruption, teeth asymmetries or even midline deviation and malocclusions can be associated with agenesis (1).

Furthermore, agenesis in general, can be defined as a missing tooth that is not extracted or accidentally lost, but initially not presented.

Rated from the most common agenesis to the least ones, permanent teeth agenesia is more common than primary’s ones. Through a meta-analysis of the prevalence of dental agenesis of permanent teeth, we can notice:

first, the most common ones, 2nd permanent mandibular premolars (35-45) > maxillary lateral incisor (12-22) and 2nd permanent maxillary premolar (15-25).

Second, the less common are: Central mandibular incisor (31-41) > lateral mandibular incisor (32-42) > 1st maxillary premolar (14-24) > maxillary canine (13-23) and mandibular 2nd molar (37-

47).

Last group, the rarest ones: maxillary 2nd molar (17-27) > maxillary 1st molar (16-26) > mandibular canine (33-43)> mandibular 1st molar (36-46) and maxillary central incisor (11-21) (3).

To resume as percentage, the third molar, followed by mandibular second premolars considered 47.5%, maxillary lateral incisors 30.5% (4). The upper second premolar is around 23.5% of agenesia. Congenital absence of the lateral incisor, in general, results in 2% of the population (1,4,5,6).

1.3. Etiology:

In our research we will focus on the agenesis of upper lateral incisors.

Etiological absence of lateral incisor is mainly related to environmental factors and/or inherited factors. It can be caused by disturbance in the early developmental stages of the ectoderm formation or by genetic mutation during establishment such as MSX1 and PAX9 (1). It can be associated with the presence of tooth ectopias, mesiodens or some dental shape malformation such as conoid tooth or peg shaped tooth on the contralateral side of the arch (7).

Others locals' factors can be involved in process of missing lateral incisor such as infections, trauma,or medications intake during pregnancy. Some syndromes factors are involved too such as down syndrome, ectodermal dysplasia affectation, and cleft lip and/or cleft palate (1,8).

1.4. Agenesis of the Lateral Incisor:

The percentage of having one or two missing lateral incisors can vary. We can find: both missing lateral incisors, or unilateral agenesis that could be the right or left-sided, or even unilateral missing lateral incisor with his contralateral: in a conoid, peg shaped or diminish size (7). In the maxilla, in the anterior sector, the last incisor to erupt is the maxillary lateral one which appears around the age of "8 years and 3 months". Upper missing lateral incisor (LI) which occur 30.5 % of all agenesis prevalence, is typically diagnosed in the interphase dentition, after the first mixed permanent phase finished, between the age of 8.4 - 11.5 years, in teenagers mainly, in other words after that the eruption of the four 1st permanent molars and the 8th permanents anterior incisors (1,2).

We can see also through some studies that the maxillary incisor is more susceptible to be missing than the mandibular one. As well we have seen that bilateral agenesis of the lateral maxillary incisor is a bit more common than unilateral **(Figure.1)** (8). These results can be controversial depending on the researches.(9)

In unilateral perception, the absent of a right-sided lateral maxillary incisor is higher (0.65%) than the left-sided lateral maxillary incisor (0.39%) (4)



Figure.1: Lateral Incisor agenesis bilateral, patient 11-years-old female with esthetic complaint (10)

From another observation, many studies show that gender features, male and female, doesn't have very significant importance (4), but some others research will show that it is more common in women (8).

1.5. Consequences:

The absence of the lateral incisor, in the oral cavity, can generate many insecurities. As a first impact, it affects mostly patient in a psychological and confidence level. The "aesthetic and psychological factors" especially, when smiling and laughing, are crucial. Moreover, hypodontia of the lateral maxillary incisor is diagnosed through a rough time: "teenager timing". That's why, during this period, patient's looks mean a lot. In other words, school environment behaviors as well as selfcare can have an impact on patient's life and his psychological stability (4).
With lateral agenesis, spaces between teeth called "diastema" can be noticed. Others can recognize some presence or absence of crowding or an unattractive smile. So not just it will create not only a major concern on patient's appearance but also occlusally/functionally problematic (1) that's why, in this situation, orthodontic treatments are the most needed and asked for.

1.6. Orthodontics Characteristics:

As we will perceive, in these cases, many orthodontics factors need to be taken into consideration before, during and after patient treatments. During this investigation, we will mainly focus, through all the treatment processes, on: patient's age, occlusion (molars and canines occlusion), smile design, teeth shape, teeth size, teeth shade, periodontal health, spaces and aesthetic outcomes (4,10,11).

These characteristics won't just help us to make the decision by studying the pre-factor's treatment but also by considering the post-treatment factor's prospections.

1.6.1.Age and Growth factors:

As patient is going into a growing phase, changes occur not just physically but also on the bone and the dental levels. Bone will still grow till the age of 18 years old to 21 years old.

Maxillary and mandibular growth will induce a lot of changes on patient's profile and teeth occlusion. Dental positions, angulations and torque are subject to continuous change too during periods of growth. At 8 years old, in LI agenesis cases, alveolar bone development is not finished yet and teeth positions neither. So, dental and bone age are a very important factors to treatment decision. That's why, early diagnosis of LI agenesis can be considered as a key

success factor for the treatment plan and the treatment outcomes of these cases. To restore agenesis teeth in an ideal situation, implant placement could be wait the end of growth, around 18y old (1,10)

1.6.2.Lateral incisor features:

Lateral incisors are significant teeth in the aesthetic anterior area. Talking mainly is this study about the maxillary lateral incisor, we need to know that even, it is very different from the mandibular lateral incisor. It is located distal to the central incisor on both sides. Clinically, its size is smaller than the central incisor and the canine mesiodistally, with more rounded angles, and a smaller convex vestibular profile.

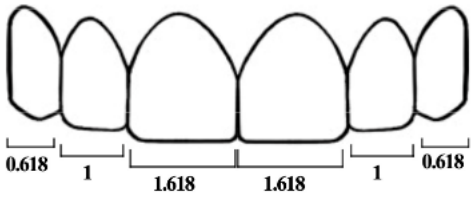


Figure.2: Levin's Golden Proportions. (12)

Following the Levin Golden proportions **(Figure.2)**, appearance size, from a frontal viewpoint, maxillary lateral incisor width would be 1, compared tothe central incisor 1.618 and canine 0.618 (12).

Also, not only shade and size differ but even the gingival zenith of Lateral incisor. The gingival zenith, is the most apical part of the gingival margin, it's different between central incisor and lateral incisor and also between canine and lateral incisor **(Figure.3)**. Lateral incisor gingiva zenith has a lower gingiva zenith than the central and canine (13).



Figure.3: The gingival zenith level for lateral incisors is approximately 1mm coronally than the gingival zenith position of the central incisor and canine (13).

1.6.3. Model and Occlusion:

Patients' profiles and malocclusions differed at lot between each other's. Model I, II or III can be or not related with specific molars malocclusion: Class I, II or III. The types of model profile growth and malocclusions are ones of the main factors to decide the type of treatment that it will be chosen.

To summarize and define, Model I is mesiofacial-normal vertical dimensions growth; Model II is an excess vertical growth called hyperdivergent pattern and Model III as horizontal growth or hypodivergent pattern.

For Angle molar classification: Class I is the normal one, Class II has a distal occlusion of the lower first molar to the upper first molar and the Class III has an excess of mesial position of the lower first molar to the upper first molar (14).

1.6.4. Smile design:

The smile design approaches gather: the smile line, the gingiva zenith, the golden ratio proportions of the teeth and the overcome smile effect of the patient. Taking all of these into account: we need to create the most natural attractive smile (10).

As explained before, the golden ratio, is the proportion dimensions of each tooth. Studying the "smile line" some patient can have a high smile line known as "gummy smile". Others could have normal or low smile line. It measures the amount of showed gum. These factors studied in the "smile design", can be very specific and important. They need to be accomplished for the most attractive, natural and symmetrical smile creation (1,5,8,15).

1.6.5. Periodontal health:

Before any treatments, periodontal state of the patient is mandatory to take into consideration. Any treatments without a stable periodontal wellbeing will not succeed and maintained in the future. We are talking here about probing depth, bone loss, bleeding, mobility, sensibility and recession. During treatments phases, plaque accumulation, gingival recession and gingivitis are mainly studied and controlled. We will need to manage all these factors and try to avoid any of them. A stable probing depth of 3mm, no bleeding and no bone loss will be needed to achieve a healthy successful and stable orthodontic treatment result, and to bypass any type of recessions in the post-treatment phase too.

These characteristics, will have a big impact on the treatment option choice.

Most significantly, before any orthodontic, surgical and prosthodontic procedure, having a good oral hygiene is fundamental to avoid any periodontal disease and failure of the esthetic functional and occlusal results (8).

1.6.6. Aesthetic – cost goals:

Aesthetically, we are taking into consideration all the different aspect: from intraoral outcome and from extraoral outcome. Profile proportions, equal vertical dimensions, overlook aspect, symmetrical, no deviation, no protrusion, no retrusion, color, shape, shade, and size etc.… All those criteria are considered during these treatments planning investigation. Aesthetic outcome is one of the main problems for the agenesia of the lateral incisor.

Cost goal, as we might not think, it is important too,and has a big reliance on patient's decision-making treatment (8).

Ideal option of treatment plan can be compromised due to financial issues decided by the patient.

All these orthodontics factors are very important to be taken into consideration. Then multiple options of treatments plan will be proposed and discussed with the patient.
Optimum treatment plan for each case will be decided.

1.7. Options:

In treatment's perception, we mainly have 2 options for managing the hypodontia of the lateral maxillary incisor.

We will need to "manage" the space of the missing lateral incisor in the arch.

We will need to close this gap with orthodontic forces or to open this gap for replacing the missing tooth.

Therefore, orthodontics approaches are known as: Space closure procedure or Space opening procedure.

We can handle these approaches through

1) Orthodontic space closure with canine camouflage as lateral incisor and premolars refunction/shape procedure **(Figure.4)**.

Figure.4: Pre and Post treatment records in OSC Bilateral Class II dental malocclusion(16).



2) Orthodontic space opening with a partial resin-bonded dental prosthetic placement (known and only will be talking in this study as Maryland Bridge) **(Figure.5)** or

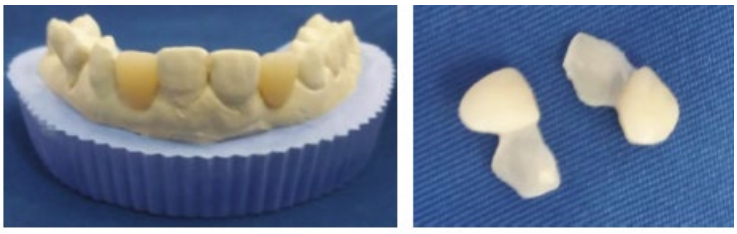


FIGURE 8: Milled cantilever CAD/CAM PMMA bridges.



FIGURE 9: Intra-oral view post-treatment.

Figure.5: Case orthodontic space opening with cantilever CAD/CAM PMMA bridges (17).

3) Using orthodontic space opening procedure for a future fixed dental prosthetic implants placement (1,5,6,11,18) **(Figure.6)**.

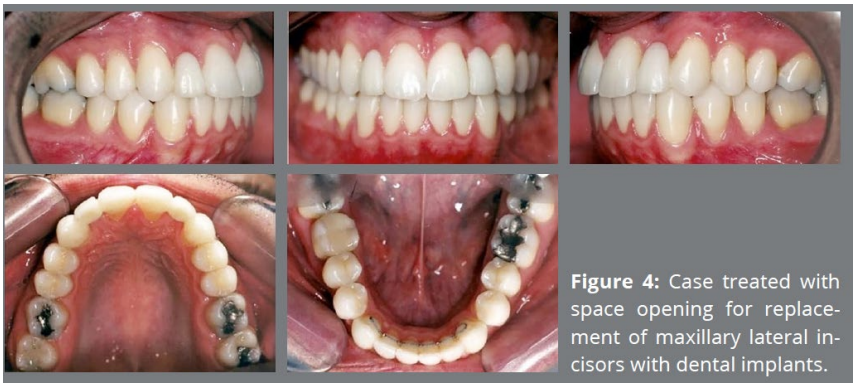


Figure 4: Case treated with space opening for replacement of maxillary lateral incisors with dental implants.

Figure.6: Case Class II with enough space for space opening and implant replacement of bilateral axillary lateral incisors agenesis. (10)

2. OBJECTIVE

2.1 PICO question:

In patient with Maxillary Lateral Incisor Agenesis (P), which orthodontics treatments (I): closing space compared to open space (C) is indicated for a better aesthetic and functional outcome (O)?

2.2 Objective:

To compare the differences treatments options in patients with maxillary lateral incisor agenesis: open space and prosthodontic rehabilitation or closing space and canine camouflage.

3. MATERIALS AND METHODS

This study was mainly based on a systematized review works, which involves reading, studies, and organizing articles and books built on specific characteristics and information about: orthodontic approaches in maxillary lateral incisor agenesis.

Articles that were used for this research, are: Cohorts Study, Retrospective study, Case Reports Study, Chapters Book, Peer-reviewed journal articles, and Clinical practice guidelines. To be able to collected them, we have used these databases such as: PubMed, Medline, Cochrane, Google scholars and Dentistry and Oral Science Sources.

We assessed that 62% of our articles (18/29) have been carefully published in the last 5 years, 31% (9/29) were published in the last 10 years and only 2 articles were published previous to 2010.

Keywords used to pursue these articles were “lateral incisor agenesis”, “permanent agenesia”, “orthodontics criteria’s”, “aesthetic outcomes for agenesia”, “orthodontic treatments for agenesis”, “orthodontics characteristics lateral incisor absence”, “open or close space for lateral incisor agenesis”. Documents in English and French were considered.

Inclusion Criteria Articles:

1- Orthodontic treatments in maxillary lateral incisor agenesis
2- Orthodontic treatments in bilateral and unilateral lateral incisor agenesis
3- Class I, II and Class III patients' cases report with lateral incisor agenesis
4- Orthodontic protocols for closing space and open space in maxillary lateral incisor agenesis
5- Criteria's for: Canine camouflage, Implants cases replacements Vs Fixed dental prosthetic replacements
6- Studies regardless of gender or race

Exclusion Criteria Articles:

1- Mandibular lateral incisor agenesis
2- Agenesis of temporal maxillary lateral incisors
3- Lateral incisor agenesis in systemic diseases: cleft palate, ectodermal dysplasia etc.…
4- Missing lateral incisor because of a trauma or caries
5- Multi-agenesia cases treatments with impacted teeth
6- Detailed protocols for the rehabilitation's placements (implants/prosthetic)
7- Articles before 2000

4. RESULTS

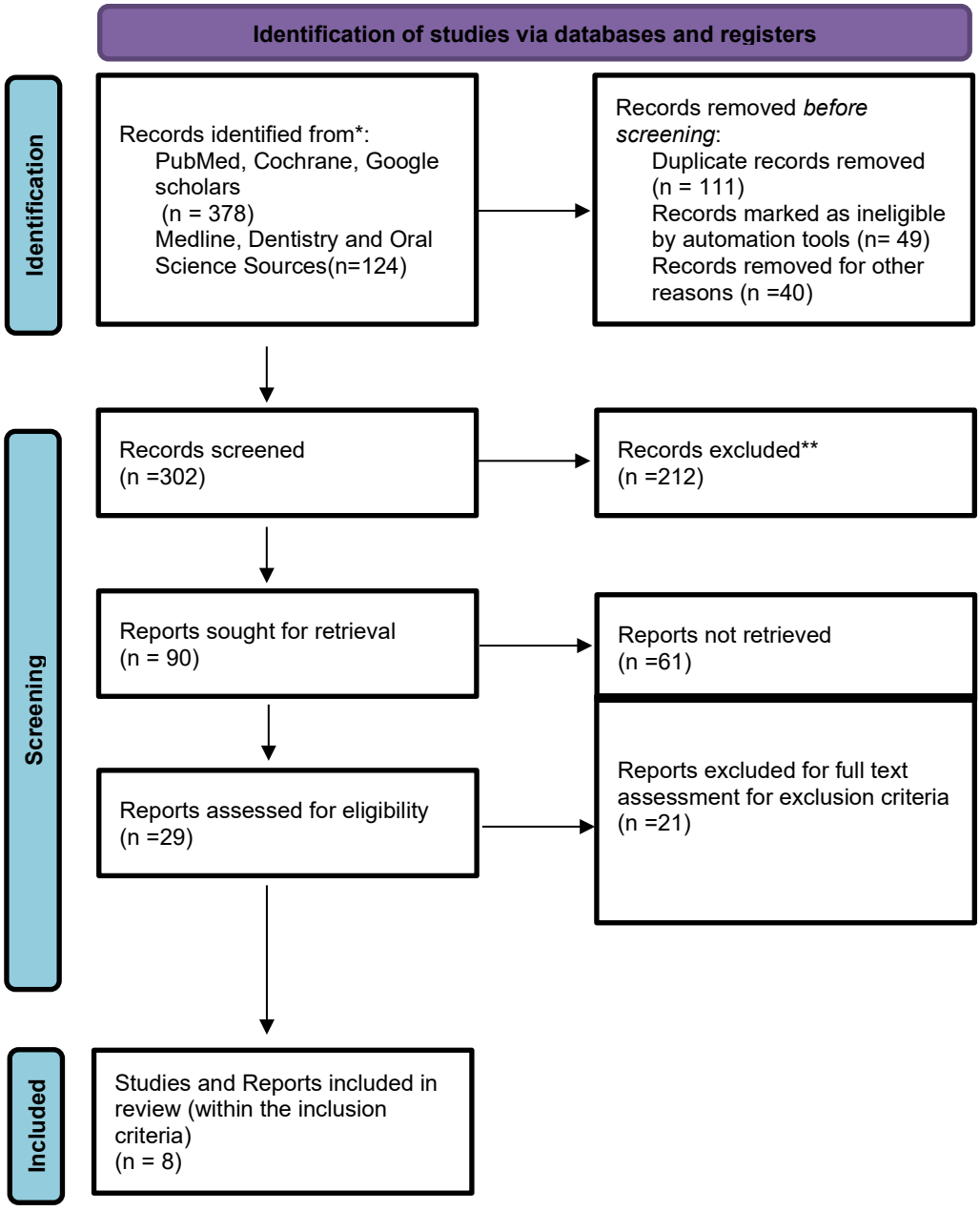


Table 1: PRISMA FLOW DIAGRAM

Table 2 shows the results for comparing orthodontic treatments of space closure with canine camouflage versus space opening and replacement of maxillary lateral incisor agenesis by implant therapy or Maryland Bridge- resin-bonded fixed dental prosthetic (RBFDP) visualizing the outcomes criteria. In the table 3 we tried to summarize the clinical parameters picked in the studied articles, comparing them in the three options of orthodontic treatments proposed for missing maxillary lateral incisor cases.

Table 2- for Comparing Orthodontic treatments SC Canine camouflage vs SO Implant outcome criteria's:

Article	Author, Year	Age	Orthodontic treatment procedure	Occlusion – Profile	Smile – Aesthetic	Periodontal health
Missing upper incisors: a retrospective study of orthodontic space closure versus implant (19) **(retrospective study)**	Abdolreza Jamilia, Letizia Perillo, Marco Rosa 2015	19 ± 2.1 years	**Orthodontic Space closure**	-Treatment done immediately -No infraocclusion -No signs and symptoms of TMJ dysfunction	-Satisfied with appearance after 5 years -Better long term aesthetic result -Risk for space reopening -Open embrasure, black triangle**	- No tooth mobility - Few Probing depth -Lack of bone loss and periodontal problem
		20 ± 1.4 years	**Orthodontic Space Opening with implant replacement**	-Wait many years before the implant insertion -Need of temporary restoration - Infraocclusion exceeding 1 mm in all implants -No signs and symptoms of TMJ dysfunction	-Satisfied with the appearance after 5 years -Very few black triangle -Disharmonious levels of the gingival margins -Disadvantage in high smile line	- Risk Tooth mobility more than 1 mm - Probing depth exceeding 3 mm -Plaque indexes increased -Blue coloring of the labial gingival reported more than 50% - Gingivitis and peri-Implantitis. -Discrepancy between the gingival margins
Treatment of missing maxillary lateral incisors: a clinical and aesthetic evaluation(20) **(retrospective cross-sectional study)**	**Eva Josefsson** **Rune Lindsten** **2019**	aged <26 years	**Orthodontic Space closure**	**Indications:** -Class I Molar occlusion -Overjet, Overbite no significant **Assessment:** -Treatment will finish at the young teenager -Risk of reopening	**Assessment:** - Not acceptable Canine crown color (21%), more yellowish -Long crown length.	**Assessment:** -Bleeding on Probing (35%) -Papilla defects (59%)
		aged <26 years	**Orthodontic Space Opening**	**Indications:** -Class I Molar occlusion -Overjet normal, Overbite no significant **Assessment:** -Upper maxillary incisor proclination -Strained lip closure -Non-acceptable appearance when smiling -Require a period of temporary prosthesis	**Assessment:** -Discolored gingiva adjacent to the implant-supported crown (61%) -Optimal crown color in all implant's cases. -Short crown length	**Assessment:** -Some gingiva recession of 0.5-2.0mm. -Bleeding on Probing (25%). -1 or 2 papilla defects (71%)

Article	Author, Year	Age	Orthodontic treatment procedure	Occlusion – Profile	Smile – Aesthetic	Periodontal health
Evaluation of the aesthetics and clinical findings in patients with missing maxillary lateral incisors treated with a 10-year interval (21) **(Cross-sectional retrospective study by Cohorts Studies)**	Cecilia Hedmo Rune Lindste Eva Josefsson 2024	19.5-31.5 years	**Orthodontic Space closure**	**Indications:** -Angle Class I, overjet and overbite normal -No Angle class III -Some spacing anteriorly in the maxilla	**Assessments:** -Canine difference color -Abnormal crown length longer	**Assessments:** -Some BoP* -No papillae defect -No significant gingiva recession -No suppuration
		23.0-33.7 years	**Orthodontic Space Opening -Implant therapy**	**Assessments:** -Proclination of maxillary incisors -Strained lip closure -Angle class I, Overjet– Overbite normal	**Assessments:** -Non-acceptable appearance when smiling -Acceptable gingiva color - Abnormal short crown length - 1/62 visible implant	**Assessments:** -Papilla defects -BoP -Peri-implantitis -Suppuration -Some buccal gingiva retraction
Missing maxillary lateral incisors: A narrative review of treatment alternatives (5) **(Narrative review)**	Eva Josefsson Cecilia Hedmo, 2025	Younger patients -In growing child	**Orthodontic space closure**	**Indications:** -Straight or protrusive profile -Increased overjet -Crowding cases -Excess space possible to close **Assessment:** -Substantially psychological and profile impact --No TMJ disorder	**Indications:** -In high smile line **Assessment:** -Different size, shape and color of the canine -Need enamel bleaching or porcelain veneers	**Assessment:** -Long-term periodontal health - Normal gingival appearance preserved - Adaptation to natural changes overtime.
		-After finishing growth patterns -Adolescent	**Orthodontic space opening** **-Implants** **-FDP**	**Indications:** - Class III Angle Molar relationship -Correctly positioned class I, with maxillary spacing and normal mandibular dentition -Retrusive profile -In case of large difference size and color between C and LI. **Assessment:** -Infraocclusion complications -Ongoing eruption and retroclination of maxillary incisors -No TMJ disorder.	**Indications:** -Need 7mm intra-arch space -Need 5mm inter-radicular space **Assessment:** -Adjacent teeth intact -Pigmentation of the gingiva (negative impact on the aesthetics) -Resin-bonded FDP can produce debonding	**Contre-indications:** -Thin periodontal phenotype can lead to poor periodontal **Assessment:** -Atrophy of the alveolar bone -Peri-implant marginal bone loss - Degeneration of soft tissue and visibility of the implant -discolored gingiva adjacent to the replacement

Article	Author, Year	Age	Orthodontic treatment procedure	Occlusion – Profile	Smile – Aesthetic	Periodontal health
Congenitally Missing Maxillary Lateral Incisors: Update on the Functional and Esthetic Parameters of Patients Treated with Implants or Space Closure and Teeth Recontouring (22)	Núbia Inocencya Pavesi Pini Luciana Manzotti De Marchi Renata Corrêa Pascotto 2014	Younger patients	**Orthodontic Space closure**	- Malocclusions Class I or II (mainly) without severe crowding. -Balanced or mild-convex profile. -Cervical abfraction in premolars could happen because of the lack of mutually-protection occlusion. - Group function occlusion. -No TMD	-Canines adequate color, size, shape, and flattening buccal side changes. -Bleaching might be need it. -Alteration width-height ratio of C -Zeniths produce of LI same or above the reference line from the zenith of central incisors to canine.	-No periodontal complications due to the maintenance of natural dentition -Alveolar bone height maintained
(Narrative review)		18-19 years for women 20-21 years for men.	**Orthodontic Space Opening -implant**	-Mutually/Canine protected Occlusion.	-Lateral incisor color, size, shape and form are designed. -Might provide ideal papilla filling and gingival zenith -Gingival change over time: color and recession	-Gingival inflammation -Increased probing depths -Lack of dental papilla.
Esthetic evaluation of treatment strategies for missing maxillary lateral incisors(23)	**Lieke E. Kooijmansa Marco M.** **2026**	21.2 ±10.2 years (range, 12–66)	**Orthodontic Space closure**	NR***	-Recurring esthetic dental (RED)higher -Make Gingiva Zenith at/or above CI and C camouflage levels.	-Promote bone formation -Develop adequate interdental papilla and healthy periodontal. -Fewer Black triangles
(Retrospective cross-sectional study)		21.2 ±10.2 years (range, 12–66).	**Orthodontic Space Opening** **-implants** **-FDP**	NR	-Vertical length position crown has higher aesthetic -resin-bonded FDP higher Black triangles -Better Gingiva Zenith	-RBFDP→ Absence of periodontal ligament and produce bone loss support. -More black triangle

*** BoP: Bleeding on Probing / ** Black triangle: Distance of the alveolar crest to the contact point of the teeth more than 5mm / ***NR: None Register.**

Table 3-SUMMARY Comparative Clinical Parameters:

Orthodontics/Clinical Outcomes Parameters	**Space Closing – canine mesialization**	**Space Opening – Implants placements**	**Space Opening – FDP (17)**
Indications	-Mesial eruption of the maxillary canines -Class I with protrusive incisors -Class II malocclusion, balanced or mild convex profile without severe crowding -Excess space possible to close -Increased OVJ -High Exposure Gingiva: Gummy Smile -Canine of adequate size and shape to camouflage into LI	-Class I with non-extraction lower arch -Class III molar relationship and/or a retrusive profile - uprighted maxillary incisors need to be protruded -Diminished OVJ and deep bite -Excess of space possible to open an adequate orthodontic implant site coronally and apically -Low smile height -In case of large difference size and color between C and LI.	-Reestablished the teenage patient's smile while conserving the space for a future implant-based placement. -Long transitional period from adolescence to adulthood -Lower budget -Short time treatment required by the patient -Surgical implant placement procedure contraindicated
Aesthetic Outcome	-Shaping canine to an "incisiform": small, flat teeth. -Lateral Incisor making crown length should be 1-1.5 mm shorter than C and CI. -Gingiva Zenith might or not have some changes -1st Premolar can be re-shaping too. -Need color adjustment	-Good crown overall color. -Better gingival zenith alignments -Discolored gingiva and blue coloring -Gingival retraction and visible implants -Resorption of the labial bone. -Proclination of maxillary incisors. -Long term follow-up implant crown might become more infra occluded and protrusive	-All-ceramic resin bonded or Zirconium bridges lead to more aesthetics outcomes -Debonding risk -Black Triangle can appear
Periodontal Outcome	-Healthy Periodontal outcome but with few BoP. -Healthy gingival tissues -Intact interdental papillae	-Infraocclusion more than 1mm. -Augmented probing depth. -Higher possibility of: Gingivitis, dental plaque, peri-implantitis, suppuration, BoP.	-Bacterial adhesion -No papillae

Functional Outcome	-Group function -No TMD	-Canine mutual protected function. -No TMD	-Canine mutual protected function -No TMD
Patient Satisfaction	-Satisfied results. -Improvement and positive impact of quality of life and self-esteem	-Satisfied results. -Waiting time was a problem	-Low Satisfied results.
Patient Age	-Young patient	-After the end of growth: men: 20 to 21 years of age Girls: 16 to 19 years of age (22,24)	-At any age, usually young patient
Cost	-Lower cost	-Higher overall cost	-Mid-cost
Treatment duration (25)	→ Shorter overall treatment duration → But longer orthodontic treatment duration -Mean: 25.7 months treatments durations.	→ The longest overall treatment duration → But shorter orthodontic treatment duration - Mean: 27.4 months treatments durations.	→ Shorter overall treatment duration than Implant replacement -Mean: 27.4 months treatments durations.
Long-term Stability	-Need Long term bonded fixed retainer -Reopening spaces	-Adjacent teeth intact for long term stability	-Mid- Long-term restauration, BUT limited durability: → wear and tear over time lead to chipping or fracturing. And debonding.
Space availability need it for replacing the MLIA (maxillary lateral incisor agenesis)	-Flexibility and metabolism of young, growing bones Respect to the Golden standard percentage.	-Bone thickness need it vestibul-lingual: 6-7mm. -Mesiodistal direction, it should be larger than the size of a lateral incisor. -Space opening should be of at least 7.5-8 mm to allow 6.5 mm for implant placement and the enlargement of the upper front teeth. Respect to the Golden standard percentage.	-5 mm space for the missing upper lateral is adequate.
Advantages	-Increase space available for the posterior teeth (3rd molar) -Immediately finished treatment after orthodontics. -Better Long-term results - Early mesial positioning of the canine helps maintain	-Preservation of the number of natural teeth -Leaves the adjacent teeth intact -Ideal intercuspation of canines and molars occlusions. -Can use Mini-Implants for temporary prosthetic crown which lead to vertical and horizontal alveolar bone growth in	-Cost-effectiveness, more affordable versus the implant replacement therapy -Appreciated by quick procedure, simple and painless solution. -More conservative in Maryland bridge towards dental tissue compared with Canine Camouflage.

	alveolar bone height in the region. -Better global harmony aesthetic outcome -Long term periodontal health	the implant future site and no alveolar bone resorption.**(26)**	
Disadvantages, Risk and Complications	-Maxillary canines' anatomy. -Canine and 1st premolar might need a Torque change and grinding. -Possible reopening of spaces -Loss Canine-protected occlusion	-Adolescents wait period implants placed -Risk Alveolar bone loss -Treatment complexity -Fear of losing osteointegration -Disharmonious gingival margins levels on long term -Potential complications -Frequently supplementary hard or soft tissue grafting procedures. -Low periodontal health long term outcome -Negative self-esteem effect - Infraocclusion shorter and protrusive implant.	- Risk of reduced alveolar bone height and thickness, as implant placement must be delayed until skeletal growth is complete. -Low durability and unstable for life-time -Less natural and aesthetic

5. DISCUSSION

Lateral Incisor agenesis is one of the orthodontic problems that we would find in our clinics. Patients will come for treatments solutions and as a practitioner, two main orthodontic treatments options would be proposed:

- Orthodontic space closure and Canine camouflage (SC)
  Or
- Orthodontic space opening and implants or Maryland Bridge replacement - RBFDP (resin bonded fixed partial denture) (SO).

In our study, we tried to compare 8 articles in our objective to find the preferable orthodontic treatment. Through this research, we compared the differences orthodontics options that we have for patients with lateral maxillary incisor agenesis. They were based on mainly tree levels, for better outcomes, such as aesthetic/smile harmony, periodontal and longevity health levels, and occlusion/functional levels. The study demonstrates a correlation between orthodontic decision making and patients age, periodontal health, future outcome, malocclusion, smile defects, and patient dental features. We have been focusing mainly (tables 2-3) on 8 studies: 1 retrospective study, 2 retrospective cross-sectional study, 2 cohort study, 1 case report, and 2 narrative review. Patients that have been studied were usually young, adolescent and end of growth phase period. We compared their orthodontic characteristics outcomes on aesthetic, occlusion and periodontal level, during a 5 to 10 years follow up. Taking into consideration the patient and the practitioner satisfaction appearance results.

From what we can extract from this study, is that all of these articles demonstrate that early diagnosis and early treatment can have a positive psychological effect on patient. Early diagnosis and early treatments happen most of the time in very young patients such as in adolescence, which result in space closure orthodontic approach. This positive effect has been found in space closure orthodontic treatment, because of the short treatment duration and the rapid profile and self-esteem changes happening. Contrary to that, the before realization of any treatment, the open and unaesthetically space that the patient have due to the missing teeth, and the long during time process of space opening (in open space treatment) have been creating a negative effect for patients. An early process into the treatment is primary considered, and it depends on the age of the patient. These findings, explained both by Cecilia Hedmo etc. in articles (5,21) demonstrate that at early age, in young and growing child: orthodontic space closure is considered and preferable. As explained too by Abdolreza Jamilian, etc... 2015 (19) orthodontic space closing is major in the case of adolescence to avoid waiting years till the end of growing phase to restore an

agenesis tooth. Opposing, studies have been showed that orthodontic space opening with implants replacement should be consider and process at beginning adulthood or end growing phase period for a complete bone growing and changes. As this study by Ciarlantini R, etc… 2017 (26) has been showing that even during young age, and depending on other factors such as malocclusion, space opening must be need it and a mini screw implant placement (as new approach nowadays) can be positioned for temporary prosthetic site. It will avoid vertical and horizontal bone resorption and bone loss with time, until future implant will be placed since it can only be done after growth completion, instead of a full and only Maryland bridge placement known as RBFDP.

Researches explain that most of space closure orthodontic treatments have been done in younger patients which lead to an early finish treatment as a young teenager with better psychological impact, contrary to an open space orthodontic treatment is more treated in older patient, after their growth finished, around the 18years old in women and 20years old in men (21). So, as the patient didn't finish his bone and morphological growth, bony and anatomically changes are still in process, so a definitive implant placement cannot be done and he will need to wait years until that, unless the case of profile and malocclusion criteria are need it for an open space orthodontic treatment and mini-implants can be studied and placed. So orthodontic space opening leads to a bigger timing in the treatment.

Occlusion and functional features have been into consideration only in the first 5 studies of table 2. In *Lieke E, Kooijmansa 's etc*... article, occlusion factors were not involved(23).

It has been shown that occlusion characteristics in pre-factor criteria for selecting orthodontic option treatments are primordial. Through this study, we can say that Angle Class I Molar has been indicated in both treatments option. For orthodontic space closure, Angle Class I with protrusive incisor, normal or increased overjet, normal overbite, or Angle Class II malocclusion without severe crowding are indicated to treat as OSC (orthodontic space closure). It can be noticed by this Case report by *L Lopes-Rocha* (27). And this review article *A. Bredariol* too (28). Through *A. Bredariol, etc...* article, we can notice too that indications for SO or SC are the same reported as in our articles. In another hand, for orthodontic space opening, Angle Class I well-aligned, with no crowding lower arch, normal or diminished overjet, normal overbite, or deep bite overbite, or Angle Class III malocclusion, are indications for OSO (orthodontic space opening). It can be seen too in this case report(29). In *Margaux Vignon, etc... article,* patient is older, more than 18years old, Class III malocclusion with enough space (6-7mm) for implants replacement, so adjusted space and prosthetic replacement has been helpful for replacing the bilateral agenesis maxillary lateral incisor (29).

In all the investigations we made, no temporo-mandibular joint disorder has been significant signaled or related with any type of treatment options (5,19,22). Others criteria has

been into account in this category, such as profile related with the occlusion. A normal - balanced or mild convex profile, with small dental spaces that spaces could be closed, are indicated for orthodontic space closure, except and opposite to this: a retrusive profile, with or without an excess dental space are indicated for orthodontic space opening. At the end of any treatment, a balanced occlusion and harmonious profile need to be achieved. So, an occlusion diagnostic study is primordial for the decision-making orthodontic approach.

After each treatment, not only the occlusion will be changed but also the functional overall occlusion and patient profile harmony too. Studies has been evaluating the functional occlusion changes in patients (22). After orthodontic space closing with canine camouflage into lateral incisor, patient will develop a group function occlusion, which lead to a biggest holding weight on the premolar's roots: forces generated by "canine guidance" are going to be placed on the first premolar smaller and thinner root. It leads to a torque premolar root change. Premolar abfraction can appear too with time. Instead, an open space treatment, implant replacement or even Maryland bridge, will maintain the canine-mutual protected occlusion.

In another hand, it has been shown that occlusion characteristics for post-treatment outcome criteria are primordial too in the selection of the orthodontic option treatments. So not only indications and contraindications mentioned before are important, but also the advantages and disadvantages taking into account for the future outcome are too. As we can extract from the results, open space with implants replacement significantly produced in the future a proclined maxillary incisors, strained lip closure and infraocclusion complications to the implant. The occlusion disadvantage in future implants placement leads to an ongoing eruption and backward tipping of the maxillary central incisors cause the implant-supported crown to appear shorter and positioned more forward from the others anterior teeth, which leads to an infraocclusion.
So even remaining to an overall occlusion ideal intercuspidation mutual-protected, orthodontic space opening procedure produce some complications in the future. Contrary to space closure, even with the group function disclusion pattern, complications involved like in SO are not present.

Aesthetic and Smile design categories differ a lot between one treatment and another. Aesthetic approaches referred to Recurring esthetic dental (RED), Gingiva zenith, overall shape/size/color dental crown, black triangles and smile harmony. Not all studies have been reported all these criteria, but agreed on the same general idea for each treatment.

Recurring esthetic dental (RED) happens in canine, it has been found more in orthodontic space closure. Gingiva zenith has better outcome in SO than SC. Gingiva zenith of lateral incisor replacement has a worst possible outcome in space closure than space opening, because it can appear more apically than the others. Replacing by the canine, it can appear above the gingiva zenith of the two adjacent teeth, than being usually 1mm coronally. Moreover, the overall shape,

size and color dental crown, has a better outcome in shape and size in space closure and the color characteristic in space opening. For the shape/size, Implant crown can produce in long term follow-up the disadvantage of looking shorter, in infraocclusion and in protrusive position. So long-term results are worsened. It is explained by the uprighted happening in maxillary incisor during adolescence to adulthood, that influence and produce a negative aesthetic result in open space implant placement cases, as the implant-supported crown will still remain in his original position during dental eruption changes and will look shorter afterward. Also, studies have been shown too that implant placement might produce a strained lip closure as negative impact aesthetically.

Crown overall heigh and width are being in dilemma with space closure and space opening implant. In space closure cases, regardless the reshaping of a big, convex, globular and long cusp canine into maxillary lateral incisor, the new dimensions can still appear disharmonious to the rest of the teeth. In SC, the maxillary lateral incisor crown replacement, can look a bit longer than SO where with time will look shorter. Differently, in SO crown implants placement is usually well-done with the lab and only produce negatively aesthetically an infraocclusion outcome.

This interpretation has a benefit for SC treatment but the only disadvantage compared to SO is that we are touching and modifying the adjacent teeth, contrary to space opening where implants placement or Maryland bridge leave the adjacent teeth intact. So, we are making some “unconservative” form of treatment in SC, by touching the adjacent teeth, as the canine is too globular, bigger and different from maxillary lateral incisors, anatomy changes will need to be achieved. Another disadvantage for the SC, is canine camouflage has the shape, volume and the color not aligned with lateral incisor position: too globular, too pointed, or too saturated in yellow as we said. For the color, it has been study that it is better in SO than SC because the canine is more yellowish than the incisors contrary to prosthetic crown replacement in SO that comes in a perfect one color. But in SC cases, color problem can be adjusted with enamel bleaching or veneers porcelain restoration, but this solution might result a bit increasing cost of the treatment.

In another hand, black triangles happen because of papillae recession and interdental papillae loss. They appear more in space opening with Maryland bridge replacement than with implants replacement, but very few in space closure, because of the bone loss exposition, which leads to a small gingiva recession with time. One aesthetic and smile inconvenient explained also in most of these studies, was the discolored and blue gingiva color. It has been only noticed in space opening with implants placement, which decrease the aesthetic outcome.

Moreover, in cases with lateral incisor agenesis with gummy smile, high smile line, the orthodontic approach needs it to project an achievable aesthetic result has been demonstrated in OSC. It is contraindicated in space opening, reason to avoid infra-positioned gingival margins during implant replacement. SO presents some potentials complications such as insufficient papillary fill, loss of alveolar bone, and discoloration of the gingival tissues. These studies have been demonstrated that

the overall smile harmony has a better result in space closure than space opening. Studies have been working too on asking the satisfaction level to patients and also practitioners, and the majority preferred and have a higher satisfied appearance with closing space treatment results (20).

Periodontal health has been assigned at different levels. Results showed that periodontal health overall, such as gingivitis, mobility, papillae and bone loss are reported.
It has less occurred and even none present in space closure cases than space opening, because of the natural dentition preservation. But opposite to this overall results, other studies have demonstrated that BoP (Bleeding on probing) in space closure is a bit more presented in space closure than space opening (21). Gingivitis (gingiva inflammation), Peri-implantitis, suppuration and bone loss are assessments that have been showed and happened in Implants replacement in SO treatments. Except for mobility, it has been shown that only in 1 case over 14 had mobility after 5 years of implant placement (19). So, mobility in Implants space opening has no significance. Infraocclusion has been seen in most all of the implant's cases and it's a disadvantage for space opening implants replacement, because it will produce in long-term follow up a disharmony smile, a short and protrusive crown appearance.

On the other side, orthodontic space closure contributes to a healthy periodontal outcome, a healthy gingival tissue and an intact interdental papilla. It preserved the alveolar bone generation. Open space treatment with resin-bonded FDP: Maryland Bridge, produce a negative periodontally outcome such as a progressive bone loss with bacterial plaque adhesion in palatal, because of the facility to food impastation and poor oral hygiene and oral health care. That's why with orthodontic space opening, it's better to use implants replacement or mini-screw implants replacements instead of RBFDP: Maryland-Bridge, to have a better hygiene, better adhesion and mainly preserving the bone height and thickness generation even in growing patient, for future implants replacement (26). As we can see, bone loss or bone resorption happen in orthodontic space opening with Maryland bridge placement more than Implants placement. But it could be minimized by a mini-implant placement instead during growth, that will allow the alveolar bone process to develop in the vertical way with the process of eruption and movement of the adjacent teeth.

In another hand, this new study, will help to maintain the width necessary for the future dental implant placement but cannot completely ignored a future need and require supplementary hard or soft tissue grafting procedures for implant replacement in the maxillary alveolar ridge.
As in space closure the patient will not undergo any type of alveolar bone loss, alveolar bone density and morphology process are maintained and no grafting procedures will be need it.

The follow up results, have distinguished advantages and disadvantages of each orthodontic space closure and space opening treatments. As orthodontic space closure, will produce an increase in space available for the posterior teeth (3rd molar) to erupt and avoid future crowding, versus orthodontic space opening will need that space for the prosthetic replacement of the agenesis tooth. SC will have an immediately finished results after treatment versus SO will have a longer duration for final result. But some study such as Jamillian et al. 2015 retrospective study, has been shown that treatment time of OSC is higher (29 months) than the OSO implant (18 months) which contradict the rest of the studies (19).

Open space preserves the number of the full upper arch dentition versus closure space will diminish one premolar to make it into Canine and one Canine to make it as the missing maxillary lateral incisor, so space opening approach will leave the adjacent teeth intact and be more dental conservative. The alveolar bone height will be maintained and promote in space closure compare to open space treatment, unless we are using a mini-implant with temporary prosthetic crown which lead to vertical and horizontal bone growth for future implant site. Periodontally speaking both parts are valid. Aesthetically and occlusion features varies a lot between both treatment as we can see. In space closure, after treatment completion, space re-opening can happen, so it is recommended to use long life fixed bonded retainer on the palatal side of maxillary anterior teeth. Moreover, in SC, presence of re-shaping a globular, convex canine, with yellowish color and occlusion-functional modification, into the missing maxillary lateral incisor is placed in the disadvantage's column. Same as in space opening, regardless the indications and positively trying to save the adjacent teeth and patient occlusion, with a better gingiva zenith than SC treatment, disadvantages such as gingiva discoloration, interdental papillae changes over time, marginal recession, and fear of losing osteointegration of the implant (in both case mini-implant or implant final placement) could happen. Orthodontic space opening treatment will make this process a complex treatment too, especially when other multidisciplinary approaches might be need it.

Orthodontic space closure cost less than orthodontic space opening. Especially if enamel bleaching or veneers porcelain restoration are neither need it, compare to implant or resin-bonded FDP placement: Maryland Bridge, which will cost more.

Some limitations have been found throughout this study. Limited number of studies comparing the two main orthodontic treatments during these 10 years with the same sample and same comparison of all the orthodontics characteristics need it. Such as in the article of Lieke E, Kooijmansa and Marco M. (2026) etc..., we have been limited by only and mainly aesthetic features, some periodontal feature but none occlusion or functional one's were involved (23). Also, it was hard to find case reports of the same author that compare orthodontic space closing

and space opening, in different and many Angle Class malocclusion in these 5 recent years. And finally, the limited number of articles with primary resources and limited number of analyzed cases and sample of each study had been restricted and impact negatively our ability to identify significantly orthodontics characteristics.

6. CONCLUSIONS

The decision of orthodontic space opening SO and orthodontic space closing SC are going to be affected by these pre and post orthodontics factors:

1. Patient with Class I occlusion can be considered for both SC or SO. Considering the space available and patient profile.
2. Patient with Class II malocclusion, protrusive tendency will be considered as SC.
3. Patient with Class III malocclusion, brachycephalic profile and retrusive tendency will be considered as SO with Implant or Maryland Bridge replacements.
4. Early age, in young and growing child, orthodontic SC is considered and preferable.
5. Temporo-mandibular joints dysfunction or dislocation had no relevant significance related to lateral incisor agenesis treatments.
6. Occlusion and function orthodontic characteristics: SC leads to group function occlusion and SO leads to mutual-protected occlusion.
7. Aesthetic and Smile design: Better Recurring esthetic dental (RED), gingiva color, overall shape/size dental crown, gummy smile, black triangles and smile harmony outcome: SC.
   Except for better gingiva zenith and dental crown color: SO.
8. Periodontal health overall outcome: Better in SC than SO.
9. More conservative treatment: SO.
10. Maryland-bridge SO are chosen mainly when young and limited budget cases.
11. SO implants replacement, need for space indicated: 6-7 mm.
12. Mini-implants procedure is used in SO cases and avoid bone loss resorption with time.
13. SC has a short duration and low-cost treatment, after RBFDP and SO implants replacement in third position (longer and costlier).

In conclusion, despite the limitations that we have been facing as explained, the decision-making of closure space orthodontic approach and open space orthodontic approach should analyze the different factors in pre-factors characteristics indications and in post-factors for better and realistic outcome results.

7. SUSTAINABILITY:

Orthodontic approaches to maxillary lateral incisor agenesis are based on important sustainability factors such as economic and social ones.

On an economic sustainable level, both orthodontic space closure and space opening differed. Space closure is usually more economic than space opening. Usually with only an orthodontic approach: space closure procedure with Enameloplasty, with the same practitioner the treatment can be done in less time and cost. Except for orthodontic space opening, that require other multidisciplinary approaches for prosthetic replacements such prosthodontic, which increase the cost of the treatment.

In another hand, social sustainability perspective, both treatments improve patient's aesthetic and smile, patient's occlusion and dental function and finally patient's self-esteem. Favoring and improving his social atmosphere especially at this young age. Adjusting and enlightening his profile and overall smile aesthetic, which indirectly making him socially confident. Also, an early and well-decision-making orthodontic interventions may reduce the need for repeated or others more complex approaches in the future, promoting a long-term and better oral health.

Finally, orthodontic treatments need to be individualized planed for supporting a sustainable oral healthcare model. Global orthodontic sustainability objectives and approaches for missing maxillary lateral incisor are need it for enhancing patient well-being, improving overall patient care and finding a good balance between cost-benefit for our patient.

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9. ANNEXES:

Figure.1: Lateral Incisor agenesis bilateral, patient 11-years-old female with esthetic complaint (10)

10. Schroeder DK, Schroeder MA, Vasconcelos V. Agenesis of maxillary lateral incisors: diagnosis and treatment options. Dent Press J Orthod. 2022;27(1):e22spe1. doi:10.1590/2177-6709.27.1.e22spe1

Figure.2: Levin's Golden Proportions

12. Cinelli F, Piva F, Bertini F, Russo DS, Giachetti L. Maxillary Anterior Teeth Dimensions and Relative Width Proportions: A Narrative Literature Review. Dent J. 2023 Dec 25;12(1):3. doi:10.3390/dj12010003

Figure.3: The gingival zenith level for lateral incisors is approximately 1mm coronally than the gingival zenith position of the central incisor and canine.

13. Chu SJ, Tan JH, Stappert CFJ, Tarnow DP. Gingival Zenith Positions and Levels of the Maxillary Anterior Dentition. J Esthet Restor Dent. 2009 Apr;21(2):113–20. doi:10.1111/j.1708-8240.2009.00242.x

Figure.4: Pre and Post treatment records in OSC Bilateral Class II dental malocclusion.

16. Greco M, Rosa M, Rombolà A. Bidimensional system for space closure treatment of missing lateral incisors: 10 years follow-up. J Orthod Sci. 2021 Jan;10(1):24. doi:10.4103/jos.JOS_78_20

Figure.5: Case orthodontic space opening with cantilever CAD/CAM PMMA bridges.

17. Karray S, Gassara Y, Boudabous E, Nasri S, Nouira Z, Hajjami H. Replacing Missing Maxillary Lateral Incisors by CAD/CAM PMMA Cantilever Bridges. Nuvvula S, editor. Case Rep Dent. 2023 Jan;2023(1):4302316. doi:10.1155/2023/4302316

Figure.6: Case Class II with enough space for space opening and implant replacement of bilateral axillary lateral incisors agenesis.

10. Schroeder DK, Schroeder MA, Vasconcelos V. Agenesis of maxillary lateral incisors: diagnosis and treatment options. Dent Press J Orthod. 2022;27(1):e22spe1. doi:10.1590/2177-6709.27.1.e22spe1

Table 1: PRISMA FLOW DIAGRAM STUDY

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71