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2. **Tietmann C,** Jepsen S, Heibrok H, Wenzel S, Jepsen K. Long-term stability of regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis: 10-year data of a retrospective study. J Periodontol 2023;94:1176-1186. doi: 10.1002/JPER.23-0081. PMID:37010261.

3. Jepsen K, **Tietmann C**, Kutschera E, Wüllenweber P, Jäger A, Cardaropoli D, Gaveglio L, Sanz Sanchez I, Martin C, Fimmers R, Jepsen S. The effect of timing of orthodontic therapy on the outcomes of regenerative periodontal surgery in patients with stage IV periodontitis: A multicenter randomized trial. J Clin Periodontol 2021;48(10):1282-1292. doi: 10.1111/jcpe.13528. PMID: 34312872.

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5. **Tietmann C**, Jepsen S, Kauer R, Jepsen K. (2024) Clinical effectiveness of regenerative periodontal surgery and orthodontic tooth movement with clear aligners in stage IV periodontitis: a case series. Quintessence International. May 30;55(5):348-357. doi: 10.3290/j.qi.b5213521. PMID: 38619257

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ABKÜRZUNGEN

AIT	Antiinfektiöse Therapie
BOP	Bleeding on Probing I Blutung auf Sondieren
CA	Clear Aligner
CAL	Clinical Attachmentlevel | Klinisches Attachmentniveau
CALg	Clinical Attachment level gain I Gewinn an klinischem Attachmentniveau
CM	Collagen Membrane I Kollagenmembran
DBBMc	Collagenous Deproteinized Bovine Bone Mineral I Deproteinisiertes kollagenes bovines Knochenmineral
EMD	Enamel Matrix Derivative | Schmelz-Matrix-Proteine
FMBS	Full Mouth Bleeding Score | Vollständiger Blutungs Index
FSPL	Final Splinting I Abschluss der kieferorthopädischen Therapie
GOHAI	General oral health assessment index
GTR	Guided Tissue Regeneration | Gesteuerte Geweberegeneration
KFO-Therapie	Kieferorthopädische Therapie
PC	Pocket Closure I Taschenelimination
PI	Plaque Index | Plaqueindex
PMPR	Professionelle mechanische Plaquereduktion
PPD	Periodontal Probing Depth | parodontale Sondierungstiefe
PPDr	Reduction of Periodontal Probing Depth I Reduktion der Sondierungstiefen
PTM	Pathologic Tooth Migration I pathologische Zahnwanderung
PROMs	Patient-Reported Outcome Measures | Ergebnisse aus Patientenangaben
OHrQoL	Oral Health related Quality of Life I Mundgesundheitsbezogene Lebensqualität
rBL	Radiographic Bone Level I radiologisches Knochenniveau
rBLg	Radiographic Bone Level Gain I Gewinn an radiologischem Knochenniveau
UPT	Unterstützende Parodontitistherapie

2. EINLEITUNG

Parodontitis im Stadium IV ist charakterisiert durch einen ähnlichen Schweregrad an parodontalem Attachmentverlust, parodontale Entzündung und vertikale Knochendefekte wie Parodontitis im Stadium III (*Papapanou et al., 2018*). Allerdings erfordert die Therapie der Parodontitis im Stadium IV aufgrund von pathologischer Zahnwanderung (PTM) (*Brunsvold, 2005*) - gekennzeichnet durch Elongationen, Auffächerungen und Lückenbildungen in Verbindung mit sekundärem okklusalem Trauma, Bisskollaps durch Verlust der posterioren Abstützung und mastikatorische Dysfunktion mit sekundärem okklusalem Trauma und Zahnbeweglichkeit ≥ Grad 2 - und/oder Verlust von fünf oder mehr Zähnen eine komplexe interdisziplinäre Rehabilitation (s. Abbildung 1).

Parodontitis Stadium STAGING		**Stadium I**	**Stadium II**	**Stadium III**	**Stadium IV**
Schweregrad	Interdentaler CAL an der Stelle mit dem größten Verlust	1-2 mm	3-4 mm	≥ 5 mm	≥ 5 mm
	Röntgenologischer Knochenabbau	Koronales Drittel (< 15 %)	Koronales Drittel (15-33 %)	Mittleres bis apikales Drittel	Mittleres bis apikales Drittel
	Zahnverlust	Kein Zahnverlust aufgrund von Parodontitis		Zahnverlust aufgrund von Parodontitis von ≤ 4 Zähnen	Zahnverlust aufgrund von Parodontitis von ≥ 5 Zähnen
Komplexität	Lokal	Maximale Sondierungstiefe ≤ 4 mm Vorwiegend horizontaler Knochenabbau	Maximale Sondierungstiefe 4-5 mm Vorwiegend horizontaler Knochenabbau	Zusätzlich zur Komplexität des Stadium II: Sondierungstiefe ≥ 6mm Vertikaler Knochenabbau ≥ 3mm Furkationsbefall Grad II oder III Moderater Kammdefekt	Zusätzlich zur Komplexität des Stadium III: Notwendigkeit einer komplexen, interdisziplinären Rehabilitation aufgrund von: Mastikatorischer Dysfunktion Sekundärem okklusalen Trauma (Zahnbeweglichkeit ≥ Grad 2) Ausgeprägtem Kammdefekt Verlust der Bisshöhe, Zahnwanderungen, Auffächerung der Front Weniger als 20 Restzähne mit 10 okkludierenden Paaren
Ausdehnung und Verteilung	Wird zur genaueren Beschreibung des Staging verwendet	Für jedes Stadium Ausdehnung als lokalisiert (< 30 % der Zähne), generalisiert oder als-Molaren/Inzisiven Muster beschreiben			

Abb. 1: Klassifikation der Parodontitis des World Workshop 2017 auf Basis von Erkrankungsstadien, definiert durch Schweregrad (interdentaler klinischer Attachmentverlust, röntgenologischer Knochenabbau und Zahnverlust) Komplexität, Ausdehnung und Verteilung (Papapanou et al. 2018)

Eine alleinige Behandlung der Parodontitis im Stadium IV, d.h. Therapiestufen 1-3 (*Sanz et al., 2020*), ist nicht ausreichend, um Funktion und Ästhetik sowie Lebensqualität der Patienten wiederherzustellen. Wird keine adäquate interdisziplinäre Behandlung der Parodontitis Stadium

IV durchgeführt, so führt dies zu weiteren parodontalen Attachmentverlusten bis hin zum Verlust der gesamten verbleibenden Dentition.

Die kürzlich erschienene S3-Leitlinie für die Therapie der Parodontitis im Stadium IV (*Herrera et al., 2022*) definiert als konkretes Ziel maximalen Zahnerhalt und Erhalt der geschlossenen Zahnreihe für die Behandlung dieses komplexen Krankheitsbildes. Eine der häufigsten klinischen Szenarien ist der Falltyp 2 gekennzeichnet durch pathologische Zahnwanderungen, Auffächerungen, Lückenbildungen sowie Elongationen (*Herrera et al., 2022*) (s. Abbildung 2a).

Abb. 2a: Parodontitis Stadium IV mit pathologischer Zahnwanderung (PTM): klinisches Bild und radiologischer Befund

Pathologische Zahnwanderungen mit sekundärem okklusalem Trauma haben eine hohe Prävalenz von 91,3 % bei Parodontitis im Stadium IV, wobei die Oberkieferdentition mit 74% häufiger betroffen ist als die Unterkieferdentition mit 60% *(Zasčiurinskienė et al., 2023a).*

Häufig werden Patienten mit pathologischer Zahnwanderung aufgrund von Parodontitis im Stadium IV nicht über die Möglichkeit kieferorthopädischer Behandlung bei Erwachsenen informiert (*Hirschfeld et al., 2019*). Stattdessen werden umfangreiche Extraktionen und Ersatz durch zahn- oder implantatgetragenen Zahnersatz als einzige Therapiealternative vorgeschlagen. Hingegen ist nach heutigem Wissensstand implantatgetragener Ersatz bei Parodontitispatienten mit einem deutlich erhöhten Risiko für Periimplantitis verbunden *(Carra et al., 2022, Montero et al., 2022).*

Patienten mit diesen ästhetischen und funktionellen Beeinträchtigungen sind an einer kieferorthopädischen Therapie interessiert (s. Abbildung 2b). Der Wunsch nach Zahnerhalt und Verbesserung der Ästhetik sind für diese Patienten die Hauptmotive für eine kieferorthopädische Therapie (*Hirschfeld et al., 2019*). Je besser Patienten über ihre Parodontalerkrankung aufgeklärt sind, desto größer ist das Interesse der Patienten an einer kieferorthopädischen Therapie *(Zasčiurinskienė et al., 2023b).*

Abb. 2b: Parodontitis Stadium IV mit PTM: klinische Situation bei Beginn der kieferorthopädischen Therapie mit Multibandapparatur in situ

Lange Zeit wurde in der Literatur diskutiert, ob eine kieferorthopädische Therapie bei Parodontitispatienten Auswirkung auf die parodontale Gesundheit hat (*Sanders, 1999, van Gastel et al., 2007, Gkantidis et al., 2010*). Bereits frühe Tierstudien haben gezeigt, dass kieferorthopädische Zahnbewegung bei unkontrollierter parodontaler Entzündung zu einem weiteren Fortschreiten der parodontalen Zerstörung und Attachmentverlust führt (*Wennström et al., 1993*). Die negative Auswirkung parodontaler Entzündung bei gleichzeitiger kieferorthopädischer Zahnbewegung wurde auch in späteren Tiermodellen bestätigt *(Kirschneck et al., 2017, Schröder et al., 2021, Rath-Deschner et al., 2022).* Ist die parodontale Entzündung hingegen kontrolliert, ist es auch bei Parodontitispatienten möglich, Defekte zu rekonstruieren und pathologisch gewanderte Zähne durch kieferorthopädische Therapie wieder in die Zahnreihe einzuordnen (*Cardaropoli et al., 2001, Corrente et al., 2003, Re et al., 2000, Sanz & Martin, 2015*).

Daher ist bei Parodontitis Stadium IV die gleiche Therapiesequenz entsprechend der Leitlinie für die Therapie der Parodontitis im Stadium I-III *(Sanz et al., 2020)* durchzuführen, allerdings unter spezieller Berücksichtigung der Komplexität des Krankheitsbildes von Parodontitis im Stadium IV. Die Rehabilitation der Funktion, Aufhebung der Bisssenkung und Behandlung des sekundären okklusalen Traumas müssen von Beginn der Therapie geplant und in die Therapiestufen 1-3 integriert sowie kontinuierlich reevaluiert werden.

Wie bei der Therapie der Parodontitis im Stadium I-III ist es erforderlich, dass der Patient in Therapiestufe 1 über sein Krankheitsbild aufgeklärt und motiviert wird, Verhaltensmuster zu ändern, Risikofaktoren wie Rauchen und Einfluss systemischer Erkrankungen kontrolliert und eine professionelle mechanische Plaquereduktion (PMPR) durchgeführt werden. Die Aufklärung des Patienten über Risiken und Nutzen der Therapie soll bei Parodontitis im Stadium IV unter Berücksichtigung des maximalen Zahnerhaltes und Erhalt der geschlossenen Zahnreihe erfolgen. Insbesondere soll herausgestellt werden, dass die Unterlassung einer adäquaten Therapie keine Therapieoption darstellt und zum Verlust der gesamten verbliebenen Dentition führen kann.

Auch parodontal stärker vorgeschädigte Zähne mit zunächst fraglicher Prognose sollen daher während Therapiestufe 1-3 erhalten und frühzeitige Extraktion vermieden werden. Regelmäßige Reevaluationen der parodontalen Befunde, Remotivation der Patienten und Kontrolle der Risikofaktoren sind bei Patienten mit Parodontitis im Stadium IV von besonderer Bedeutung für eine erfolgreiche Parodontitistherapie, die als Voraussetzung für den Beginn der kieferorthopädischen Zahnbewegung erforderlich ist.

Ergänzend ist aufgrund der Komplexität der Therapie von Parodontitis im Stadium IV, Falltyp 2 ein frühzeitiges kieferorthopädisches Konsil während Therapiestufe 2 indiziert, um einen gemeinsamen personalisierten interdisziplinären Behandlungsplan abzustimmen. Der Schweregrad und die Art des parodontalen Attachmentverlustes -horizontaler Attachmentverlust oder vertikale Knochendefekte- bestimmen die therapeutische Sequenz der parodontalen Therapie (Therapiestufe 2 und 3) sowie die Art der kieferorthopädischen Zahnbewegung. Aufgrund des nach apikal verschobenen Widerstandszentrums im parodontal reduzierten Gebiss müssen die kieferorthopädischen Kräfte dosiert eingesetzt und insbesondere intrusive kieferorthopädische Zahnbewegungen elongierter Zähne sorgfältig geplant werden.

Systematische Reviews zeigten, dass bei erfolgreich behandelten Parodontitispatienten keine klinisch relevanten Auswirkungen auf Sondierungstiefen (PPD), klinisches Attachmentniveau (CAL) und Bluten auf Sondieren (BOP) durch kieferorthopädische Zahnbewegung mit Multibandapparaturen im Vergleich zu parodontal gesunden Patienten beobachtet werden konnten (*Bollen et al., 2008, Martin et al., 2022, Papageorgiou et al., 2018 und 2022*).

Häufig sind jedoch bei Patienten mit Parodontitis im Stadium IV aufgrund vertikaler Knochendefekte nach parodontaler Therapie die geforderten Endpunkte (keine Stellen mit Sondierungstiefen von 5 mm und BOP und keine Sondierungstiefen $\geq$6 mm (*Sanz et al., 2020*)) für den Beginn einer kieferorthopädischen Therapie nicht erreicht (*Herrera et al., 2022*) und

regenerative parodontalchirurgische Maßnahmen werden erforderlich. Die Effektivität regenerativer Verfahren bei vertikalen Knochendefekten ist belegt und zu einem etablierten Therapieverfahren bei Parodontitis im Stadium III geworden wie Langzeitstudien zeigen (*Sculean et al., 2008, Cortellini & Tonetti, 2015, Cortellini et al., 2017, Bröseler et al., 2017, Nibali et al., 2020, Sanz et al., 2020, Stavropoulos et al., 2021*). Selbst als „hoffnungslos" geltende Zähne können langzeitstabil erhalten und deren Prognose in „günstig" umgewandelt werden (*Cortellini et al., 2017 und 2020, Tietmann et al., 2023b*). Gleichzeitig sind die langfristigen Gesamtkosten für regenerativ therapierte Zähne niedriger als für implantologischen Ersatz der Zähne (*Cortellini et al., 2020*).
Die Kombination regenerativer parodontalchirurgischer Therapie mit anschließender kieferorthopädischer Zahnbewegung bei Parodontitis Stadium IV hingegen war nur in Fallberichten (*Re et al., 2000, Cardaropoli et al., 2001 und 2006; Jepsen et al., 2015*) oder Fallserien (*Ghezzi et al., 2008 und 2013, Rocuzzo et al., 2018, Aimetti et al., 2020*) beschrieben worden.

Histologische Untersuchungen in Tierstudien bei der Ratte zeigten, dass kieferorthopädische Zahnbewegungen in Knochendefekte hinein einen „stimulierenden" Effekt auf die Knochenneubildung haben können (*Vardimon et al., 2001, Nemcovsky et al., 2004*) oder in Verbindung mit dem Einsatz regenerativer Materialien die parodontale Regeneration verbessern. So konnten *Diedrich et al. (2003)* im Tiermodell histologisch nachweisen, dass die Verwendung von Schmelzmatrixproteinen und anschließender kieferorthopädischer Zahnbewegung zu einer 70-80% höheren Zementogenese und Osteogenese sowie Ausbildung Sharpey´scher Fasern führt und so die Ausbildung eines langen Saumepithels verhindert. In gleicher Weise wurde in einer Tierstudie gezeigt, dass der Einsatz von bovinem Knochenersatzmaterial (DBBMc) in intraossären Defekten die kieferorthopädische Zahnbewegung nicht behindert (*Araujo et al., 2001*).
Eine Übertragung der Erkenntnisse aus Tierstudien bezüglich der Wechselwirkungen zwischen kieferorthopädischer und parodontaler Therapie auf den Menschen ist nicht immer einfach möglich. Art der parodontalen Therapie und der Zeitpunkt des Beginns der kieferorthopädischen

Zahnbewegung nach Parodontitistherapie sowie die Auswirkungen auf die parodontalen Gewebe waren lange Zeit unzureichend untersucht (*Gorbunkova et al., 2016, Zasčiurinskienė et al., 2016*). Einige Autoren warteten den Endpunkt der parodontalen Wundheilung nach regenerativer Therapie ab und erzielten mit einem verzögerten Beginn der kieferorthopädischen Therapie (6-12 Monate) gute Ergebnisse (*Ghezzi et al., 2008, Jepsen et al., 2015, Roccuzzo et al., 2018, Aimetti et al., 2020*). Andere Studien zeigten hingegen, dass ein früher Beginn der kieferorthopädischen Therapie – unmittelbar oder bis zu drei Monate nach regenerativer Therapie – möglich ist und zu keinen ungünstigen Nebenwirkungen führt (*Cardaropoli et al., 2001 und 2006, Ogihara & Wang, 2010, Attia et al., 2012a, Ghezzi et al., 2013*). Darüber hinaus vermuteten die Autoren sogar, dass möglichst frühe kieferorthopädische Zahnbewegungen die parodontale Wundheilung stimulieren könnten wie histomorphometrische Untersuchungen einer Tierstudie (*Attia et al., 2012b*) zeigten. Allerdings handelt es sich bei diesen Berichten um Fallserien mit geringer Anzahl von Patienten und Defekten sowie einer kurzen Nachbeobachtungszeit (<12 Monate).

Patienten mit schwerer Parodontitis nehmen dieses Krankheitsbild als stärkere Beeinträchtigung ihrer Mundgesundheitsbezogenen Lebensqualität (OHrQoL) wahr als Patienten mit einem geringeren Schweregrad der Parodontitis (*Needleman et al., 2004, Aslund et al., 2008, Buset et al., 2016, Ferreira et al., 2017*). Besonders pathologische Zahnwanderung, Auffächerungen, Lückenbildungen und Elongationen in Verbindung mit Bisssenkung und mastikatorischer Dysfunktion stellen für diese Patienten ästhetische und funktionelle Beeinträchtigungen dar und sind Hauptmotive für eine kieferorthopädische Therapie (*Hirschfeld et al., 2019*). Ebenso wird Zahnerhalt durch eine regenerative Parodontitistherapie und langfristige unterstützende Parodontitistherapie (UPT) von den Patienten positiv bewertet (*Franke et al., 2015*).

Der Fokus der vorliegenden Arbeit war die Fragestellung, ob die kombinierte, regenerativ-parodontalchirurgische und kieferorthopädische Therapie bei Patienten mit Parodontitis im

Stadium IV und pathologischer Zahnwanderung erfolgreich und langzeitstabil möglich ist. Daher wurden die beiden ersten Studien anhand einer großen Patientenkohorte in einer parodontologischen Fachzahnarztpraxis durchgeführt. Die in diese beiden retrospektiven Studien eingeschlossenen Patienten wurden im Zeitraum von 2001-2010 mit der kombinierten Therapie behandelt.

Der optimale Zeitpunkt des Beginns der kieferorthopädischen Zahnbewegung nach regenerativer Parodontalchirurgie war in der Vergangenheit unklar. Daher war es eine der zentralen Fragestellungen im Rahmen einer prospektiven randomisierten multizentrischen Studie, ob ein früher oder später Beginn der kieferorthopädischen Therapie nach regenerativer Therapie von Vorteil sei. In gleicher Weise sollte im Rahmen dieser prospektiven, multizentrischen Studie die Auswirkung auf die Mundgesundheitsbezogene Lebensqualität (OHrQoL) der Patienten mit Parodontitis Stadium IV untersucht werden.

Da der Einsatz festsitzender kieferorthopädischer Multibandapparaturen bei erwachsenen Patienten häufig mit ästhetischen und funktionellen Beeinträchtigungen verbunden ist, sollte in einer weiteren retrospektiven Studie überprüft werden, ob alternativ auch durch den Einsatz von kaum sichtbaren kieferorthopädischen „Clear Alignern" die kombinierte, regenerativ-parodontalchirurgische und kieferorthopädische Therapie bei Patienten mit Stadium IV Parodontitis zur Einordnung und Stabilisierung von Zähnen mit pathologischer Zahnwanderung (PTM) möglich ist.

3. ERGEBNISSE

3.1 Tietmann C, Bröseler F, Axelrad T, Jepsen K, Jepsen S. Regenerative periodontal surgery and orthodontic tooth movements in stage IV periodontitis: A retrospective practice-based cohort study. J Clin Periodontol 2021;48(5):668-678. doi: 10.1111/jcpe.13442.

Zielsetzung der Arbeit

Frühere Fallberichte und Fallserien mit zumeist wenigen Patienten konnten zeigen, dass pathologisch gewanderte Zähne durch die Kombination von parodontaler und kieferorthopädischer Therapie wieder in die Zahnreihe eingeordnet und Knochendefekte rekonstruiert werden können. Ziel dieser retrospektiven Studie war es, die Wirksamkeit der kombinierten regenerativ-parodontalchirurgischen Therapie intraossärer Defekte mit anschließender kieferorthopädischer Zahnbewegung auch in einer großen Kohorte von Patienten mit Stadium IV Parodontitis und PTM zu untersuchen.

Methoden und Ergebnisse

Achtundvierzig Patienten mit Stadium IV Parodontitis und pathologischer Zahnwanderung (PTM) mit insgesamt 526 intraossären Defekten wurden nach erfolgreicher antiinfektiöser Therapie (AIT) parodontalchirurgisch regenerativ mit DBBMc mit oder ohne CM oder EMD in einer parodontologischen Facharztpraxis therapiert. Bereits während Therapiestufe 1 und 2 wurde ein frühzeitiges kieferorthopädisches Konsil zur interdisziplinären Therapieplanung eingeholt. Drei Monate nach regenerativer Parodontalchirurgie wurde die kieferorthopädische Zahnbewegung mittels Multibandapparatur zur Einordnung der Zähne mit PTM begonnen. Patienten- und Defektcharakteristika sind der Tabelle 1 der zugrundeliegenden Publikation zu entnehmen. Die Veränderung des radiologischen Knochenniveaus (rBL) und der Sondierungstiefen (PPD) nach einem Jahr und nach bis zu vier Jahren wurden nachuntersucht. Ein Jahr nach regenerativer Therapie wurde ein mittlerer radiologischer signifikanter Knochengewinn (rBL change) von 4,67

± 2,5mm beobachtet, der auch bis zu vier Jahre postoperativ stabil blieb. Die Sondierungstiefen (PPD) wurden signifikant von 6,00 ± 2,09mm zu Beginn der Therapie auf 3,45 ± 1,2mm ein Jahr postoperativ reduziert. In 87% aller Defekte konnten pathologische Sondierungstiefen >4 mm (PPD) eliminiert werden. Rauchen und der FMPS zum Zeitpunkt ein Jahr nach regenerativer Parodontalchirurgie hatten statistisch signifikanten Einfluss auf die Ergebnisse. Einzelheiten der Ergebnisse sind in Tabelle 2, 3 und 4 der zugrunde liegenden Originalpublikation aufgeführt.

Schlussfolgerung

Das Hauptergebnis dieser Studie ist, dass die kombinierte regenerativ-parodontalchirurgische Therapie mit anschließender kieferorthopädischer Zahnbewegung bei Patienten mit Parodontitis Stadium IV und PTM zu deutlichen radiologischen Knochengewinnen und Taschenreduktionen führt. Das geringe Ausmaß an Zahnverlusten von 0.57% bei der großen Defektanzahl und Patientenkohorte belegt die Vorhersagbarkeit dieser kombinierten Therapie bei Parodontitis Stadium IV und PTM unter den Bedingungen einer spezialisierten Fachzahnarztpraxis.

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Regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis: A retrospective practice-based cohort study

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Abstract

Aim: Evaluation of the effectiveness of regenerative treatment of intra-bony defects in combination with consecutive orthodontic tooth movements in stage IV periodontitis.

Material and methods: A total of 526 intra-bony defects in 48 patients were analysed after regenerative therapy using collagen-deproteinized bovine bone mineral with or without collagen membrane or enamel matrix derivative followed by orthodontic tooth movement initiated 3 months after surgery. Changes in radiographic bone levels (BL) and probing pocket depths (PPD) were evaluated after 1 year and up to 4 years.

Results: Tooth loss amounted to 0.57%. Mean BL gain was 4.67 mm (±2.5 mm) after 1 year and 4.85 mm (±2.55 mm) after up to 4 years. Mean PPD was significantly reduced from 6.00 mm (±2.09 mm) at baseline to 3.45 mm (±1.2 mm) after 1 year, and to 3.12 mm (±1.36 mm) after 2–4 years. Pocket closure (PPD ≤4 mm) was accomplished in 87% of all defects. Adjunctive antibiotic therapy did not show any statistically significant impact on treatment outcomes.

Conclusions: Within the limits of this retrospective study design, the findings suggest that the combination of regenerative treatment and consecutive orthodontic tooth movements resulted in favourable results up to 4 years.

KEYWORDS
bone level, bovine bone mineral, collagen, enamel matrix derivative, membrane, orthodontic tooth movement, pathologic tooth migration, regenerative periodontal therapy

1 | INTRODUCTION

Stage IV periodontitis is characterized by severe periodontal attachment loss, vertical bone loss and pathologic tooth migration (PTM) (Brunsvold, 2005), requiring complex rehabilitation due to masticatory dysfunction, secondary occlusal trauma, bite collapse, and drifting and flaring of the remaining teeth (Papapanou et al. 2018; Tonetti & Sanz, 2019). Many patients affected by such a condition are interested in orthodontic treatment because of the aesthetic and functional changes caused by PTM, as shown by a recent survey (Hirschfeld et al. 2019). If the periodontal inflammation remains uncontrolled during the orthodontic treatment this will accelerate the progression of periodontal destruction leading to further loss of attachment (Wennström et al., 1993). An interdisciplinary approach is therefore required to control the periodontal infection, reconstruct the defects and realign the migrated teeth (Re et al. 2000; Gkantidis et al. 2010; Cardaropoli et al. 2014; Sanz & Martin, 2015).

It is well known that orthodontic treatment with fixed appliances has little to no clinically relevant effect on clinical attachment levels (periodontal conditions) in healthy adults or adolescents (Bollen et al. 2008; Papageorgiou et al., 2018). However, the interaction between orthodontic and periodontal treatment has been scarcely investigated in patients with periodontitis. Type of periodontal therapy, timing of orthodontic treatment following periodontal therapy and the impact of orthodontic tooth movement on periodontal conditions are poorly documented (Gorbunkova et al., 2016; Zasciurinskiene et al., 2016).

While the value of regenerative procedures in intra-bony defects in stage III periodontitis is well established (Cortellini & Tonetti, 2015; Bröseler et al. 2017; Nibali et al. 2019; Sanz et al. 2020), the literature remains unclear with regard to the best time point to initiate orthodontic therapy after regenerative surgery of migrated teeth with intra-bony defects—as typically present in stage VI periodontitis. It may be safe to wait until an endpoint of regenerative therapy has been reached (usually between 6 and 12 months) and not to interfere with early periodontal wound healing (Pini Prato & Chambrone, 2020). Indeed, several longer-term case series and reports with a follow-up of at least 3 years after regenerative surgery have shown favourable outcomes with such a delayed approach (Ghezzi et al. 2008; Jepsen et al. 2015; Roccuzzo et al. 2018; Aimetti et al. 2020). In contrast, other reports have suggested that orthodontic therapy may be initiated much earlier (either immediately up to 3 months after the regenerative procedure) (Cardaropoli et al. 2001; Cardaropoli et al. 2006; Ogihara & Wang, 2010; Attia et al., 2012; Ghezzi et al. 2013; Attia et al. 2019). The authors reported no adverse effects and speculated that early tooth movement could even stimulate periodontal wound healing. In the only available comparative study with 15 patients, Attia et al. (2012) observed more favourable regenerative outcomes following immediate orthodontic therapy compared to a delayed approach after 2 months.

Even though these data are encouraging and have the prospect to shorten the overall treatment time for the affected patients considerably, it has to be realized, that these reports are mainly case series with a short-term follow-up of ≤12 months involving a small number of patients and defects.

Therefore, it was the aim of the present retrospective analysis to evaluate periodontal treatment outcomes in a cohort of patients with a large number of intra-bony defects at migrated teeth, where orthodontic tooth movement had been initiated as early as 3 months after regenerative periodontal surgery with a follow-up of up to 4 years.

Clinical Relevance

Scientific rationale for study: While the value of regenerative periodontal treatment of vertical defects is well established, there are only few studies on the effectiveness of regenerative surgery followed by orthodontic therapy in patients with stage IV periodontitis.

Principal findings: In this retrospective cohort study, significant radiographic bone fill and pocket reduction could be obtained and maintained for up to 4 years.

Practical implications: In the setting of a specialized practice, even teeth severely compromised by vertical defects and pathologic tooth migration can be treated successfully and maintained for several years in compliant patients with adequate oral hygiene.

2 | MATERIAL AND METHODS

2.1 | Patients

A total of 52 patients who presented with severe periodontitis and pathologic tooth migration (Stage IV periodontitis according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, Papapanou et al. 2018) in a periodontal specialty practice (CT and FB) in Aachen, Germany were treated with comprehensive periodontal therapy including regenerative surgery and consecutive orthodontic tooth movement in the period of 2001 and 2010. Data from these patients were available for a retrospective analysis of the outcomes of this combined treatment.

The analysis was conducted in accordance with the Helsinki Declaration (version 2008) and the Ethical committee of the University of Bonn was notified. Patients gave their written informed consent for a retrospective evaluation of their clinical and radiographical data.

Inclusion criteria for the analysis were:

- one- or two-wall intra-bony defects with indication for periodontal regenerative therapy
- pathologic tooth migration due to loss of periodontal tissues
- orthodontic tooth movement starting 3 months after surgery
- clinical and radiographic data of a consecutive follow-up from at least 1 year after regenerative therapy

Exclusion criteria were as follows:

- non-compliance
- incomplete probing or radiographic data
- additional periodontal or maxillofacial treatment

Smokers and patients with systemic diseases (i.e. controlled diabetes) were not excluded.

Based on the criteria defined above, 48 patients with a total of 526 intra-bony defects and consecutive orthodontic tooth movement could be included in the analysis.

2.2 | Treatment

Prior to regenerative therapy patients underwent successful anti-infective therapy with oral hygiene instructions and scaling and root

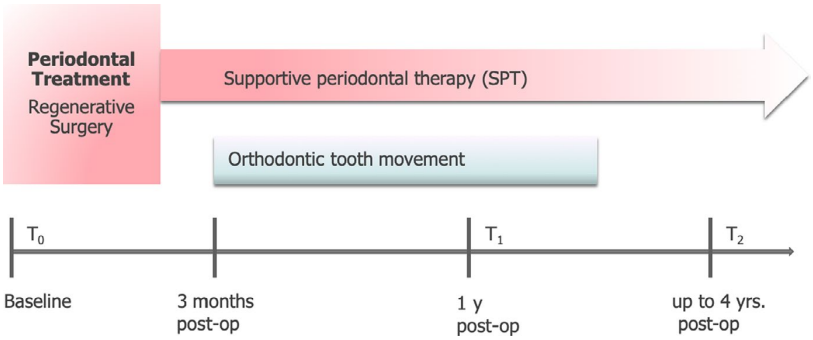

FIGURE 1 Chronical sequence of treatment and examinations (T0, T1, T2)

planing performed by a trained dental hygienist. In order to proceed with regenerative therapy, parameters after anti-infective therapy had to meet the following criteria: Plaque-Score and bleeding on probing (BOP) ≤15% and absence of suppuration. If the clinical parameters such as BOP did not improve despite good patient compliance subgingival plaque samples were taken for microbial analysis (micro-Ident®; Hain Diagnostics). In accordance with the levels of periodontopathogens (levels >10^4), 33 out of 48 patients underwent adjunctive systemic antibiotic therapy during regenerative therapy. A combination of amoxicillin and metronidazole served as a standard medication, while ciprofloxacin was administered in the case of penicillin allergy.

Within the context of anti-infective therapy, interdisciplinary orthodontic counselling prior to surgery was performed. Teeth with mobility grade >1 (O'Leary, 1969) were temporarily splinted by removable acrylic splints, semi-permanent lingual retainers or long-term provisionals to provide best stabilization of the clot and graft during and after the regenerative surgical procedure.

In case of advanced tooth mobility (> grade II) of multiple adjacent teeth, orthodontic appliances were inserted prior to surgery and served as a stabilization splint during and after surgery.

Regenerative surgical procedures and post-operative care have been previously described (Bröseler et al. 2017). In brief, surgery was performed by one of two experienced periodontists (CT and FB). Under local anaesthesia, access to the defect was achieved by intra-sulcular incisions with a microsurgical blade (SM 69, Swann Morton Ltd.), release of the flap and apical split-flap preparation was performed always under the premises maintaining best gingival thickness and blood supply of the flap. Therefore, flap design was rather extended to the adjacent teeth for tension-free flap closure to avoid vertical releasing incisions compromising blood supply of the flap. After releasing the flap, granulation tissue was removed by hand instruments and rotating instruments. After debridement with curettes, ultrasonic device (Cavitron/Slimline; DENTSPLY) and rotating instruments (Desmo-Clean®; Komet or Intensiv Finishing Diamond #4310S; Perio Set®; Intensiv SA) the intra-bony defects were filled with collagen-added deproteinized bovine bone mineral (DBBMc, Bio Oss® Collagen; Geistlich). If the graft material was at risk for dislocation in non-contained defects, a collagen membrane (Bio Gide® Perio; Geistlich) was applied without pin or suture fixation.

If the flap did not need any further support by a graft or to enhance early epithelial wound healing in compromised soft tissue quality and to avoid shrinkage of the soft tissues for aesthetics in anterior regions enamel matrix derivate (EMD, Emdogain®; Straumann) was applied as an adjunct to the root surface after debridement. The flap was coronally positioned without tension and sutured with modified horizontal mattress sutures and additional single interrupted sutures for papilla adaptation (6–0 Monofilament single sutures Premilene® USP6/0-DS13, B. Braun; Seralene® USP6/0-DS12 SeragWiessner; Seralene®USP6/0-DS15; SeragWiessner).

Postoperatively, patients were advised to rinse with 0.2% chlorhexidine solution three times a day for 2 weeks or until complete wound healing. To avoid mechanical stress to the flap and the graft patients had to refrain from mechanical tooth cleaning in the surgically treated regions until soft tissues were re-keratinized. Sutures were removed after 10–14 days, depending on individual wound healing progression.

Orthodontic tooth movements were initiated three months after periodontal regenerative surgery, using fixed orthodontic appliances (straight-wire-technique) performed by one and the same orthodontist. In only two patients, orthodontic tooth movement was accomplished with aligner technology (Invisalign®; Align Technology Inc.) by a second orthodontist. Duration of orthodontic therapy depended on the amount of treatment needs of the patient and varied from 9 to 28 months with a mean range of 18 months.

Postoperatively, patients were followed in a tight recall interval beginning with 4 weeks up to 3 months during orthodontic tooth movements according to the practice standard protocol. Control of inflammation during orthodontic tooth movement was achieved by cautious professional tooth cleaning and hygiene reinforcement according to the individual patient needs; particular emphasis was given to teeth undergoing orthodontic intrusion movements. After completion of orthodontic tooth movements supportive care was rendered according to the individual patient's need with a recall interval of three times a year during the longest observation period of 4 years (Figure 1).

2.3 | Clinical and radiographic measurements

Preoperatively, clinical periodontal parameters, including probing pocket depth (PPD) at four sites per tooth, were measured and a full set of periapical radiographs were taken. Intra-operatively, the bone level (BL) was measured as the distance between the cemento-enamel junction and the deepest point of the intra-bony defect using a periodontal probe (PCP11; Hu-Friedy) parallel to the long axis of the tooth. If the cemento-enamel junction could not be defined due to restorations, the margin of the restoration served as reference point.

Intra-operative BL was applied for calibration of the pre-operative periapical radiograph, as previously described (Bröseler et al. 2017). In brief, radiographs were taken by a long-cone parallel technique using film holders (HAWE Super-bite Senso; Kerr GmbH) to allow for parallel orientation (3 × 4 cm single tooth F-speed films; Kodak, using Dürr Periomat plus or Dürr XR24 developing machine; Dürr Dental AG, Bietigheim-Bissingen). After digitizing the radiographs (Digital Camera Casio EX-Z40, Casio Computer Co., LTD Tokyo, Japan) calibration was performed (ImageJ Software Version 1.43 u, National Institutes of Health). To obtain the reference distance, the clinically determined BL was marked on the pre-operative radiograph. For calibration and to allow comparison with subsequent radiographs, the overall tooth length was used.

All radiographs were analysed by a trained and calibrated examiner who was not involved in the surgeries.

One year after surgery, complete clinical and radiographic data were obtained. PPD was recorded every year during regular maintenance, radiographic BL after 1 year and 2–4 years postoperatively (Figure 1):

T_0– time of regenerative surgery (baseline).

T_1–1 year post-op.

T_2–mid-term follow-up (2–4 years).

For T_2 the data measured at the latest point of follow-up within this time frame was chosen for each patient. Means for T_2 were 3.05 ± 0.88 years for BL, and 3.04 ± 0.87 years for PPD.

2.4 | Statistical analysis

The statistical analysis was performed using R version 2.13.0 (The R Foundation for Statistical Computing). Change of radiographic bone level (BL) was the primary outcome parameter, whereas change in PPD served as secondary outcome. Data were evaluated for all regeneratively treated teeth as well as per patient (means). For teeth with all three observation time points present, the change over time was analysed on tooth and patient level. In addition, change over time was evaluated for the most severe defect per patient.

Numeric variables such as certain patient characteristics and endpoints (radiographic bone level, PPD and their changes over time) are summarized by means and standard deviations. Categorical information is presented by providing absolute and/or relative counts. If not clear from the context, in the text it is mentioned whether these numbers relate to patients or defects as observational units.

To test for gains in radiographic bone level over time, a version of Wilcoxon's signed-rank test for clustered data (Rosner et al., 2006) was applied to account for intra-patient correlations. All *p*-values belong to two-tailed tests and are of purely exploratory nature. The level of significance of each test was set to 0.05.

Inductive statistical analysis of p-values concerning the influence of the confounder 'adjunct antibiotics on radiographic bone level and PPD' was performed by the use of a version of Wilcoxon's signed-rank test for clustered data (Rosner et al., 2006) and ANOVA test.

Defects were classified based on their baseline morphology determined during surgery as one- and two-wall defects and (measured by clinical probing from BL to CEJ) as shallow (≤ 6 mm), moderate (>6 mm and <11 mm) and deep (≥ 11 mm). In additional subgroup analyses, the radiographic bone level changes with and without adjunctive antibiotic treatment were compared to each other.

A multilevel analysis was conducted to explore the effect of explanatory variables "smoking," "full mouth bleeding scores and plaques scores at T1," "treatment modality," "radiographic bone level at baseline (T0)" and "antibiotic treatment" on the change in radiographic bone level from T0 to T1. Linear mixed models were run with patient as random intercept to account for the correlation within patient. To compare models, *p*-values from an *F*-test with the Satterthwaite method (Fai & Cornelius, 1996) were compared against 0.05. To assess the explanatory power of a model also the conditional and marginal R2 as developed by Nakagawa et al. (2017) were computed. The marginal R2 gives the proportion of variance explained by the fixed effects only, the conditional R2 gives the proportion of variance explained by fixed and random effects. Starting from the minimal model with radiographic bone level at T0 as only fixed effect, first models were run with only one more fixed effect included. Variables were only retained when significant and an interaction term was only tested if the main effect was significant. Then, only variables were added if they showed a significant improvement of the model.

3 | RESULTS

3.1 | Patient and defect characteristics

Of the 52 patients treated, 4 patients (with 28 defects) were excluded from the retrospective analysis because of missing follow-up data due to non-compliance.

Compliance was defined as previously described (Franke et al. 2015):

C0: Patients who failed to attend more than two scheduled appointments within the first 2 years of SPT or did not comply with Supportive periodontal therapy (SPT) appointments for more than

2 years during follow-up period were classified as non-compliant. These patients were not included into the study.

C1: patients who complied to SPT as scheduled at any time during the observation period.

C2: patients who missed at least one appointment in at least 1 year of ongoing SPT, but were not more than 1 year without SPT.

Due to the complex multidisciplinary treatment—regenerative periodontal therapy and orthodontic tooth movement—only patients showing full compliance (C1) attending SPT as scheduled at any time during the observation period were included into the analysis. This applied to 48 patients with a total of 526 intra-bony defects.

The number of defects per patient ranged from 2 to 14 defects with an average of 10.96. Overall, 38.2% were one-wall defects while 61.8% were two-wall defects. At baseline, mean radiographic BL was 8.31 ± 1.51 mm (4.00–12.14 mm). Complete data for the longest observation time (T_2) 2–4 were available for 27 patients with 214 defects. An overview on patient and defect characteristics is presented in Table 1.

DBBMc alone was used in 23.6% of the defects (15.42% for one-wall defects/28.62% for two-wall defects), whereas in 27.8% of the defects DBBMc + CM was applied (30.35% for one-wall defects/26.15% for two-wall defects), DBBMc + EMD was used in 20.3% of the defects (22.89 for one-wall defects/18.77% for two-wall defects), and DBBMc + CM + EMD in 17.3% of defects (23.3% for one-wall defects/13.54% for two-wall defects). EMD alone was applied in 11% of the defects (7.96% for one-wall defects/12.92% for two-wall defects).

3.2 | Post-operative findings

A representative example of a treated patient included in the present analysis is illustrated in Figure 2. Soft tissue healing was generally uneventful. There were no allergic reactions, suppuration or abscesses. Minor complications such as post-operative swelling and pain in the surgically treated area disappeared within a few days after surgery. If membrane exposures occurred (3% of the treated sites), membranes were left in place and infection managed by reinforcement of post-operative care and chemical plaque control (0.2% chlorhexidine mouth rinse, 3 times per day). These sites healed with no further complications by intensive clinical care.

TABLE 1 Patient and defect characteristics at baseline (T0)

N patients	48
Female gender	60.4%
Mean age (range)	45.3 (29–66) years
Smokers	12.5% of patients (with 13.3% of defects)
N defects	526
Single-rooted teeth	342/65.02%
Multi-rooted teeth	184/34.98%
Defect “shallow” ≤6 mm	104/19.8%
Defect “moderate” >6 mm <11 mm	321/61%
Defect “deep” >11 mm	101/19.2%
Mean bone level “shallow”	5.38 ± 0.73 mm
Mean bone level “moderate”	8.14 ± 1.03 mm
Mean bone level “deep”	12.73 ± 2.26 mm
Mean bone level all	8.31 ± 1.51 mm

Tooth loss amounted to 0.57% (3 molars in 3 patients) and was due to furcation caries (100%) after completion of orthodontic therapy.

Radiographic bone levels could be evaluated in 48 patients with 526 teeth at baseline and after 1 year $_{(t1),}$ and in 27 patients with 214 defects at $_{t2}$ (after 3.05 + 0.88 years).

Analysis of change in radiographic BL over time in these 214 defects, where data for all time points were available revealed a significant gain in radiographic bone level after 1 year from 8.40 + 2.72 mm to 3.73 ± 2.08 mm with further gain from $_{t1}$ to $_{t2}$ with 3.55 ± 1.8 mm (Table 2, Figure 3a). Similar changes were observed when data were analysed on the patient level. Even more pronounced radiographic bone level gain was obtained when the deepest defects per patient were included in the analysis (Figure 3b,c, Table 2).

Radiographic bone level changes in different subgroups are displayed in Figure 3d,f. Adjunctive systemic antibiotic administration did not show any statistically significant impact (Figure 3d,e), and different treatment modalities led to similar bone level changes over time (Figure 3f).

The multilevel analysis revealed that only smoking (p = 0.023) and full mouth plaque scores at T1 (p = 0.047) were significant when added as single variables to the minimal model, in particular, in interaction with the radiographic bone level at T0 (p < 0.001 in both cases). Adding any other variables to the model did not show any significant improvement. When both variables were combined in one model they became both non-significant probably due to their strong correlation. Smoking was chosen over plaque at T1 in the final model due to its better explanatory power. The results of the final model are displayed in Table 3. The greater the distance between the CEJ and the deepest point of the intra-bony defect (BL) at baseline the greater was the change of BL from T0 to T1 (p < 0.0001). However, this was less the case in smokers. Especially in smokers with a greater BL at T0 this change in BL was significantly less (p < 0.001).

Mean PPD as documented in 300 defects for all time points improved from 6.00 mm (±2.09 mm) at baseline to 3.45 mm (±1.20 mm) after 1 year and was further reduced to 3.12 mm (±1.36 mm) after 2–4 years. The frequency distribution of residual probing pocket depths for the subsample of patients who attended all visits from baseline to t_2 is presented in Table 4. The frequency of sites with PPD ≤4 mm improved from 27% at baseline to 84% at t_1 and remained stable with 87% at t_2.

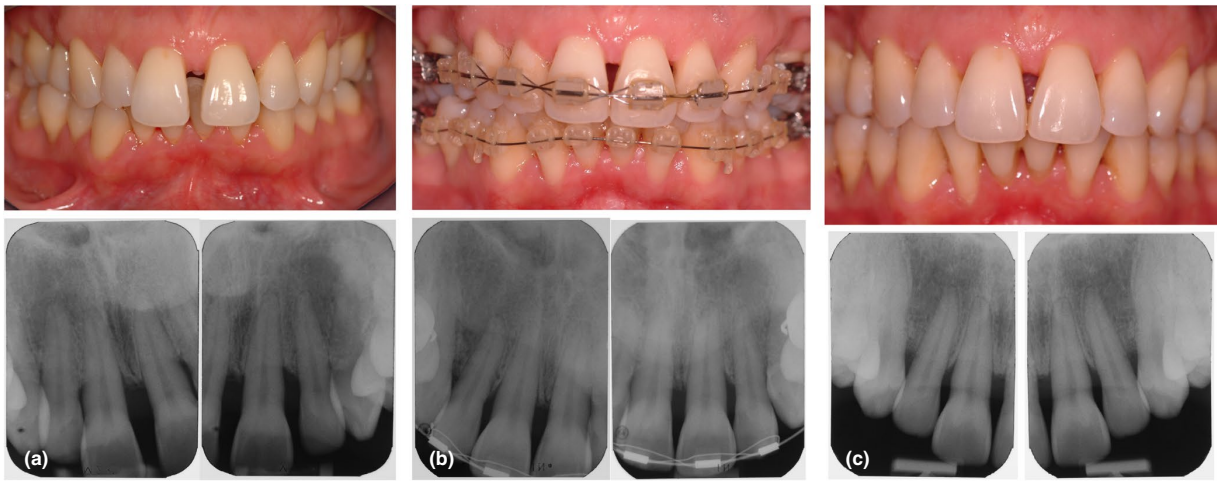

FIGURE 2 (a) Clinical and radiographical situation after initial therapy. (b) Clinical and radiographical situation 1 year after regenerative therapy. (c) Clinical and radiographical situation 4 years after regenerative therapy

TABLE 2 Mean radiographic bone level (BL) ± standard deviation (mm) over time calculated for patients and teeth with different length of follow-up

	Baseline	t_1	t_2
BL per teeth (n = 526)	8.52 ± 2.59	3.98 ± 2.09	n.a.
BL per patient (n = 48)	8.31 ± 1.51	3.89 ± 1.26	n.a.
BL in deepest defect per patient (n = 48)	12.10 ± 3.30	5.62 ± 2.74	n.a.
BL per teeth (n = 214)	8.40 ± 2.72	3.73 ± 2.08 $p < 0.000001^{*}$	3.55 ± 1.80 $p = 0.28631^{**}$
BL per patient (n = 27)	8.48 ± 1.00	3.65 ± 1.27 $p < 0.000001^{*}$	3.44 ± 1.13 $p = 0.47105^{**}$
BL deepest defect per patient (n = 27)	12.67 ± 3.00	5.25 ± 2.63 $p < 0.000001^{*}$	4.65 ± 1.78 $p = 0.24712^{**}$

Note: Means for t_2 (2–4 years) were 3.05 ± 0.88 years. Analyses on the level of teeth, patient and deepest defect per patient.

*p-Values for comparison baseline versus T1.

**p-Values for comparison T1 versus T2.

4 | DISCUSSION

The results of this study demonstrate favourable outcomes following a combined regenerative and orthodontic treatment in patients with stage IV periodontitis that could be maintained for up to 4 years. Treatment with deproteinized bovine bone mineral with collagen alone or in combination with a collagen membrane or EMD resulted in significant radiographic bone level gain and probing pocket reduction in a large number of teeth severely compromised by intra-bony defects and pathologic tooth migration. Pocket closure was accomplished in the vast majority of sites. The results indicate that in the setting of a specialized practice patients with stage IV periodontitis in need of orthodontic therapy can be treated successfully and maintained for several years with good prognosis if compliant with SPT and adequate oral hygiene. Orthodontic tooth movement as early as 3 months after regenerative surgical therapy did not appear to have a negative impact on treatment outcomes. Based on these data, the treatment approach can be considered to be effective, shortening the overall treatment time for the patients considerably.

The study question is of great relevance as available information on the treatment of stage IV periodontitis in need of orthodontic therapy is still rather limited. The study analysed the outcomes of regenerative therapy with subsequent orthodontic tooth movement in a total of 48 patients with 526 teeth over an observation period of up to 4 years and is to the best of our knowledge, the report including the largest number of patients and defects on this combined treatment approach that has been published so far. This comparatively high number of participants and defects, the long observation time, the fact that all patients were treated by the same two experienced surgeons and that radiographs were evaluated by the same blinded examiner are certainly strengths of the study. The setting of a private practice can be considered as an advantage for the generalizability of the

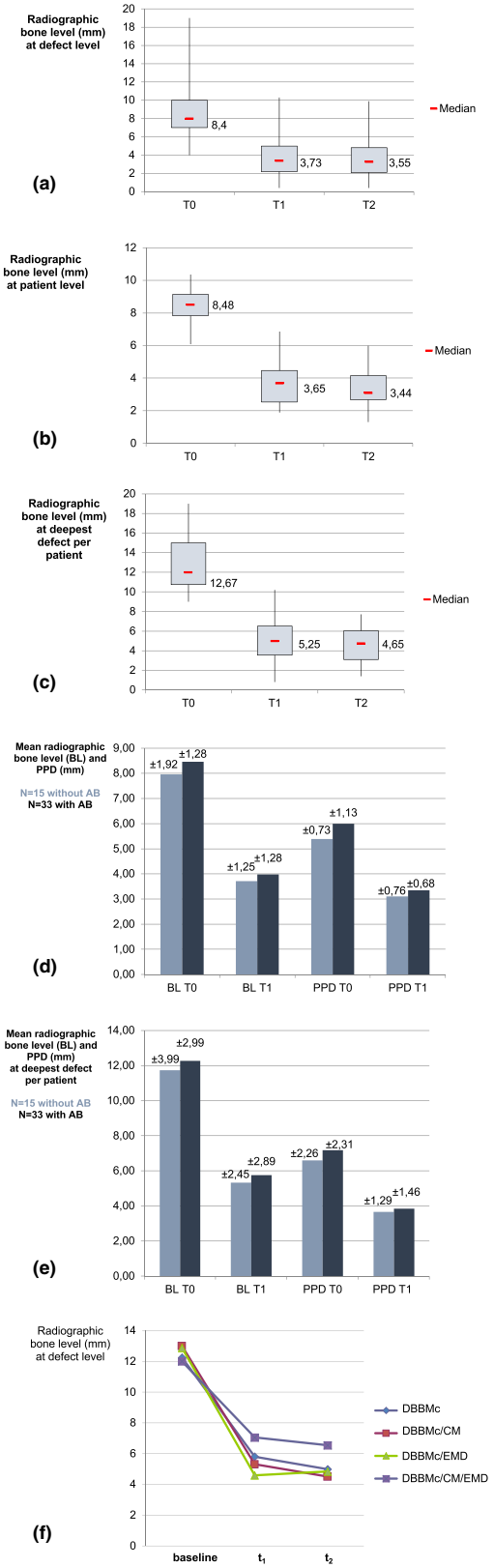

FIGURE 3 Changes in radiographic bone level over time (mean ± SD): (a) at defect level n = 214, (b) at patient level, (c) at deepest defect per patient n = 24, (d) and (e) with or without adjunctive antibiotic treatment, (f) for different treatment modalities

results. Furthermore, the study was conducted independently and not funded by industry. However, the study design has also some inherent limitations, in particular, the retrospective nature and the lack of a comparison group. Thus, the study has to be considered as an extensive feasibility study that may be of great value for the planning of future carefully controlled well designed prospective randomized trials.

The results of the present study cannot be easily compared to previously published studies because of differences in study protocols with regard to regenerative procedures, choice of biomaterials, selection of outcome measures, time points of initiation of orthodontic therapy and lengths of follow-up.

Nevertheless, the mean radiographic bone level gain of 4.6 mm after one year observed in our study compares favourably with reported bone gains in previously published case series, ranging from 1.3 to 4.4 mm (Corrente et al. 2003; Cardaropoli et al. 2006; Ogihara & Wang, 2010; Attia et al. 2012; Ghezzi et al. 2013; Attia et al. 2019). The mean PPD reduction of 2.9 mm for the 300 defects monitored for up to 4 years in the present study is comparable to the 3.2 mm in a 10-year follow-up of 36 defects by Roccuzzo et al. (2018). Higher

TABLE 3 Final model for the change of radiographic bone level from T0 to T1

Fixed effects	Estimate (SE)	p
(Intercept)	**−0.77 (0.30)**	**<0.05**
BL at T0	0.64 (0.03)	<0.0001
Smoking	1.65 (0.86)	0.057
BL at T0 + smoking	−0.29 (0.08)	<0.001
Random effects		
Patient standard deviation	0.88	

TABLE 4 Frequency distribution of residual PPD for the subsample of patients who attended all visits from baseline to t_2, N = 300

PPD (mm)	Baseline	t_1	t_2
≤4	82	252	262
5	28	27	18
6	70	15	15
7	42	3	1
8	50	3	4
9	11	0	0
10	10	0	0
11	7	0	0

values for mean PPD reduction ranging from 3.7 to 4.4 mm, however, were reported in studies with immediate application of orthodontic forces (Attia et al. 2012; Ghezzi et al., 2013; Attia et al. 2019). The frequency of pocket probing depths >4 mm in or study was reduced from 73% at baseline to 16% at t_1 and remained stable with 13% at t_2. These values are in agreement with a reported frequency of 17% of residual PPD >4 mm after 10 years by Rocuzzo et al. (2018). Tooth loss of regeneratively treated teeth in the present study was 0.5% due to furcation caries and occurred after completion of orthodontic therapy. Long-term studies on a combined regenerative-orthodontic therapy (Roccuzzo et al. 2018; Aimetti et al. 2020) showed no tooth loss due to periodontal reasons after successful completion of periodontal therapy. Tooth loss in these studies amounted to 2.7% and 1.5%, respectively, and was due to root fracture.

It was of particular interest to compare the results of the present analysis with data obtained from another cohort of patients that were treated in the same practice with the same protocol, including surgical procedure, outcome measures and follow-up, but with no need for orthodontic tooth movement (Bröseler et al. 2017). Within all limitations of such an indirect comparison using a "historical control group," it was striking to observe that the improvements with regard to bone level gain and PPD reduction in the present study with combined perio-ortho therapy were even higher than in the previous study, where patients did not undergo orthodontic therapy. Mean bone level gain after 1 and 2–4 years amounted to 4.6 mm and 4.8 mm per tooth, respectively, in the present study and 3.9 mm and 4.1 mm per tooth in our previous report (Bröseler et al. 2017). Corresponding values for PPD gain were 2.5 after one year and 2.8 mm after 2–4 years, respectively, in the present study and 2.4 mm in our previous report. It has to be emphasized that baseline characteristics of the treated defects with regard to mean bone level and PPD were similar in both cohorts. These findings seem to indicate a possible "stimulating" effect of orthodontic tooth movement in the early healing phase on the regenerative outcomes, as previously suggested (Vardimon et al. 2001; Diedrich et al. 2003; Nemcovsky et al. 2004). However, as stated above this observation should be interpreted with great caution. Well-controlled preclinical experiments would be needed to elucidate the effects of mechanical loading on the early and late healing events after regenerative procedures.

Moreover, another source of possible bias inherent to orthodontic studies could have been introduced by the possibility of orthodontically induced root resorption. This aspect has been rarely addressed when interpreting results of perio-orthodontic studies, even though it will impact on radiographic as well as on clinical measures for the assessment of regenerative periodontal outcomes. There is only limited data available on root resorption following orthodontic treatment of periodontitis patients. Melsen et al. (1989) found 1 to 3 mm of root resorption in treated incisors, whereas Corrente et al. (2003) reported no resorption of the orthodontically intruded teeth. Orthodontic treatment in patients with periodontal disease resulted in external apical root resorption on an average of 81% of all single-rooted teeth treated. In 82.3% of them, resorption was 2 mm or less. Severe root resorption (more than 4 mm) was found in 8% of patients (Zasčiurinskienė et al. 2019a,b).

The radiographic evaluation performed in this study had to rely on radiographs that were obtained in a standardized fashion using a long-cone paralleling technique; however, no customized film holders were used to permit an even higher reproducibility. Measurement errors may exist due to the fact that no customized film holder stents were used; however, we compensated for the possible distortion between sets of radiographs by calculating the ratios of root length from baseline and follow-up radiographs. This ratio was used to correct posttreatment linear measurements of bone changes (Tonetti et al., 1993). Still, the amount of orthodontically induced root resorption—if present—could not be assessed. Thus, assuming in a worst-case-scenario 2.0 mm of root resorption of the teeth treated in the present study, the impact on the radiographic bone level gain that we have calculated would have been an underestimation of gain in the magnitude of approximately 10 per cent. Therefore, we are confident that any possible root resorption has not introduced a major bias into our analysis.

Nevertheless, these challenges in the selection and interpretation of outcome data in perio-ortho studies need to be addressed in future studies.

A radio-opaque bone filler was used which does not allow to distinguish graft from newly regenerated bone. However, based on human histological studies, it can be presumed that the applied biomaterials can promote periodontal regeneration (Sculean et al., 2015). There was obviously no obstruction of tooth movements into sites previously regeneratively treated with non-autogenous bone as already shown histologically (Araujo et al. 2001) and clinically (Corrente et al. 2003; Cardaropoli et al. 2006; Roccuzzo et al. 2018).

The results of the present study also indicated that adjunctive systemic antibiotic administration did not yield superior outcomes in radiographic and clinical findings. Even though this exploratory sub-analysis has to be viewed with caution, this observation is in line with previous RCTs evaluating the possible effect of adjunctive systemic antibiotics on outcomes of regenerative surgery (Sculean et al., 2001; Röllke et al. 2012). Recently published periodontal treatment guidelines for stage III periodontitis call for a prudent and restrictive usage of systemic antibiotics in the context of antibiotic stewardship and the rising problem of antibiotic resistance, however, acknowledge their possible benefit for special patient categories (Sanz et al. 2020; Teughels et al. 2020). Thus, future randomized trials will have to clarify, whether adjunctive antibiotics will be indicated for stage IV periodontitis patients in need of a combined perio-regenerative-ortho therapy.

According to a recently published commentary, the lack of an accurate "gold standard," a research-based moment for initiating orthodontic tooth movement after periodontal therapy, demonstrates that a "grey zone" of evidence remains and knowledge on

periodontal wound healing dynamics may be considered the best "biologic starting point" of orthodontic treatment for treated periodontitis patients (Pini Prato & Chambrone, 2020). The authors proposed a personalized periodontal algorithm and postulated that orthodontic therapy should be initiated 1 year after regenerative treatment. The findings of the present study indicate the feasibility of initiating orthodontic therapy much earlier with the prospect of a shortened overall treatment time for the patient.

In conclusion, within the given limitations of a retrospective study design, the combination of regenerative surgery and consecutive orthodontic tooth movement resulted in favourable results up to 4 years. The results of this large feasibility study suggest that orthodontic tooth movements as early as 3 months after regenerative therapy of intra-bony defects had no negative effect on radiographic bone level gains and probing pocket reductions. Prospective well planned randomized controlled clinical trials that also include patient-related and orthodontic outcome measures are needed to define the most suitable protocol for the combined regenerative and orthodontic treatment of patients with Stage IV periodontitis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest with regard to this study.

AUTHOR CONTRIBUTIONS

C. Tietmann conceived the idea for the study, performed the surgeries, collection and analysis of data, interpretation of the results and manuscript writing. F. Bröseler contributed with surgeries and interpretation of the results. T. Axelrad contributed to examinations and data collection. K. Jepsen contributed by critical reading of the manuscript. S. Jepsen contributed with supervision of the study, statistical analysis and interpretation of the results and writing/revising of the manuscript.

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki (version 2008). The Ethical committee of the University of Bonn was notified.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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3.2 Tietmann C, Jepsen S, Heibrok H, Wenzel S, Jepsen K. Long-term stability of regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis: 10-year data of a retrospective study. J Periodontol 2023;94:1176-1186. doi: 10.1002/JPER.23-0081.

Zielsetzung der Arbeit

Nachdem in der vorherigen Arbeit (*Tietmann et al., 2021*) gezeigt wurde, dass die kombinierte regenerativ-parodontalchirurgische Therapie intraossärer Defekte mit anschließender kieferorthopädischer Zahnbewegung durch Multibandapparatur bei Patienten mit Stadium IV Parodontitis und PTM zu einem deutlichen radiologischen Knochengewinn und Reduktion der PPD führt, sollte in einer Follow-up-Studie untersucht werden, ob die Wirksamkeit dieser Therapie auch zu langzeitstabilen Ergebnissen nach 10 Jahren führt.

Methoden und Ergebnisse

Von ehemals 48 Patienten aus der Studie *Tietmann et al. (2021)* konnten nach 10 Jahren noch 22 Patienten mit insgesamt 256 intraossären Defekten nach regenerativer Therapie mit anschließender kieferorthopädischer Zahnbewegung nachuntersucht werden. Die Patienten hatten sowohl während als auch nach Abschluss der kombinierten Therapie eine engmaschige, auf den einzelnen Patienten abgestimmte UPT erhalten. Das radiologische Knochenniveau (rBL) und Sondierungstiefen (PPD) wurden ein Jahr nach regenerativer Therapie, nach Abschluss der kieferorthopädischen Therapie (FSPL) und 10 Jahre nach regenerativer Therapie erhoben.

Der mittlere Gewinn an radiologischem Knochenniveau (rBL) nach 1 Jahr postoperativ war signifikant mit 4,63 $\pm$ 2,43mm und zeigte auch nach Abschluss der kieferorthopädischen Therapie (FSPL) und nach 10 Jahren mit 4,48 $\pm$ 2,62mm langzeitstabile Ergebnisse. In 90% aller Defekte konnten PPD $\leq$4mm nach 10 Jahren erzielt werden. Nach 10 Jahren war nur ein geringer Zahnverlust von 4,5 % zu beobachten, der nicht durch parodontale, sondern endodontische Komplikationen bedingt war. Einzelheiten der Patienten- und

Defektcharakteristika sowie Ergebnisse sind den Tabellen 1, 2 sowie Abbildung 4 der zugrunde liegenden Originalpublikation zu entnehmen.

Schlussfolgerung

Diese Arbeit zeigt, dass die kombinierte regenerativ-parodontalchirurgische Therapie mit anschließender kieferorthopädischer Zahnbewegung bei Patienten mit Parodontitis Stadium IV und PTM auch langfristig zu deutlichen radiologischen Knochengewinnen, Taschenreduktionen und Zahnerhalt führt. Voraussetzung für die Langzeitstabilität der Ergebnisse ist die langfristige und regelmäßige Teilnahme der Patienten an einer individualisierten UPT.

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ORIGINAL ARTICLE

Long-term stability of regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis: 10-year data of a retrospective study

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Abstract

Background: This study aimed to evaluate the long-term effectiveness of regenerative treatment of intra-bony defects in combination with consecutive orthodontic therapy (OT) in stage IV periodontitis.

Methods: Twenty-two patients with a total of 256 intra-bony defects were analyzed after regenerative surgery followed by OT initiated 3 months later. Changes in radiographic bone level (rBL) and probing pocket depths (PPD) were evaluated after 1 year (T1), final splinting (T2), and 10 years (T10).

Results: Mean rBL gain was significant with 4.63 mm (±2.43 mm) after 1 year (T1), 4.19 mm (±2.61 mm) at final splinting (T2), and 4.48 mm (±2.62 mm) after 10 years (T10). Mean PPD was significantly reduced from 5.84 mm (±2.05 mm) at baseline to 3.19 mm (±1.23 mm) at T1, to 3.07 mm (±1.23 mm) at T2, and to 2.93 mm (±1.24 mm) at T10. Pocket closure (PPD ≤ 4 mm) was achieved in 90% of all defects. Tooth loss amounted to 4.5%.

Conclusions: Within the limitations of this retrospective study design, these 10-year findings suggest that in motivated and compliant patients with stage IV periodontitis and in need of OT an inter-disciplinary treatment can lead to favorable and stable long-term results.

KEYWORDS

bovine bone mineral, long-term, orthodontic tooth movement, pathologic tooth migration, regenerative periodontal therapy, stage IV periodontitis

1 | INTRODUCTION

Stage IV periodontitis is characterized by similar severity and complexity as stage III periodontitis in terms of attachment loss, vertical bone loss, and periodontal inflammation. However, adding to the severity and complexity in stage IV periodontitis the presence of pathologic tooth migration (PTM)[1] with drifting and flaring of the remaining teeth, hypermobility and secondary occlusal trauma, bite collapse, and masticatory

dysfunction requires a complex rehabilitation.[2] Patients affected by such a condition are interested to seek orthodontic treatment because of the functional and esthetic changes caused by PTM.[3] An interdisciplinary approach of comprehensive periodontal and orthodontic therapy (OT) is needed to control periodontal infection, reconstruct the defects, and realign the migrated teeth in order to regain and stabilize function and esthetics for the patients.[4,5]

OT with fixed appliances does not seem to have clinically adverse effects on clinical attachment levels in healthy patients or in successfully treated periodontitis patients.[6–8] However, only limited data exist on the combined treatment of periodontal therapy and OT in patients with stage IV periodontitis.[9,10]

The recently published EFP S3 level clinical practical guideline (CPG) for the treatment of stage IV periodontitis[11] gives guidance for these complex interdisciplinary therapies based on explicitly commissioned reviews with regard to quality and strength of evidence. In a structured consensus process a concise treatment algorithm and specific evidence-based and expert-based recommendations were adopted for the interdisciplinary treatment for patients in need of OT diagnosed with stage IV periodontitis (case type 2). As emphasized in the EFP S3 CPG tooth retention should be considered first in the long-term management of stage IV periodontitis. Accordingly, given the value of regenerative procedures in intra-bony defects,[12–17] the EFP S3 CPG recommends the combination of regenerative therapy and consecutive OT in patients with stage IV periodontitis presenting with intra-bony defects and in need of OT.[11] Concerning the timing of OT following periodontal regenerative therapy – based on two recent clinical studies [18,19] – the EFP S3 CPG recommends a time interval between 4 weeks and 6 months.[11]

However, there is still only limited data on the long-term outcomes of such a combined therapy.[20,21] In these two studies, OT was initiated much later (12 months after surgery) and they either reported on a small number of regeneratively treated defects[20] or did not distinguish in their outcomes between defects treated either in a resective or regenerative way before consecutive OT.[21] Thus, although both studies presented encouraging long-term results the effect of a combined regenerative-orthodontic treatment approach in line with the current recommendations cannot be fully appreciated.

Therefore, the aim of this retrospective analysis was to evaluate the long-term effectiveness and stability after 10 years of regenerative treatment of a large number of intra-bony defects at migrated teeth in combination with early consecutive OT in stage IV periodontitis.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This retrospective analysis included data from a 10-year follow-up of patients presenting with severe periodontitis and PTM (stage IV periodontitis).[2] All of them had been treated by an interdisciplinary approach in a periodontal specialty practice (C.T.) in Aachen, Germany. The interdisciplinary treatment consisted of a comprehensive periodontal therapy including regenerative periodontal surgery and consecutive orthodontic tooth movement in the period of 2001 and 2010 as previously reported for 27 patients after 2–4 years.[18] Twenty-two patients were still available 10 years after regenerative surgery, while 5 patients were lost to follow-up because they had either moved, had returned to their referring dentist, or had died.

The study was conducted in accordance with the Helsinki Declaration (version 2008) and approved by the Ethics committee of the University of Bonn (#16/23). Patients had given their written informed consent for a retrospective evaluation of their clinical and radiographical data.

Inclusion criteria for the analysis were:

- Successful steps 1 and 2 of periodontal therapy: adequate oral hygiene and control of inflammation: full-mouth plaque score (FMPS) of ≤15% and full-mouth bleeding score (FMBS) of ≤15%
- one- or two-wall intra-bony defects with indication for periodontal regenerative therapy
- PTM due to destruction of periodontal tissues
- orthodontic tooth movement starting 3 months after surgery
- clinical and radiographic data of a continuous follow-up for 10 years after regenerative surgery.

Exclusion criteria were:

- non-compliance to maintenance protocol
- incomplete probing or radiographic data
- additional periodontal or maxillofacial treatment in the areas of interest.

Patients with systemic diseases (i.e., controlled diabetes) and smokers were not excluded.

Based on these criteria, 22 patients with a total of 256 regeneratively treated intra-bony defects and consecutive orthodontic tooth movement were included in the analysis.

2.2 | Treatment

2.2.1 | Regenerative periodontal surgery

Regenerative surgery of teeth with intra-bony defects was performed by one single experienced periodontist (C.T.) after successful anti-infective therapy and orthodontic consultation in the period of 2001–2010. Surgical regenerative procedures were performed under local anesthesia as previously described,[13,18] vertical releasing incisions were avoided by extending flap design to adjacent teeth, apical split flap preparation was only performed if needed for primary tension-free flap closure. After debridement of the defect the biomaterial was chosen depending on the configuration of the intra-bony defect. To prevent a soft-tissue collapse into the defect a bone filler was used (DBBMc, Bio Oss Collagen; Geistlich, Wolhusen, Switzerland). If the graft material was at risk for dislocation in non-contained defects, a collagen membrane (Bio GidePerio; Geistlich, Wolhusen, Switzerland) was applied without pin or suture fixation. Enamel matrix derivative (EMD, Emdogain; Straumann, Basel, Switzerland) was applied in contained defects to enhance periodontal wound healing. Primary tension-free closure of the coronally positioned flap was achieved by modified horizontal mattress sutures and additional single interrupted sutures for papilla adaptation (6-0 Monofilament single sutures Premilene USP6/0-DS13, B. Braun, Tuttlingen, Germany; Seralene USP6/0-DS12 SeragWiessner, Naila, Germany; SeraleneUSP6/0-DS15; SeragWiessner, Naila, Germany).

A strict anti-infective protocol postoperatively was advised to the patient including the rinse with 0.2% chlorhexidine solution three times a day and abstention from mechanical tooth cleaning in the surgically treated areas for 4 weeks or until complete wound healing. Antibiotics were prescribed at the discretion of the surgeon.

Sutures were removed after 10–14 days depending on individual wound healing progression.

2.2.2 | Orthodontic therapy

Early orthodontic consultation was performed within the context of step 2 of periodontal therapy to define the individual interdisciplinary treatment options. For best stabilization of the clot and graft during and after regenerative therapy, the type of splinting was chosen with regard to the grade of tooth mobility.[22] In cases of increased tooth mobility (>grade II) of multiple adjacent teeth, passive fixed orthodontic appliances were inserted prior to periodontal surgery. This applied to nine patients. Otherwise, if not needed during surgery for stabilization, removable acrylic splints or semi-permanent lingual retainers were used to facilitate best stabilization of the blood clot and graft after regenerative surgery.

Active orthodontic tooth movements with low forces and moments started 3 months after periodontal regenerative surgery, using fixed orthodontic appliances (straight-wire-technique) in all patients performed by one and the same experienced orthodontist. In brief, orthodontic movement was started with a 0.012 nickel-titanium (Ni-Ti) wire, followed by the alignment with the sequence of 0.014 Ni-Ti, 0.016 Ni-Ti, 0.018 Ni-Ti, and 0.016*0.016 stainless steel wire. A 0.0175-inch seven time twist flex in the upper jaw and a 0.0155 inch seven time twist flex in the lower jaw were used as fixed retainers and controlled on a regular basis.

Active OT was considered completed when the predefined treatment goals for aesthetic and function in each patient had been achieved. Time span of active orthodontic tooth movements was determined by the individual extent of treatment needs of the patient and varied from 10 to 31 months with a mean duration of 22 months.

Stabilization of treatment outcomes was accomplished either by fixed bonded retainers (10 patients), removable splints (9 patients) which also served as a night-guard because of bruxism, or a combination of both (3 patients).

2.2.3 | Supportive periodontal therapy

After periodontal surgery, supportive periodontal therapy (SPT) started with a tight interval of 4 weeks up to 3 months during the period of OT. Control of inflammation was accomplished by cautious professional tooth cleaning and oral hygiene reinforcement with particular emphasis on teeth undergoing orthodontic intrusive movements.

After completion of active OT periodontal supportive care was provided corresponding to individual patient's need with a minimum recall interval of three times a year during the observation period of 10 years.

2.3 | Outcomes

2.3.1 | Clinical and radiographic measurements

Clinical and radiographic measurements were assessed as previously described.[18] In brief, probing pocket depths (PPD) at four sites per tooth and periapical radiographs were taken preoperatively. During surgery, the tooth site measured with the most advanced bone loss mesially or

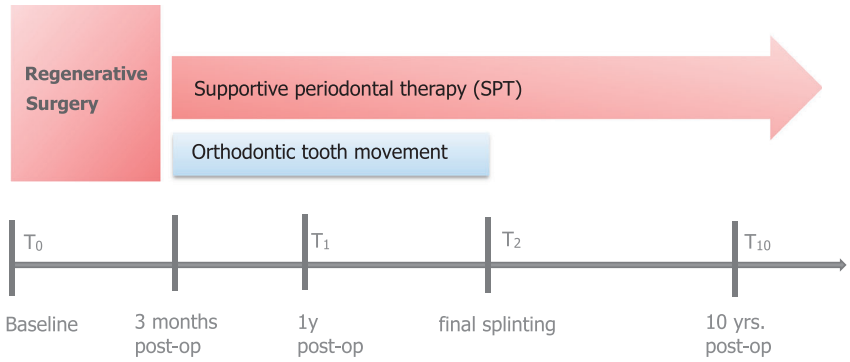

FIGURE 1 Chronical sequence of treatment and examinations (T_0, T_1, T_2, T_{10}).

distally (distance between the cemento-enamel junction or restoration to the bottom of the defect) became the target site. Intra-operative bone level (BL) was used for calibration of the pre-operative periapical radiograph by using the overall tooth length as a reference length, as previously described.[13]

After calibration, the radiographs were analyzed using ImageJ Software (Version 1.43u, National Institutes of Health, Bethesda, Maryland, USA) by a trained and calibrated examiner (H.H.) who was not involved in the surgeries.

Complete clinical and radiographic data at all time-points were obtained from 256 defects in 22 patients. PPD was recorded at baseline and every year during supportive periodontal care, radiographic BL (rBL) at baseline (T_0), 1 year (T_1), at final splinting (T_2), and 10 years (T_{10}) after surgery. (Figure 1).

2.4 | Statistical analysis

All statistical analyses were performed using the statistical software R, version 3.6.3 (R Core Team, 2020).[23] Change of rBL was the primary outcome parameter, change in PPD and frequency of pocket closure (sites with PPD≤4 mm) served as secondary outcomes. Descriptive analysis was outlined for rBL and pocket probing depth (PPD) with change over time for the four time points T_0, T_1, T_2, and T_{10} on defect and patient level and for the most severe defect per patient by means and standard deviations per defect as well as per patient.

Comparisons of rBL and PPD between time points were analyzed by a Wilcoxon signed-rank test; a Wilcoxon signed-rank test for clustered data was used to take possible clustering within patient into account.[24]

To compare the BL gain and pocket closures between time points a logistic regression with time as fixed and patient and defect as random effects was run.

To explore the effect of explanatory variables "smoking", "full-mouth-bleeding and plaque scores" at T_{10} a multilevel analysis was conducted using a mixed effect linear regression with patient as random factor and "radiographic bone at baseline" as covariate. *p*-values were derived with the Satterthwaite method.[25] The level of significance of each test was set to 0.05. Starting from the minimal model with rBL at T_0 as only fixed effect, first models were run with only one more fixed effect included. Variables were only retained if significant and interaction term was only tested if the main effect was significant. Then, only variables were added if they showed a significant improvement of the model.

Since adjunctive antibiotic treatment had not shown any additional effect as previously described,[18] no further statistical investigation of the 10-year data was performed.

Statistical analyses of the clinical and radiographic data were performed by an independent expert biostatistician.

3 | RESULTS

3.1 | Patient and defect characteristics

For all 22 patients included in this analysis data up to 10 years postoperatively was available. All of them were diagnosed with stage IV periodontitis and -based on calculation of percentage bone loss/age baseline – with Grade C except for three patients with Grade B. The collection of the 10-year follow-up data were completed by April 2022. All of the patients had shown full adherence to the scheduled appointments of supportive therapy during the observation period of 10 years. The number of defects per patient ranged from 4 to 15 with an average of 11 defects. In total, 34.2% were one-wall defects while 65.8% were two-wall defects. At baseline, mean radiographic BL of 268 defects was 8.33 ± 2.45 mm. Tooth loss at T_2 amounted to 1.2%

TABLE 1 Patient and defect characteristics at baseline (T_0).

***N* patients**	**22**	
Female sex	59.1% (13)	
Mean age (range)	43.9 (29–62) years	
Smokers	9.1% of patients (8.21% of all defects)	
N defects	268 baseline	256 complete cases 10 years
Single-rooted teeth	165/61.57%	165/64.45%
Multi-rooted teeth	103/38.43%	91/35.55%
Mean bone level all	8.33 ± 2.45 mm	8.32 ± 2.49 mm
Two wall defects	176/65.47%	171/66,80%
One wall defects	92/34.33%	85/33,20%
DBBMc	90/33.58%	
DBBMC + CM	62/23.13%	
DBBMC + EMD	46/17.2%	
DBBMc + CM + EMD	35/13%	
EMD	35/13%	

Abbreviations: CM, collagen membrane; DBBMc, collagenous demineralized bovine bone mineral; EMD, enamel matrix derivative.

(3 teeth in two patients) and at T_{10} to 4.5% (12 teeth in eight patients) due to endodontic complications (5 teeth) and root fracture (7 teeth). No tooth loss was observed at T_1. Hence, complete observation data at T_{10} were present for 256 defects with a mean radiographic BL at baseline of 8.32 ± 2.49 mm. DBBMc alone was used in 33.58% of the defects, whereas in 23.13% of the defects DBBMc + CM was applied, DBBMc + EMD was used in 17.2% of the defects and DBBMc + CM + EMD in 13.0% of defects. EMD alone was applied in 13% of the defects. Patient and defect characteristics are presented in Table 1.

3.2 | Outcomes

Surgeries and soft tissue healing were generally uneventful. None of the patients developed any major complications. There were no allergic reactions, suppuration, or abscesses. Minor complications such as postoperative swelling and pain in the surgically treated area resolved within a few days after surgery. In the rare case of wound dehiscencies, no further complications of wound healing could be observed following reinforcement of postoperative intensive clinical care. Representative examples of treated patients included in the present analysis are illustrated in Figures 2 and 3.

The analysis of the primary outcome-change in radiographic BL over time of 256 defects revealed a significant gain in rBL with 4.63 mm (±2.43 mm) ($p < 0.0001$) at T_1, 4.19 mm (±2.61 mm) at T_2 ($p < 0.0001$) and 4.48 mm (±2.62 mm) ($p < 0.0001$) at T_{10}. Change in radiographic BL on patient level was comparable to the analyzed data on defect level. When looking at the deepest defect per patient rBL gain was even more evident ($p < 0.0001$) (Table 2A and B; Figure 4A–C).[26]

As previously reported,[18] different treatment modalities did not show any impact on rBL change over time (Figure 4D).

Mean PPD was significantly reduced at T_1, with further reduction at T_2 and T_{10} ($p < 0.0001$). Mean PPD reduction was even more pronounced when looking at the deepest defect and statistically significant ($p < 0.0001$) at all time points. The frequency of sites with PPD ≤ 4 mm improved from 33% at baseline (T_0) to 87% at T_1, to 86% at T_2, and remained stable with 90% at T_{10} (Table 2C and D).

A multilevel analysis showed that only smoking ($p = 0.017$) was significant when added as a single variable to the minimal model only containing rBL at baseline, however, not in interaction with the rBL at T_0 ($p = 0.564$). Adding other variables such as plaque at T_{10} or BOP at T_{10} did not show any significant improvement. For smokers the change of rBL was on average less from T_0 to T_{10} ($p = 0.017$). The results of the final model are presented as Table A1 in the appendix.

4 | DISCUSSION

The 10-year data of this retrospective clinical cohort study reveal the long-term effectiveness of a combined regenerative and orthodontic treatment in patients with stage IV periodontitis.

TABLE 2 (a) Mean radiographic bone level (rBL) ± standard deviation (mm) and confidence intervals (CI in the format mean) over time (T_0 = baseline, T_1 = 1 year, T_2 = final splinting, T_{10} = 10 years) calculated for patients and defects with different length of follow-up (b) *p*-values for testing rBL between time points (statistics Wilcoxon signed-rank test from the R-library coin version 1.3.1 [Hothorn et al., 2008]) (c) Frequency distribution of residual PPD for all defects $N = 256$, complete observation time (d) *p*-values for testing proportion of pocket closure (pc) between time points (statistics: Logistic regression with time as fixed and patient and defect as random effects)

(a)	***N***	**T_0**	**T_1**	**T_2**	**T_{10}**
rBL per defect ($n = 268$)	268	8.33 ± 2.45 CI (8.03, 8.62)	3.66 ± 1.92 CI (3.42, 3.89)	NA ± NA	NA ± NA
rBL per defect in complete cases ($n = 256$)	256	8.32 ± 2.49 CI (8.01, 8.62)	3.69 ± 1.94 CI (3.45, 3.93)	4.13 ± 2.01 CI (3.88, 4.38)	3.84 ± 2.10 CI (3.59, 4.10)
rBL per patient ($n = 22$)	22	8.36 ± 1.24 CI (7.81, 8.91)	3.53 ± 1.30 CI (2.95, 4.10)	4.02 ± 1.24 CI (3.47, 4.57)	3.64 ± 1.29 CI (3.07, 4.22)
rBL deepest defect per patient ($n = 22$)	22	12.27 ± 3.09 CI (10.90, 13.64)	5.15 ± 2.49 CI (4.05, 6.26)	5.35 ± 2.49 CI (4.11, 6.59)	5.48 ± 2.76 CI (4.26, 6.71)

(b)	***p*-Values for testing BL between time points**				
	T_0.T_1	**T_1.T_2**	**T_2.T_{10}**	**T_0.T_{10}**	**T_1.T_{10}**
rBL per defect, complete cases ($n = 256$)	1.31e−05	0.018	0.012	1.55e−05	0.97
rBL per patient ($n = 22$)	4.77e−07	0.0042	0.074	4.77e−07	0.42
rBL deepest defect per patient ($n = 22$)	4.77e−07	0.51	1.00	4.77e−07	0.40

(c)				
PPD (mm)	**Baseline T_0**	**T_1**	**T_2**	**T_{10}**
≤4	85 (33.20%)	223 (87.11%)	220 (85.94%)	230 (89.84%)
5	27 (10.55%)	18 (7.03%)	18 (7.03%)	12 (4.69%)
6	48 (18.75%)	10 (3.91%)	17 (6.64%)	11 (4.30%)
7	37 (14.45%)	2 (0.78%)	0 (0.00%)	0 (0.00%)
8	38 (14.84%)	3 (1.17%)	1 (0.39%)	2 (0.78%)
9	9 (3.52%)	0 (0.00%)	0 (0.00%)	1 (0.39%)
10	6 (2.34%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
11	6 (2.34%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

(d) Comparison	***p*-Value**
pc0 – pc1	<1e−05
pc0 – pc2	<1e−05
pc0 – pc10	<1e−05
pc1 – pc2	0.262
pc1 – pc10	0.649
pc2 – pc10	0.117

Regenerative periodontal treatment with consecutive early orthodontic tooth movement led to significant rBL gain 10 years postoperatively, as demonstrated by mean rBL gain of 4.48 mm as well as pocket closure in 90% in a large number of teeth severely compromised by intrabony defects and PTM. The long-term data compare well with the results of our former report with data of 2–4 years observation time[18] and are a proof for the feasibility of successful retention of the natural dentition in an adequate state of health and function. While the mean radiographic bone gain at final splinting T_2 dropped slightly to 4.19 mm, it advanced again to 4.48 mm at T_{10}. The slightly reduced mean bone gain at T_2 may be explained by the fact that bone remodeling due to orthodontic tooth movements is still not accomplished at final splinting. However, the clinical findings of a continuous pocket reduction from baseline

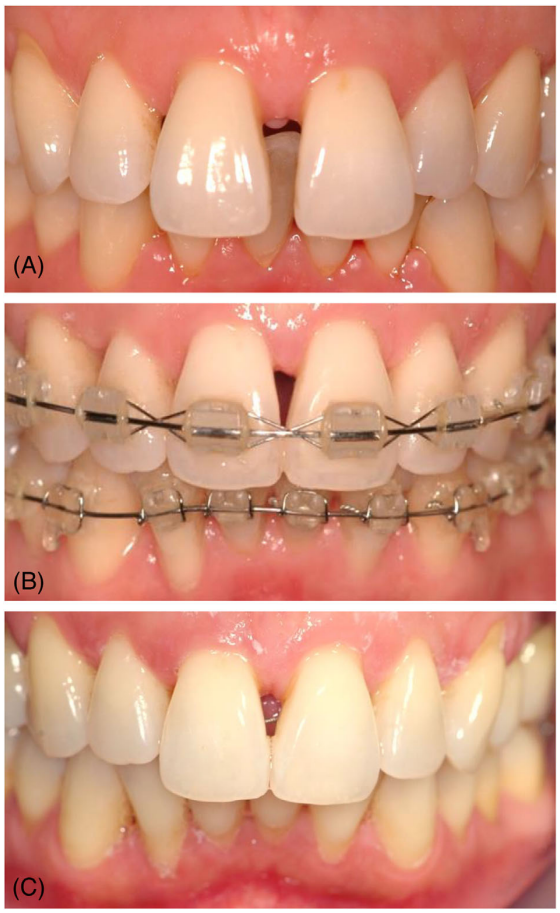

FIGURE 2 Clinical situation of a 35-year-old patient diagnosed with stage IV periodontitis with pathological tooth migration (spacing and flaring) (A) after step 1 and 2 of periodontal therapy (T0 = baseline), (B) 1 year after regenerative surgery (T1), (C) 10 years after regenerative therapy (T10).

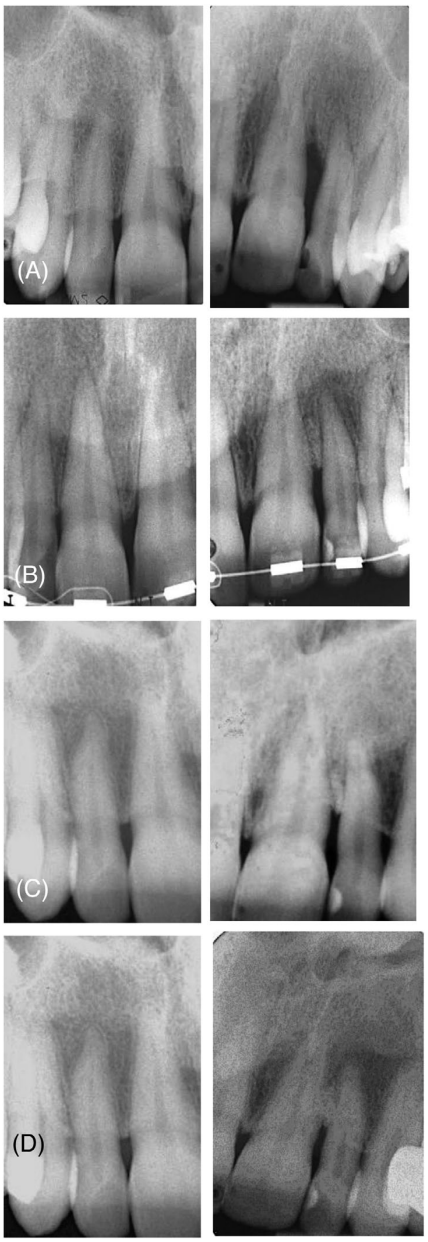

FIGURE 3 (A–D): Radiographical situation of 48-year-old patient diagnosed with stage IV periodontitis (A) after step 1 and 2 of periodontal therapy (T0 = baseline), (B) 1 year after regenerative therapy (T1), (C) at final splinting (T2), (D) 10 years after regenerative therapy (T10).

to T_1, to T_2 and to T_{10} underline the benefit of the combined regenerative-OT. Mean PPD reduction and pocket closure at final splinting in this study are similar to the data of the mid-term follow up of 2–4 years as previously reported.[18] The long-term effectiveness of this combined regenerative therapy and orthodontic treatment is shown by further improvement of rBL and pocket closure at 10 years. The low number of sites with residual deeper pockets could be maintained by regular re-instrumentation during SPT visits. This indicates that, in the setting of a specialized practice, a good prognosis even for severely periodontally compromised patients can be achieved if compliant with SPT and adequate oral hygiene.[27]

The present study analyzing the stability and long-term effectiveness of regenerative periodontal therapy combined with early orthodontic tooth movement is -to our knowledge- the study with the largest number of defects and longest observation time of this kind of interdisciplinary treatment approach published so far. The high number of participants and defects treated in the setting of a private practice strengthen the generalizability of the results. Adding to the strengths of the study, the radiographs were evaluated by the same blinded exam-

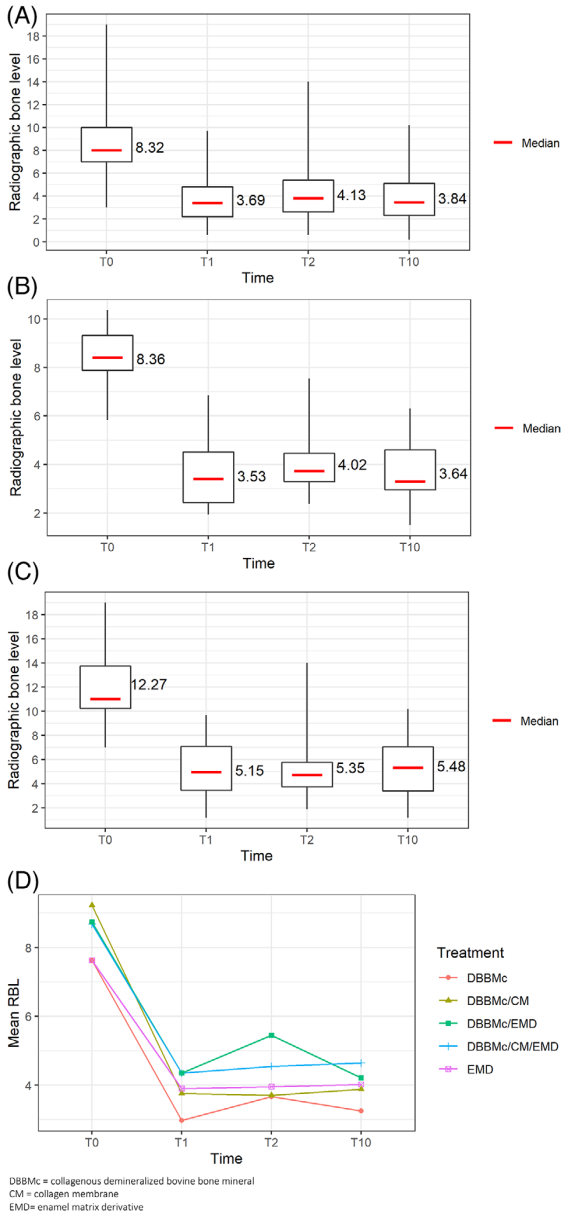

FIGURE 4 (A–D) Box plots showing mean changes in radiographic bone level over time (256 defects in 22 patients) (A) at defect level (B) at patient level, average over all defects (C) at deepest defect per patient $n = 22$ (D) for different treatment modalities. CM, collagen membrane; DBBMc, collagenous demineralized bovine bone mineral; EMD, enamel matrix derivative.

iner, data analysis was performed by an independent expert statistician, both not being involved in the clinical phases of the study. Furthermore, the study was conducted independently and not funded by industry.

However, the present study also has inherent limitations, primarily due its retrospective study design and a missing comparison group. Therefore, the study has to be regarded as a large-scale feasibility study for the design of further prospective randomized clinical trials.

Possible sources of bias, such as orthodontically induced root resorption, the use of radio-opaque bone fillers, measurement errors of rBL due to change of tooth position have been discussed previously in great detail.[18]

The present results cannot be easily compared to those of previously published studies because of differences in study protocols with regard to regenerative procedures, patient and defect selection, choice of outcome measures, time points between regenerative and OT and lengths of follow-up.

However, the protocol of our study and the observed long-term tooth retention by this combined periodontal-regenerative and orthodontic treatment are in line with and in support of the recently published EFP S3 clinical practice guideline (CPG) on the treatment of stage IV periodontitis.[9–11] According to the evidence-based CPG there is a clear recommendation for orthodontic treatment of regeneratively treated intra-bony defects since this combined treatment significantly improves periodontal outcomes and significantly reduces inflammation as long as guidelines of regenerative periodontal treatment[16] and sequences of therapeutic interventions are followed.[11] Based on the recommendation of the evidence-based EFP-S3 level CPG for the treatment of stage IV periodontitis,[11] inflammation has to be under control before, during, and after OT, as it was accomplished in the present study by a rigorous supportive care program over a long period of time.

There is only one earlier study reporting 10-year data following the interdisciplinary treatment of regenerative periodontal therapy and consecutive orthodontic tooth movements which can serve as a direct comparison,[20] however, with a far smaller number of regeneratively treated defects ($n = 36$) compared to our study ($n = 256$). The authors focused on clinical parameters and not on rBL gain. They reported a mean PPD reduction of 3.2 mm and pocket closure of 83% at the 10-year follow-up which is comparable to 2.9 mm mean PPD reduction and 90% of pocket closure observed in the present study. A second long-term follow-up with an average of 11 years[21] on the combined perio/orthodontic therapy did not distinguish in their outcomes between resectively and regeneratively treated defects. Mean PPD reduction was therefore much less with 1.6 mm. However, the observed pocket closure of 87% reveals the same tendency for stability of treatment outcomes as in our study for successful combined periodontal/regenerative and OT. A major difference between these two studies and the present one is the time point of orthodontic intervention (12 months vs. 3 months after periodontal surgery). A

reduced overall treatment time should be viewed as an advantage.

Early orthodontic tooth movements, 3 months after regenerative surgical therapy in this study, did not have a negative impact on long-term outcomes in patients with stage IV periodontitis. This is not only in agreement with the 1-year findings of a multi-center randomized clinical trial on timing of OT – early versus late-stating that there is no adverse effect of early application of orthodontic forces after regenerative therapy – thus reducing overall treatment time[19] and the according CPG recommendation,[11] but indicates that early OT does not preclude but may even support favorable long-term outcomes.

Retention of teeth—as strongly recommended being the first line of treatment strategy by the EFP CPG for stage IV periodontitis[11]—was possible over 10 years in our study with only 4.5% of tooth loss due to non-periodontal reasons, in particular, due to root fracture and endodontic lesions. This is in line with 2.7% of tooth loss due to root fracture as reported in a previous study.[20] The primary outcome of our study—change of rBL—has not been investigated in previous long-term studies[20,21] or cannot be compared due to the lack of distinction between resective or regenerative periodontal therapy before orthodontic tooth movements.[21]

As already stated in our former report[18] the comparison of two independent retrospective cohort studies with regeneratively treated intra-bony defects in the same practice with the same protocol, including surgical procedures, outcome measures and follow-up with and without orthodontic tooth movement[13] was in favor of the combined therapy. With all limitations of such an indirect comparison using a "historical control group," it was remarkable to observe—when now looking at the 10-year follow-up in both cohort groups- that the improvements with regard to mean BL gain in the present study with combined perio/orthodontic therapy were even higher (4.48 mm, 256 defects) than in the cohort, where patients did not undergo OT (3.9 mm, 226 defects). The same applies to PPD reduction with 2.91 mm in the present study and 2.28 mm in the group without OT at the 10-year follow-up. Since the baseline characteristics of the treated defects with regard to mean PPD were similar in both cohorts these findings seem to indicate a possible "stimulating" effect of orthodontic tooth movement in the early healing phase on the regenerative outcomes, as previously suggested by pre-clinical investigations.[28–30] However, this observation should be interpreted with great caution. Further preclinical trials and well controlled clinical research are warranted to decode the effects of mechanical loading after regenerative procedures.

5 | CONCLUSION

Within the limitations of the retrospective study design, the present results suggest that the combination of regenerative treatment and consecutive early OT in patients with stage IV periodontitis well adherent to a strict maintenance protocol can lead to favorable and stable long-term results after 10 years. These findings are in line with and support the current recommendations for this clinical case type 2 of stage IV periodontitis and at the same time provide a promising long-term perspective that has not been available so far.

In the future, well planned prospective randomized clinical trials that also include patient-related and orthodontic outcome measures will further refine the most suitable protocol for the combined regenerative and orthodontic treatment of patients with stage IV periodontitis.

AUTHOR CONTRIBUTIONS

Christina Tietmann conceived the idea of the study, performed the surgeries, interpretation of the results, and manuscript writing. Karin Jepsen and Søren Jepsen contributed to supervision, interpretation of the results, and writing/revising of the manuscript. Helen Heibrok collected the data. Sven Wenzel contributed by supervising the supportive care program. All authors critically reviewed and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest with regard to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki (version 2008) and was approved by the Ethical committee of the University of Bonn (#16/23).

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APPENDIX

TABLE A1 Results from final model for the change of radiographic bone level from T_0 to T_{10}.

	Estimate (SE)	*p*-Value
Fixed effects		
(Intercept)	−1.00 (0.46)	0.031
rBl at T0	0.69 (0.05)	<0.0001
Smoking	−1.99 (0.76)	0.017
Random effects:		
Patient standard deviation	0.836	
Residual standard deviation	1.76	
R2:		
R2m/R2c	0.474/0.571	

3.3 Jepsen K, Tietmann C, Kutschera E, Wüllenweber P, Jäger A, Cardaropoli D, Gaveglio L, Sanz Sanchez I, Martin C, Fimmers R, Jepsen S. The effect of timing of orthodontic therapy on the outcomes of regenerative periodontal surgery in patients with stage IV periodontitis: A multicenter randomized trial. J Clin Periodontol 2021;48(10):1282-1292. doi: 10.1111/jcpe.13528.

Zielsetzung der Arbeit

Lange Zeit wurde über den bestmöglichen Zeitpunkt für den Beginn der kieferorthopädischen Zahnbewegung nach regenerativer Parodontitistherapie bei Stadium IV Parodontitis mit PTM diskutiert. Während einige Autoren empfahlen, dass die parodontale Wundheilung nach regenerativer Parodontitistherapie vor kieferorthopädischer Zahnbewegung abgeschlossen sein sollte, kamen andere zu dem Schluss, dass der frühe Beginn kieferorthopädischer Zahnbewegung nicht nur keine negativen, sondern sogar positive Effekte auf die parodontalen Parameter haben könnte. Der optimale Zeitpunkt des Beginns kieferorthopädischer Zahnbewegung nach regenerativ-parodontalchirurgischer Therapie wurde deswegen bis vor Kurzem als „grey zone" bezeichnet (*Pini Prato & Chambrone, 2020*).

Daher war es das Ziel dieser prospektiven randomisierten Studie, die Auswirkung eines frühen oder späten Beginns kieferorthopädischer Zahnbewegung nach regenerativ-parodontalchirurgischer Therapie bei Stadium IV Parodontitis mit PTM zu untersuchen und miteinander zu vergleichen.

Methoden und Ergebnisse

Diese Untersuchung war eine multizentrische, multinationale, randomisierte prospektive klinische Studie. Insgesamt wurden 43 Patienten mit Parodontitis Stadium IV mit PTM aus vier verschiedenen Zentren (Deutschland (n=2), Spanien, Italien) zur Teilnahme an der Studie ausgewählt. Nach Randomisierung der Patienten wurde die kieferorthopädische Zahnbewegung

entweder ein Monat (n=23) oder sechs Monate (n=20) nach regenerativer parodontalchirurgischer Therapie begonnen. Einzelheiten dazu sind der Abbildung 1 der zugrunde liegenden Originalarbeit zu entnehmen. Im Rahmen der parodontalchirurgischen Therapie wurde der Zahn mit der ausgeprägtesten PTM als „target tooth", der tiefste intraoperative messbare Knochendefekt als „target site" ausgewählt und regenerativ therapiert.

Ein Jahr nach regenerativer Therapie wurde die Veränderung des CAL, PPD, BOP und PC überprüft. Es zeigten sich keine signifikanten Unterschiede zwischen frühem oder spätem Beginn der kieferorthopädischen Zahnbewegung nach vorheriger regenerativer Therapie intraossärer Defekte bezüglich CALg (5,4 ±2,1mm versus 4,5mm ± 1,7mm), PPDr (4,2 ± 1,9mm versus 3,9 ± 1,5mm) und PC (91% versus 85%).

Schlussfolgerung:

Die Ergebnisse dieser multizentrischen, multinationalen und randomisierten Studie konnten zeigen, dass kieferorthopädische Zahnbewegungen schon früh nach regenerativer Therapie vertikaler Defekte bei Stadium IV Parodontitis, Typ 2 begonnen werden können. Das randomisierte prospektive Design erlaubte erstmalig den Nachweis, dass der frühe Beginn zu (nicht-signifikant) besseren Ergebnissen als der späte Beginn der kieferorthopädischen Zahnbewegung mit dem Vorteil einer deutlichen Reduktion der Gesamtdauer der interdisziplinären parodontalchirurgischen und kieferorthopädischen Therapie führt.

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ORIGINAL ARTICLE

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The effect of timing of orthodontic therapy on the outcomes of regenerative periodontal surgery in patients with stage IV periodontitis: A multicenter randomized trial

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Abstract

Aim: To compare the outcomes after early (4 weeks post surgery) or late (6 months post surgery) orthodontic therapy (OT) following regenerative surgery of intra-bony defects (IDs).

Materials and methods: In a multi-center, parallel-group, randomized clinical trial, 43 patients with stage IV periodontitis were randomized to receive either early ($n = 23$) or late OT ($n = 20$) following regenerative surgery of IDs. Primary outcome was change in clinical attachment level (CAL) in one target ID at 12 months after surgery. Secondary outcomes were changes of probing pocket depth (PPD), bleeding on probing (BOP), and frequency of pocket closure.

Results: No statistically significant differences between groups could be observed for CAL gain (5.4 mm [±2.1 mm] for early; 4.5 mm [±1.7 mm] for late OT). PPD was reduced by 4.2 mm (±1.9 mm) in the early group and by 3.9 mm (±1.5 mm) in the late group ($p > .05$). Pocket closure (PPD ≤ 4 mm) was obtained in 91% of defects in early compared to 85% in late OT.

Conclusion: In the inter-disciplinary treatment of periodontitis stage IV, OT can be initiated already 4 weeks after regenerative surgery of IDs with favourable results, thus reducing the overall treatment time.

KEYWORDS
orthodontic tooth movement, pathologic tooth migration, regenerative periodontal therapy, stage IV periodontitis

Clinical Relevance

Scientific rationale for study: Information on the treatment of patients with stage IV periodontitis with intra-bony defects (IDs) and pathological tooth migration (PTM) in need of orthodontic therapy (OT) is limited. The optimal interval between regenerative periodontal surgery and OT is a matter of ongoing debate.

Principal findings: After 12 months, significant periodontal improvements of similar magnitude were observed following early (after 4 weeks) and late (after 6 months) initiation of OT.
Practical implications: Teeth severely compromised by IDs and PTM can be treated successfully by regenerative surgery followed by early OT with the advantage of an overall reduced treatment time.

1 | INTRODUCTION

The presence of severe periodontal attachment loss, vertical bone loss, and pathological tooth migration (PTM) (Brunsvold, 2005) is a key clinical feature of stage IV periodontitis (Papapanou et al., 2018; Tonetti & Sanz, 2019). An inter-disciplinary approach is required to control the periodontal infection, reconstruct the defects, and realign the migrated teeth (Re et al., 2000; Gkantidis et al., 2010; Cardaropoli et al., 2014; Sanz & Martin, 2015). Such a comprehensive treatment includes the steps 1 and 2 of periodontal therapy followed by step 3 including regenerative periodontal surgery (Sanz et al., 2020) and subsequent orthodontic therapy (OT).

However, only limited data exist on these combined periodontal regenerative and orthodontic approaches (Martin et al., 2021). At present, clinicians have to rely mainly on case reports and prospective as well as retrospective clinical case series. In particular, the optimal time interval between periodontal surgery and the initiation of OT is a matter of ongoing debate. It may be safe to wait until the end point of regenerative therapy has been reached (usually between 6 and 12 months) and not to interfere with periodontal wound-healing (Pini Prato & Chambrone, 2020). Case reports and series with long-term follow-ups have reported favourable periodontal outcomes using such a delayed approach (Ghezzi et al., 2008; Jepsen et al., 2015; Roccuzzo et al., 2018; Aimetti et al., 2020).

Other reports have suggested that OT may be initiated almost immediately or up to 3 months after regenerative surgery (Cardaropoli et al., 2006; Ogihara & Wang, 2010; Attia et al., 2012a, 2019; Ghezzi et al., 2013). No adverse effects were reported, and some authors speculated that early tooth movement could even stimulate periodontal wound-healing. Very recently, a large retrospective case series of patients with stage IV periodontitis, where OT was started 3 months after regenerative surgery, showed substantial improvements after 12 months and could be maintained up to 4 years (Tietmann et al., 2021).

At present, there are no data available from randomized clinical trials (RCTs) that have compared the periodontal outcomes following early versus late initiation of OT in stage IV periodontitis (Martin et al., 2021). As many patients affected by such a condition are interested to seek orthodontic treatment because of the aesthetic and functional changes caused by PTM (Hirschfeld et al., 2019), this question is of high clinical relevance.

The aim of this randomized, multicentre trial was to compare two different protocols of a combined treatment comprising regenerative periodontal surgery and subsequent orthodontic tooth movement in subjects with periodontitis stage IV in order to establish whether one treatment protocol is superior to the other with regard to periodontal outcomes. The two treatment groups differed by the time point of initiation of OT (early: 4 weeks vs. late: 6 months following regenerative periodontal surgery).

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study was designed as a prospective, multicentre, multinational, randomized parallel-group clinical trial with a 12-month follow-up (ClinicalTrials.gov, identifier: NCT 02761668). All investigators attended calibration meetings to standardize case selection by discussion of prospective cases, clinical measurement techniques, and surgical and orthodontic procedures. On-site rules for the compilation of the data collection sheets for appropriate oversight were frequently re-evaluated to ensure the validity of the data. The study was designed to test the hypothesis that one treatment protocol was superior to the other with regard to periodontal outcomes after 12 months. An overview of study procedures and exams is presented in Figure 1.

Study participants were consecutively recruited from patients treated by experienced periodontists and orthodontists in Germany (University of Bonn and Private Practice, Aachen), in Italy (Private Practice, Torino), and in Spain (Complutense University of Madrid).

Ethical approval was obtained by the Ethical Committee, University of Bonn (code 034/16) for the centres Bonn and Aachen and by the competent local authorities for the centres Torino (code PROT 04-2017) and Madrid (code 16/492-E). All subjects gave their informed consent after the investigators had provided a thorough explanation of the study procedure and its associated risks and benefits. All study procedures were performed according to the Declaration of Helsinki (1975, revised in 2008) on experimentation involving human subjects.

Individuals presenting severe periodontitis and PTM (stage IV periodontitis; Papapanou et al., 2018) who fulfilled the following inclusion and exclusion criteria were invited to participate:

2.1.1 | Inclusion criteria

- Completed steps 1, 2, and 3 (except for experimental regions) of periodontal therapy;
- Presence of ID(s) (3 mm or deeper) with indication for periodontal regenerative surgery at incisors, canines, or premolars with PTM requiring OT;

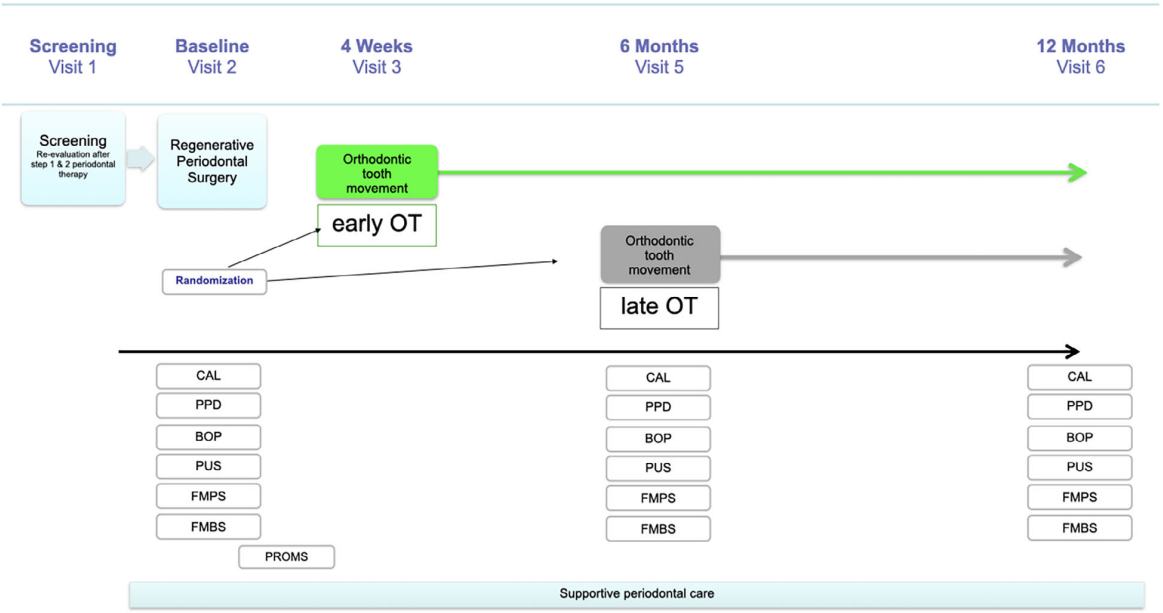

FIGURE 1 Chronological sequence of examinations, periodontal and orthodontic therapy (OT), early OT initiated 4 weeks after, and late OT initiated 6 months after regenerative periodontal surgery

- Adequate oral hygiene and control of inflammation in the whole dentition as demonstrated by a full-mouth plaque score (FMPS) of <25% and a full-mouth bleeding score (FMBS) of <25%.

2.1.2 | Exclusion criteria

- Furcation involvement of the teeth to be treated;
- Smoking exceeding five cigarettes per day or pipe or cigar smoking;
- Uncontrolled metabolic disorders;
- Presence of medical contraindications for oral surgical procedures;
- Known sensitization to collagen-based medical products.

In patients with more than one ID meeting the inclusion criteria, only one tooth was defined as the target tooth and the most severe defect as the target site.

2.2 | Interventions

2.2.1 | Regenerative periodontal surgery

Selected areas for surgery were anaesthetized by block and/or infiltration. The surgical procedures were adapted to the treatment algorithm introduced by Cortellini and Tonetti (2015). Minimally invasive microsurgical approaches including access by papilla preservation flaps were used. Depending on the defect configuration and/or prevention of soft tissue collapse into the defect, a bone filler (DBBMc, Bio Oss® Collagen; Geistlich, Wolhusen, Switzerland) was used. If the graft material was at risk for dislocation in non-contained defects, a collagen membrane (Bio Gide®Perio; Geistlich, Wolhusen, Switzerland) was applied without pin or suture fixation. Enamel matrix derivative (EMD, Emdogain®; Straumann, Basel, Switzerland) was applied as an adjunct to the root surface after debridement for contained defects. In some cases, a periosteal fenestration at the base of the flap was used to facilitate coronal repositioning of the soft tissue. Suturing techniques using non-resorbable 6–0 and 7–0 monofilament sutures (e-PTFE, W.L. Gore, Phoenix, AZ) included internal offset vertical mattress suture, interrupted single suture, double sling suture, or a combination of these. Primary closure of the surgical site was confirmed with magnification (3.5- to 4.4-fold) at the end of surgery. In all centres, one single experienced periodontal surgeon performed all procedures (Karin Jepsen, Christina Tietmann, Daniele Cardaropoli, Ignacio Sanz Sanchez).

A stringent anti-infective regimen was enforced post operation, including the use of a chlorhexidine mouth rinse (0.2%) three times daily for the first 4 weeks. Pain control consisted of 600 mg ibuprofen or 500 mg paracetamol; patients were instructed to take one tablet at the end of the procedure and one 6 h later, and to continue as needed in case of pain. Antibiotics were prescribed at the discretion of the surgeon. After 10–14 days, sutures were removed. Regular tooth brushing was resumed 4 weeks post surgery.

2.2.2 | Orthodontic therapy

For each subject individual, the treatment objectives were defined and visualized with manual or virtual set-ups. Prior to periodontal therapy, passive fixed appliances were inserted for stabilization in cases of increased tooth mobility (>grade 1). Initiation of active OT

was commenced at 4 weeks (early) or 6 months (late) after periodontal surgery according to randomization, involving fixed orthodontic appliances and individualized segmented arch mechanics. Maximum emphasis was on applying low forces and moments. Bone-borne temporary anchorage devices, splints, as well as trans-palatal and lingual arches served for anchorage reinforcement. After the pre-defined tooth positions were accomplished, orthodontic appliances were removed and teeth were stabilized with a combination of splints for the night and bonded retainers or fibre-reinforced restorations.

2.2.3 | Supportive periodontal therapy

Following periodontal surgery, recall visits were scheduled at 2 days, 2 weeks, and 4 weeks; thereafter, all subjects received regular supportive care every 2 months for the whole duration of the study. In case of recurrence of signs of inflammation, OT would be discontinued until controlled by gentle professional tooth cleaning and oral hygiene reinforcement.

2.3 | Outcomes

The primary outcome measure was the change in clinical attachment level (CAL) on the pre-determined tooth site (target site) after 12 months. During surgery, the tooth site with the most advanced bone loss (cemento-enamel junction [CEJ] to bottom of the defect) was determined and became the target site. Secondary outcomes were probing pocket depth (PPD), recession (REC), bleeding on probing (BOP), suppuration, pocket closure (PPD ≤4 mm; PPD ≤4 mm; no BOP), wound-healing, and patient-reported outcomes with respect to pain.

Prior to initiation of the study, all investigators participated in a calibration meeting. Intra-examiner agreement level for CAL/PPD within 1 mm (±1 mm) was set at 97%.

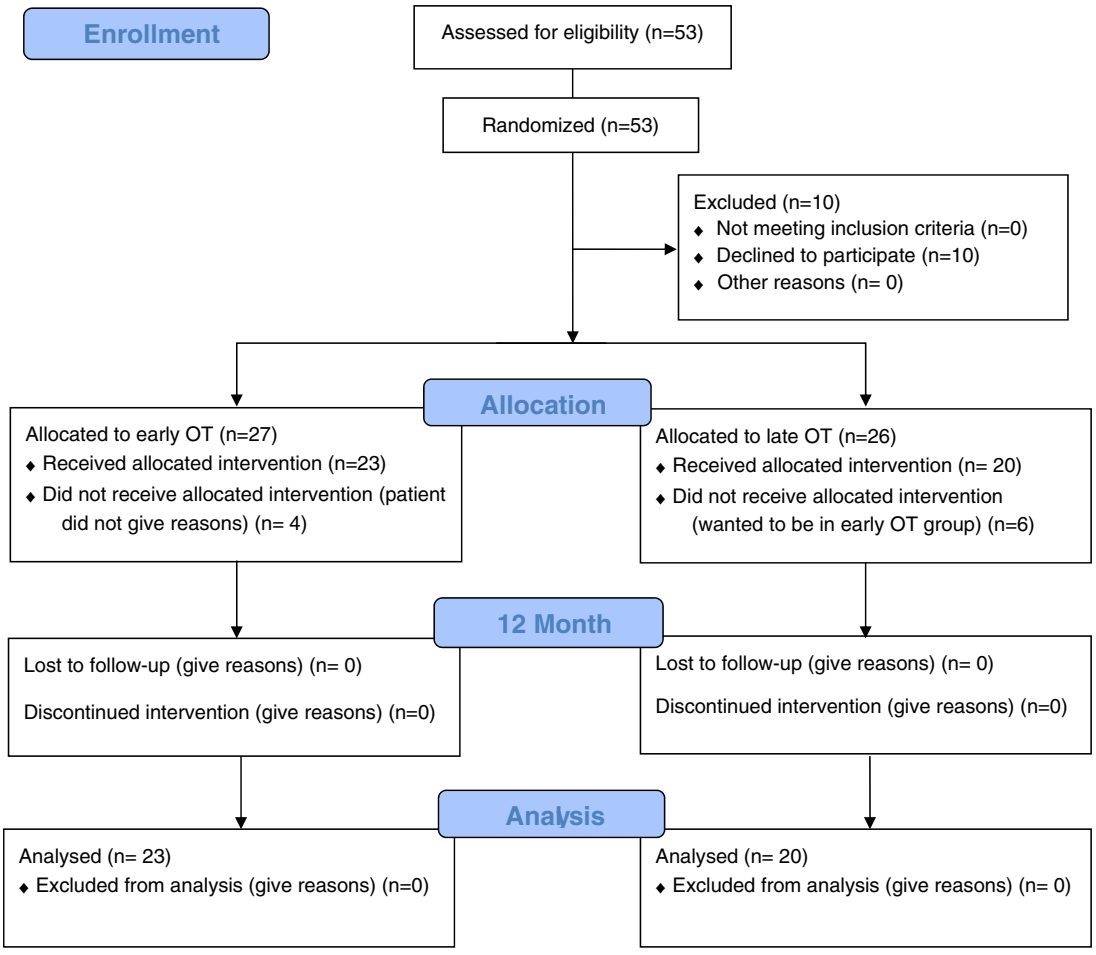

FIGURE 2 Study flowchart following CONSORT guidelines for clinical trials. Fifty-three patients met the inclusion criteria, and 26 patients were allocated to the group with late orthodontic therapy (OT) after regenerative periodontal surgery and 27 to the group with early OT after regenerative periodontal surgery. Ten patients withdrew from the study: six expected to be part of the early and withdrew after allocation to the late treatment group, and four (allocated to the test group) did not want to continue the study without giving any reason

2.3.1 | Clinical measurements

Three to six months after completion of steps 1, 2, and 3 (except for study regions) of periodontal therapy, baseline clinical parameters were recorded. All measurements were repeated 6 and 12 months after regenerative periodontal surgery (Figure 1).

The measurements of CAL and PPD were obtained with a pressure-sensitive probe (Click-Probe, Kerr, Switzerland; or Florida Probe, Gainesville, FL) to the nearest millimetre at six sites per tooth. BOP and suppuration were assessed dichotomously (as present or absent); BOP was positive if it occurred within 15 s after periodontal probing. Bleeding scores were recorded at six sites (mesio-buccal, buccal, disto-buccal and mesio-oral, oral, and disto-oral). FMBS were then calculated. FMPS were recorded at four sites (mesial, buccal, distal, and oral) of each tooth present and calculated as the percentage of the total surfaces exhibiting plaque (O'Leary et al., 1972).

2.3.2 | Clinical characterization of intra-bony defects during surgery

Using intra-operative exploration, defects were described as one-, two- and three-wall defects (Papapanou & Tonetti, 2000). The distance from the CEJ to the bottom of the defect was measured, and the depth of the intra-bony component was recorded as the distance between the marginal bone crest and the deepest location of the osseous defect.

The site with the most advanced bone loss, as measured from CEJ to the bottom of the defect, was determined and became the target site.

2.3.3 | Assessment of wound-healing and pain

Complete flap closure of the surgical site was confirmed with magnification at the end of surgery and then re-evaluated at the 2- and 4-week follow-up appointment. The presence of any dehiscence in the soft tissues was noted. Local adverse events such as hematoma, oedema, or signs of inflammation at the treated site were recorded. Patient perceptions of pain were rated using a 100-mm visual analogue scale (VAS) in a questionnaire given to the patient.

2.4 | Sample size

2.4.1 | Sample size calculation

The calculation of the number of patients to be treated was based on the primary objective of detecting a true mean difference of at least 1 mm difference in CAL change after 12 months between both groups (early vs. late). Assuming a standard deviation of 1.71 mm for the CAL change (Ghezzi et al., 2013), the intended sample size of 20 patients per treatment group was calculated to be sufficient to detect the established CAL difference between groups with a power of 80%.

2.5 | Randomization and blinding

Study registration and treatment assignment procedures were done by the clinical research centre at the University Bonn, Germany. Subjects were randomized to early or late OT based on computer-generated random codes using random permuted blocks. Allocation was concealed to the surgeon by sealed opaque envelopes. The calibrated examiner in each centre was blinded to the treatment assignment. Study nurses administering questionnaires were masked with respect to treatment allocation.

2.6 | Statistical analysis

Computerized chairside data entry into a periodontal electronic database (Parostatus, Berlin, Germany or Florida Probe database) allowed export via Excel into the statistical software program. Descriptive statistics were summarized as means and standard deviations for quantitative data and frequencies and percentages for qualitative data. Means for each treatment group and differences between treatment groups were presented, along with the associated 95% confidence intervals as well as *p*-values for differences within treatment groups. The primary comparison of CAL change after 12 months between treatment groups was based on a two-sided (95% confidence limits) two-sample *t*-test, at the 5% level of significance.

TABLE 1 Patient, tooth, and defect characteristics at baseline

	Early OT, $n = 23$	Late OT, $n = 20$
Age (years)	45.4 ± 11.9	52.0 ± 9.4
Gender (female/male)	17/6	9/11
Smoking status		
Current (<5 cigarettes)	3	3
Former	1	0
Never	19	17
FMPS	12.9 ± 4.9	15.2 ± 6.2
FMBS	10.5 ± 4.8	12.7 ± 6.9
Tooth		
Incisor/canine/premolar	21/2/0	13/6/1
PPD (mm)	7.3 ± 1.6	7.1 ± 1.7
CAL (mm)	9.8 ± 2.5	9.2 ± 2.5
Defect characteristics		
CEJ–bottom of defect (mm)	11.2 ± 2.6	10.0 ± 3.5
Depth intra-bony component (mm)	5.9 ± 2.7	5.2 ± 1.8
Three walls	11	13
Two to three walls	6	4
Two walls	6	3

Abbreviations: CAL, clinical attachment level; CEJ, cemento-enamel junction; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; OT, orthodontic treatment; PPD, probing pocket depth.

The effect of centres on the primary outcome was checked with a two-factorial analysis of variance for the factor treatment and centre including treatment by centre interaction. Since no evidence for interaction was found, the centre-controlled treatment effect was estimated from a second model, dropping the interaction term.

Statistical analysis of the clinical data was performed by an independent biostatistician (Rolf Fimmers) using the software SAS version 9.2 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Patient and defect characteristics

Between July 2016 and July 2019, a total of 53 patients were consecutively recruited and screened at the four study centres (7–26 per centre). All screened and potentially to be included subjects had received steps 1, 2, and 3 (except for study regions) of periodontal therapy (Sanz et al., 2020). Following the screening visit 3–6 months after therapy,

FIGURE 3 A 25-year-old patient diagnosed with periodontitis stage IV with pathological tooth migration (spacing and flaring). (a) Clinical situation after steps 1 and 2 of periodontal therapy, flaring teeth 12, 11 and 21, 22 with advanced attachment loss, labially displaced and elongated. Target site 21b, with CAL = 7 mm and PPD = 7 mm. (b) Regenerative surgical procedure for an intra-bony two-wall defect, 6 mm deep; follow-up 1 week and 2 weeks. (c) Clinical situation 12 months after regenerative surgery (early OT group): Target site 21b, with CAL = 2 mm and PPD = 3 mm. (d) Radiographic situation at baseline (left) and 12 months after (right) regenerative surgery

subjects were included in the study if the inclusion/exclusion criteria were met. A total 10 patients withdrew from the study: 6 expected to be part of the early treatment group and withdrew after allocation to the late treatment group, and 4 dropped out without giving any reason. After surgery, 43 patients remained in the study (early = 23; late = 20). The 12-month follow-up was completed by July 2020. A study flowchart is presented in Figure 2. Baseline patient and defect characteristics showed to be well balanced for the two study groups and are displayed in Table 1. All 43 patients had been diagnosed with periodontitis stage IV and—based on a calculation of percent bone loss/age at baseline—with grade C, except for 6 patients with grade B (2 in early and 4 in late OT). A combination therapy of EMD + DBBM was used in 35 defects (17 in early and 18 in late OT), and a combination of collagen membrane and DBBM in 4 defects (2 in early and 2 I late OT); 4 defects in the early OT group received EMD alone because these patients had not consented to the application of a bovine-derived graft. A representative example of a treated patient included in the present analysis is displayed in Figure 3 and in Figure S1.

3.2 | Outcomes

The analysis for the primary outcome—namely CAL change after 12 months—revealed a difference in CAL gain of 0.89 mm (95% confidence interval: [−0.36 to 2.15], $p = .159$) in favour of the early treatment group, formally not rejecting the null hypothesis of no difference in treatment effects between both groups (Table 2).

Clinical findings at baseline and at 6 and 12 months after regenerative surgery are presented as group means for the target sites (Table 3). Both groups were well balanced at baseline with regard to CAL and PPD and showed statistically significant improved outcomes after 12 months ($p < .0001$). After 12 months, in groups with early and with late initiation of OT, the percentage of target sites showing pocket closure (PPD ≤ 4 mm) was similar (91% vs. 85%). Pocket closure in combination with the absence of BOP was seen in 69% of the target sites in the group with early OT compared to 75% in the group with late OT (Table 3).

Low baseline FMPS of 12.9 ± 4.9% versus 15.2 ± 6.2% (early vs. late) were well maintained over the study period with values of 15.0 ± 5.8% versus 15.0 ± 7.0% at 6 months and 16.9 ± 10.1% versus 17.0 ± 8.6% at 12 months. These scores were accompanied by low FMBS of 10.5 ± 4.8% versus 12.7 ± 6.8% at baseline, 10.6 ± 4.9% versus 7.7 ± 4.9% at 6 months, and 14.7 ± 13.1% versus 11.3 ± 9.1% at 12 months.

Surgeries and post-operative sequelae were uneventful, and no patient in any group developed major complications. Patient perceptions after surgery and wound-healing scores were very similar in both

TABLE 2 Changes in clinical parameters clinical attachment level (CAL) and probing pocket depth (PPD) compared to baseline at 6 and 12 months (mean ± standard deviation [SD]) for target sites in early and late treatment group and differences between both groups in CAL change after 12 months (primary outcome)

		Early OT $n = 23$, BL—6 months	BL—12 months	Late OT $n = 20$, BL—6 months	BL—12 months	Early versus late OT, Δchange BL—12 months	
ΔCAL (mean ± SD)	mm	4.69 ± 1.7	5.39 ± 2.2	4.05 ± 2.0	4.45 ± 1.7	0.89	$p = .16$
Estimate	95% CI	5.4–3.9	6.3–4.4	4.9–3.1	5.3–3.6	2.2 to −0.3	
ΔPPD (mean ± SD)	mm	4.34 ± 1.7	4.21 ± 1.9	3.80 ± 1.3	3.90 ± 1.5	0.31	$p = .51$
Estimate	95% CI	5.1–3.6	5.0–3.4	4.4–3.2	4.6–3.2	1.3 to −0.6	

Abbreviations: BL, baseline; CI, confidence interval; OT, orthodontic treatment.

TABLE 3 Clinical parameters (mean ± standard deviation [SD]) for target sites in early and late orthodontic treatment (OT) group at baseline, 6 months, and 12 months

Variable		Early OT baseline	$n = 23$, 6 months	12 months	BL versus 12 months	Late OT baseline	$n = 20$, 6 months	12 months	BL versus 12 months
CAL (mean ± SD)	mm	9.8 ± 2.5	5.1 ± 1.9	4.4 ± 1.7	$p < .0001$	9.2 ± 2.5	5.1 ± 2.1	4.7 ± 2.4	$p < .0001$
Estimate	95% CI	8.8– 10.9	4.3–5.9	3.7–5.2		8.0–10.4	4.1–6.1	3.6–5.8	
PPD (mean ± SD)	mm	7.3 ± 1.6	3.0 ± 0.9	3.1 ± 0.9	$p < .0001$	7.1 ± 1.7	3.2 ± 0.9	3.2 ± 1.1	$p < .0001$
Estimate	95% CI	6.6–8.0	2.6–3.4	2.7–3.5		6.3–7.9	2.7–3.6	2.7–3.7	
Plaque (+)	*n* (%)	4 (17%)	3 (13%)	3 (13%)		1 (5%)	1 (5%)	2 (10%)	
BOP (+)	*n* (%)	13 (53%)	6 (26%)	7 (30%)		9 (45%)	4 (20%)	3 (15%)	
PUS (+)	n (%)	1	0	0		2	0	0	
Pocket closure (PPD ≤ 4 mm)	*n* (%)	n/a	22 (95%)	21 (91%)		n/a	17 (85%)	17 (85%)	
Pocket closure (PPD ≤ 4 mm, no BOP)	*n* (%)	n/a	16 (69%)	16 (69%)		n/a	15 (75%)	15 (75%)	

Abbreviations: BL, baseline; BOP, bleeding on probing; CAL, clinical attachment level; CI, confidence interval; PPD, probing pocket depth; PUS, suppuration.

groups. Two weeks after surgery, 7/23 patients (early OT) and 6/20 patients (late OT) reported having experienced some pain (VAS ranges: 4–49, 9–50). None of the patients presented with signs of swelling or complications at the second and fourth week visit. At these time points, primary closure was noted in 21/23 defects of the early OT group, with 2 defects showing a slight dehiscence. All defects in the late OT group healed with primary closure. No patients showed recurrence of signs of inflammation.

A subsequent additional analysis with the intention to assess possible effects due to the centre revealed a significant difference of CAL change between centres ($p = .030$), without evidence for a treatment–centre interaction ($p = .635$). An estimation of the treatment effect controlling for centres revealed a difference in CAL change after 12 months of 1.30 mm ([0.12–2.47], $p = .032$) between the groups in favour of the early treatment group (Figure S2).

4 | DISCUSSION

The present multicentre, randomized trial was designed to test the hypothesis that one protocol for a combined perio-regenerative/OT (early or late OT after regenerative surgery) would be superior to the other. Our results did not provide evidence for superiority of one over the other treatment approach with regard to the primary outcome of CAL after 12 months. Even though in the group with early OT, on average, 0.9 mm more CAL gain was observed, this difference failed to reach statistical significance. Both treatment modalities led to significant periodontal improvements, as demonstrated by mean CAL gains of 5.4 and 4.5 mm, respectively, as well as pocket closure (PPD ≤ 4 mm) in the vast majority of the treated defects. An additional analysis, taking any centre effect into account, pointed to a significant advantage of early OT. Taken together, these findings show for the first time in a large randomized trial that in the interdisciplinary treatment of periodontitis stage IV with PTM and IDs, OT can be initiated already 4 weeks after regenerative surgery with favourable results, thus reducing the overall treatment time for the patients.

The question addressed in this study is of high relevance for clinicians and for patients, as, so far, the available information to guide the decision making on the treatment of stage IV periodontitis patients in need of OT is scarce (Martin et al., 2021). Based on the outcomes of the present study, the clinician together with the patient can select the treatment protocol that will best suit the individual needs of the patient. The selected study design—a randomized trial—is the only way to answer the study question. The trial was based on an adequate sample size calculation and had sufficient statistical power. The multicentre approach enabled recruitment of sufficient suitable participants in a reasonable period of time and, together with the multi-national distribution of the centers, added to the generalizability of our findings. Both patient groups were well matched with regard to their baseline characteristics. Furthermore, all patients were treated by experienced, calibrated, and blinded surgeons and examined by experienced, calibrated, and blinded assessors using pressure-sensitive periodontal probes. Importantly, the study was conducted independently of industry and employed a variety of biomaterials from different manufacturers. The selection of these biomaterials was well justified based on the recommendations of a recent clinical guideline workshop for the regenerative treatment of IDs (Nibali et al., 2020; Sanz et al., 2020). That in most defects a combination approach of either DBBM + EMD or DBMM + collagen membrane was used is supported by current evidence that such combination therapies yield the most favourable results (Stavropoulos et al., 2020; Tsai et al., 2020). Finally, the data analysis was conducted by an independent expert statistician who was not involved in the clinical phases of the trial.

Interestingly, the direction and magnitude of the between-group effect (favouring early vs. late OT) on the primary outcome was very similar in three of the four centers, whereas no obvious differences were observed in one center. The size of the within-group treatment effect in the four centers could have been affected by the respective patient, by the case/defect selection, and also by slight variations in treatment, such as directions of tooth movements and others.

However, the present study has also some limitations, which are inherent to the study design. It was not possible to blind the examiners for the 6 months' evaluation because at this time point one group of patients (early OT) presented with orthodontic appliances, whereas the other (late OT) group did not. Likewise, a blinding of the orthodontists was not always possible. Furthermore, probing measurements at all six tooth sites were sometimes impaired by the orthodontic appliances. The use of a stent with grooves for guiding the probe at the "target sites" was not possible, because teeth would change their position over time. This also precluded the use of reproducible radiographs for the analysis of radiographic bone changes. Altogether, these limitations illustrate the challenges faced during the design and conduct of studies on combined perio-regenerative-orthodontic therapies.

Because of the differences in study protocols with regard to patient and defect selection, regenerative procedures, choice of outcome measures, intervals between periodontal and OT, and lengths of follow-up, the present results cannot be easily compared with those of previously published studies. Only one earlier study has evaluated in a comparative non-randomized fashion the effectiveness of different time points of initiating active orthodontic tooth movement on the regenerative potential of IDs (Attia et al., 2012a). Using a split-mouth design, the authors compared in 15 patients with malocclusion, each contributing three IDs, three protocols: regenerative therapy with bioactive glass and a collagen membrane followed by (1) immediate OT, (2) OT starting after 2 months, and (3) no OT. In defects treated according to modality (1) CAL gains of 5.1 ± 1.4 mm and PPD reductions of 4.0 ± 0.8 mm were found after 12 months as compared to 4.3 ± 0.6 mm and 3.7 ± 0.9 mm in group 2. However, these differences between immediate and delayed OT were not statistically significant. Owing to lack of a sample size calculation, no randomization, and information on treatment allocation and blinding, the study has obviously a high risk of bias as judged by current standards. Still, the authors are to be commended to have addressed the question of

timing and early orthodontic treatment for the first time. It is of interest to note that their results are comparable in magnitude with the outcomes of the present large multicentre trial. With regard to the primary outcome, that is, CAL change after 12 months, the mean CAL gains after early and late OT obtained in our study amounted to 5.4 and 4.5 mm, respectively. Previous studies had reported mean values of 5.8 mm (Ghezzi et al., 2008), 4.4 mm (Ghezzi et al., 2013), 3.7 mm (Ogihara & Wang, 2010), and 3.1 mm (Attia et al., 2019). As indicated above, there is an ongoing debate whether the application of orthodontic forces during the healing after regenerative surgery may be detrimental or rather beneficial for the periodontal outcomes.

In order to put the magnitude of CAL gains into perspective, a comparison with reported CAL changes following regenerative procedures in IDs in stage III periodontitis are of interest. Here, in a recent systematic review which included 79 RCTs and various regenerative techniques, CAL gains between 1.3 and 4.8 mm were reported (Nibali et al., 2020). Thus, the measured CAL gains in the present study following combined perio-regenerative/orthodontic treatment are on the higher end of the scale. This can be due to differences in initial defect selection and in particular baseline defect morphology in the different studies, as shown by Nibali et al. (2021). However, this comparison may also indicate an enhancement of healing due to the applied biomechanical forces and the resulting occlusal equilibration when regenerative procedures are combined with OT.

Up to now, only one RCT has compared regenerative surgery without or with "limited" orthodontics after 4 weeks (Ogihara & Wang, 2010). The authors assessed periodontal outcomes after the application of slight extrusive forces 4 weeks after regenerative surgery of IDs mainly in molar teeth. At 12 months, no significant differences in CAL gains and PPD reduction could be found between the groups. Data of the 6-month follow-up from the present randomized multicentre trial also allowed a direct comparison between the clinical healing of IDs with or without the influence of OT. The CAL gain after 6 months in the early OT group (under the influence of 5 months of active orthodontic tooth movement) amounted to 4.7 mm, whereas in the late OT group (no orthodontic tooth movement), 4.1 mm of CAL gain was obtained. Even though the present RCT was not primarily designed for this comparison because the predetermined study end point was at 12 months, these observations can be cautiously interpreted as OT having no detrimental but perhaps a slight beneficial effect on the periodontal outcome after 6 months.

These findings are in line with indirect evidence that was put forward and discussed in a previous publication (Tietmann et al., 2021). The authors compared data from two independent retrospective cohort studies; in both of them patients with IDs with similar baseline characteristics with regard to mean bone level and PPD were treated in the same practice with the same protocol, including the regenerative surgical procedure, outcome measures, and follow-up. In one of the cohorts, there was no need for orthodontic tooth movement (Bröseler et al., 2017), whereas in the other cohort the necessary OT was initiated 3 months after regenerative surgery (Tietmann et al., 2021). Within all limitations of such an indirect comparison using a "historical control group", it was interesting to observe that the improvements with regard to mean radiographic bone level gain in the cohort with combined perio/orthodontic therapy were higher (4.6 mm) than in the cohort, where patients did not undergo OT (3.9 mm). Even though in these studies the mean radiographic bone level gain was the primary outcome as compared to the CAL gain in the present RCT, the magnitude of differences in outcome between groups with and without OT was quite similar. Moreover, in the cohort studies (Bröseler et al., 2017; Tietmann et al., 2021) the selection of biomaterials was very similar to that in the present RCT.

Taken together, these findings seem to indicate a possible "stimulating" effect of orthodontic tooth movement in the early healing phase on the regenerative outcomes, as previously suggested (Vardimon et al., 2001; Diedrich et al., 2003; Nemcovsky et al., 2004; Attia et al., 2012b). However, as stated above, these observations should be interpreted with great caution. Further well-controlled, pre-clinical experiments are needed to elucidate the effects of mechanical loading on the early and late healing events after regenerative procedures.

With regard to secondary outcomes, the mean PPD reduction we observed following early and late OT of 4.2 and 3.9 mm, respectively, are in agreement with the mean PPD reduction ranging from 3.2 to 5.5 mm in previous studies (Ghezzi et al., 2008; Ogihara & Wang, 2010; Attia et al., 2012a; Ghezzi et al., 2013; Roccuzzo et al., 2018). The frequency of pocket closure (PPD ≤ 4 mm) in the present study was 91% and 85%, respectively. These values compare well to the 84% observed by Tietmann et al. (2021) and are also in agreement with a reported frequency of 17% of pockets with residual PPD >4 mm after 10 years, by Roccuzzo et al. (2018).

According to a recently published commentary, the lack of an accurate "gold standard", a research-based moment for initiating orthodontic tooth movement after periodontal therapy, would demonstrate that a "grey zone" of evidence remains and knowledge on periodontal wound-healing dynamics may be considered the best "biologic starting point" of orthodontic treatment for treated periodontitis patients (Pini Prato & Chambrone, 2020). The authors proposed a personalized periodontal algorithm and postulated that OT should be initiated 1 year after regenerative treatment. In view of the present new evidence, such a cautious approach should be revisited. OT may be initiated much earlier with no detrimental effects on the healing outcomes and with the prospect of a shortened overall treatment time for the patient.

5 | CONCLUSION

The findings of the present randomized trial have demonstrated that in stage IV periodontitis, teeth with IDs and in need of orthodontic tooth movement, in patients who adhered well to regular SPT and maintained a high level of oral hygiene, OT can be initiated as early as 4 weeks after regenerative surgery with favourable periodontal outcomes that are at least as good as those obtained after delayed OT.

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ETHICS STATEMENT

Ethical approval was obtained by the Ethical Committee, University of Bonn (code 034/16) for the centres Bonn and Aachen and by the competent local authorities for the centres Torino (code PROT 04-2017) and Madrid (code 16/492-E).

CONFLICT OF INTEREST

The authors declare no conflict of interest with regard to this study, that was partially funded by an Advanced Researcher Grant (15-249) of the Osteology Foundation to KJ and S.

AUTHOR CONTRIBUTIONS

Karin Jepsen and Søren Jepsen contributed to the conception and design of the study; Karin Jepsen, Christina Tietmann, Eric Kutschera, Peter Wüllenweber, Daniele Cardaropoli, Lorena Gaveglio, Ignacio Sanz Sanchez, and Conchita Martin contributed to the clinical phases of the study and collected the data; Rolf Fimmers contributed to the statistical analysis; Karin Jepsen and Søren Jepsen contributed to interpretation of the data and drafted and finalized the manuscript. All authors critically reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Zielsetzung der Arbeit

Diese Arbeit hatte als Fortführung der multizentrischen randomisierten Studie das Ziel, die Auswirkung der kombinierten, regenerativ-parodontalchirurgischen und kieferorthopädischen Therapie auf die parodontalen Parameter und die Mundgesundheitsbezogene Lebensqualität (OHrQoL) der Patienten nach 24 Monaten zu untersuchen.

Methoden und Ergebnisse

Den 43 Patienten der multizentrischen prospektiven Studie *Jepsen et al. (2021)* wurden zwölf Fragen bezüglich der allgemeinen Mundgesundheit „general oral health assessment index" GOHAI bei Beginn der Behandlung und nach 6, 12 und 24 Monaten gestellt, die sie nach einer Likert-Skala (0=nie bis 4= sehr oft) beantworten mussten. Die Ergebnisse der Fragen wurden addiert bzw. bei inversen Fragen umgekehrt und dann zu einer Endskala von 0-48 Punkten reichend addiert. Hohe Punkte der Endskala ließen auf starke Beeinträchtigung, niedrige auf geringe Beeinträchtigung der OHrQoL schließen.

Gleichzeitig wurden die Ergebnisse bezüglich der klinischen Parameter CAL und PPD in den beiden Gruppen – früher (4 Wochen) vs. später Beginn (6 Monate) der kieferorthopädischen Therapie – nach 24 Monaten nachuntersucht.

Alle Patienten wurden in einem UPT-Programm während der Studie in kurzen Intervallabständen betreut.

Nach 24 Monaten zeigten sich statistisch signifikant bessere Ergebnisse bezüglich CALg in der Gruppe mit frühem Beginn der kieferorthopädischen Zahnbewegung (CALg 5,96 ± 2,1 mm) im Vergleich zu spätem Beginn (CALg 4,65 ± 1,7 mm) nach regenerativer Therapie. Im Vergleich zu den Ergebnissen 12 Monate nach regenerativer Therapie (*Jepsen et al., 2021*) war eine weitere statistisch signifikante Verbesserung nach 24 Monaten mit 1.31mm CALg zu Gunsten der frühen kieferorthopädischen Zahnbewegung nach regenerativer Parodontalchirurgie zu beobachten. In gleicher Weise konnten die PPD zwischen 12 und 24 Monaten bei frühem und spätem Beginn der kieferorthopädischen Therapie konstant gehalten und eine Taschenelimination (PC) von 91% bzw. 90% erzielt werden.

Der Gewinn an OHrQoL verbesserte sich in beiden Gruppen während der fortlaufenden Therapie, ohne dass Unterschiede bezüglich früher oder später beginnender kieferorthopädischer Zahnbewegung nach regenerativer Therapie festgestellt werden konnten. Patienten, die nach 24 Monaten die kombinierte Therapie beendet hatten, zeigten eine höhere Zufriedenheit als Patienten, bei denen die kieferorthopädische Therapie zu diesem Zeitpunkt noch nicht abgeschlossen war. Einzelheiten sind der Abbildung 2 der zugrunde Originalpublikation zu entnehmen.

Schlussfolgerung

In dieser randomisierten multizentrischen Studie konnte erstmalig gezeigt werden, dass die kombinierte regenerativ-parodontalchirurgische Therapie mit anschließender kieferorthopädischer Zahnbewegung auch nach 24 Monaten zu signifikant verbesserten parodontalen Parametern geführt hatte. Dabei war bei frühem Beginn der kieferorthopädischen Zahnbewegung nach regenerativer Therapie ein statistisch signifikant höherer Gewinn an CAL zu beobachten. Die Patienten nehmen die kombinierte Therapie als deutlichen Gewinn an Lebensqualität in Bezug auf die Mundgesundheit (OHrQoL) wahr.

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Synergy of Regenerative Periodontal Surgery and Orthodontics Improves Quality of Life of Patients with Stage IV Periodontitis: 24-Month Outcomes of a Multicenter RCT

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Abstract: In stage IV periodontitis patients with pathologic tooth migration (PTM), interdisciplinary treatment includes regenerative periodontal surgery (RPS) with an application of biomaterials and orthodontic therapy (OT) to restore function, esthetics and thereby quality of life (QoL). In a 24-month randomized trial we explored the synergy between regenerative medicine and biomechanical force application. The following methods were used: Forty-three patients had been randomized to a combined treatment comprising RPS and subsequent OT starting either 4 weeks (early OT) or 6 months (late OT) post-operatively. Clinical periodontal parameters and oral health-related QoL (GOHAI) were recorded up to 24 months. We obtained the following results: Mean clinical attachment gain (ΔCAL $\pm$ SD) was significantly higher with early OT (5.96 $\pm$ 2.1 mm) versus late OT (4.65 $\pm$ 1.76 mm) (p = 0.034). Pocket closure (PPD $\leq$ 4 mm) was obtained in 91% of defects with early OT compared to 90% with late OT. GOHAI-scores decreased significantly from 26.1 $\pm$ 7.5 to 9.6 $\pm$ 4.7 (early OT) and 25.1 $\pm$ 7.1 to 12.7 $\pm$ 5.6 (late OT). Inconclusion, teeth severely compromised by intrabony defects and PTM can be treated successfully by RPS followed by early OT with the advantage of an overall reduced treatment time. As a result of the combined periodontal-orthodontic therapy, the oral health-related QoL of patients was significantly improved. Early stimulation of wound healing with orthodontic forces had a favorable impact on the outcomes of regenerative periodontal surgery.

Keywords: oral health-related quality of life; oral rehabilitation; regenerative periodontal therapy; orthodontic tooth movement; pathologic tooth migration; bovine bone mineral; collagen; enamel matrix derivative; stage IV periodontitis; randomized clinical trial

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1. Introduction

In stage IV periodontitis patients with pathologic tooth migration (PTM), the sole treatment of periodontitis is usually not sufficient to restore oral health, correct masticatory dysfunction/malocclusion and improve their quality of life (QoL). The periodontal status of these patients is characterized by a similar severity and complexity in terms of inflammation, attachment and bone loss, as in stage III periodontitis, but may require a combined periodontal/orthodontic treatment (OT) for oral rehabilitation in order to restore function and esthetics [1–4].

It is well established that a regenerative periodontal treatment of intrabony defects can be successfully performed using various surgical procedures and biomaterials [5–9], provided that periodontal inflammation is under control by means of steps 1 and 2 of periodontal therapy. The combination of periodontal regenerative surgery (RPS) and consecutive orthodontic tooth movements in stage IV periodontitis patients was found to be efficient effective in the short-term [10], and the outcomes to be stable for up to 10 years under the premise of an adherence to a strict oral hygiene/maintenance protocol [11–15].

The optimal time interval between regenerative periodontal surgery and the initiation of OT has always been a matter of debate. Pini Prato and Chambrone (2020) [16] proposed waiting until the endpoint of regenerative therapy has been reached in order not to interfere with periodontal wound healing. In contrast, other authors have suggested a "stimulating" effect of early orthodontic tooth movement on the regenerative outcomes [17–19]. Several case reports [20–24], and a randomized clinical trial (RCT) [10], demonstrate that teeth severely compromised by intrabony defects and PTM can be treated successfully by regenerative surgery followed by early OT, with the advantage of an overall reduced treatment time.

Nevertheless, a gain in clinical attachment (CAL) and radiographic bone level, as well as reduction in probing pocket depths (PPD) and bleeding on probing (BOP) alone, may not be sufficient to evaluate the overall success of stage IV periodontitis treatment. Patient-related outcomes (PROMs) as "true endpoints" are reported to be equally or more relevant to patients' daily lives [25,26] and it has been suggested that appropriate oral health-related quality of life (OHrQoL) outcomes should be included in the design of clinical studies [27]. Based on the rationale of a broader view of oral health and its rehabilitation, a number of tools have been introduced in order to measure the extent to which oral conditions affect an individual's behavior and social life, as well as to complement the conventional clinical assessments of oral health [28–33].

Several studies reported that patients with more severe periodontitis rated their OHrQoL as poorer than those who had less severe periodontitis [29,34–36]. In addition, a positive perception by patients of the outcomes of long-term supportive therapy after regenerative surgery could be shown [37].

Malocclusion is an important and prevalent oral health problem worldwide [38,39] and has a negative impact on OHrQoL [40,41]. However, at present, there are no data from studies available that have evaluated the impact on OHrQoL in stage IV periodontitis with pathological tooth migration. Likewise, to the best of our knowledge, no studies have investigated the impact on OHrQoL of a combined periodontal and orthodontic treatment to restore function and esthetics in these patients [4].

A recent multi-center randomized trial [10] evaluated the periodontal outcomes of regenerative surgery in stage IV periodontitis patients in combination with staged orthodontic therapy after 12 months. Secondary outcomes of the study protocol also included OHrQoL measures at the baseline and up to 24 months. Here, we report the impact of the combined periodontal–orthodontic treatment on changes of clinical periodontal parameters and oral health-related quality of life.

2. Materials & Methods

2.1. Study Design and Patients

The present manuscript reports secondary outcomes of a prospective multicenter, multinational, randomized, parallel-group clinical trial (ClinicalTrials.gov, identifier: NCT 02761668) after 24 months. Special emphasis was given to patient-reported outcomes. The study protocol had been previously approved by the respective ethical committees for human subject trials from the centers participating in the study. The lead ethics committee was at the University of Bonn (code 034/16).

In brief, 43 patients with stage IV periodontitis were periodontally treated (steps 1–3 of periodontal therapy). Teeth with pathologic tooth migration and intrabony defects received regenerative periodontal surgery as described by Cortellini and Tonetti [5], fol-

lowed by orthodontic treatment (OT) initiated 4 weeks after regenerative surgery (early OT, n = 23 patients) or 6 months after regenerative surgery (late OT, n = 20 patients) (Figure 1).

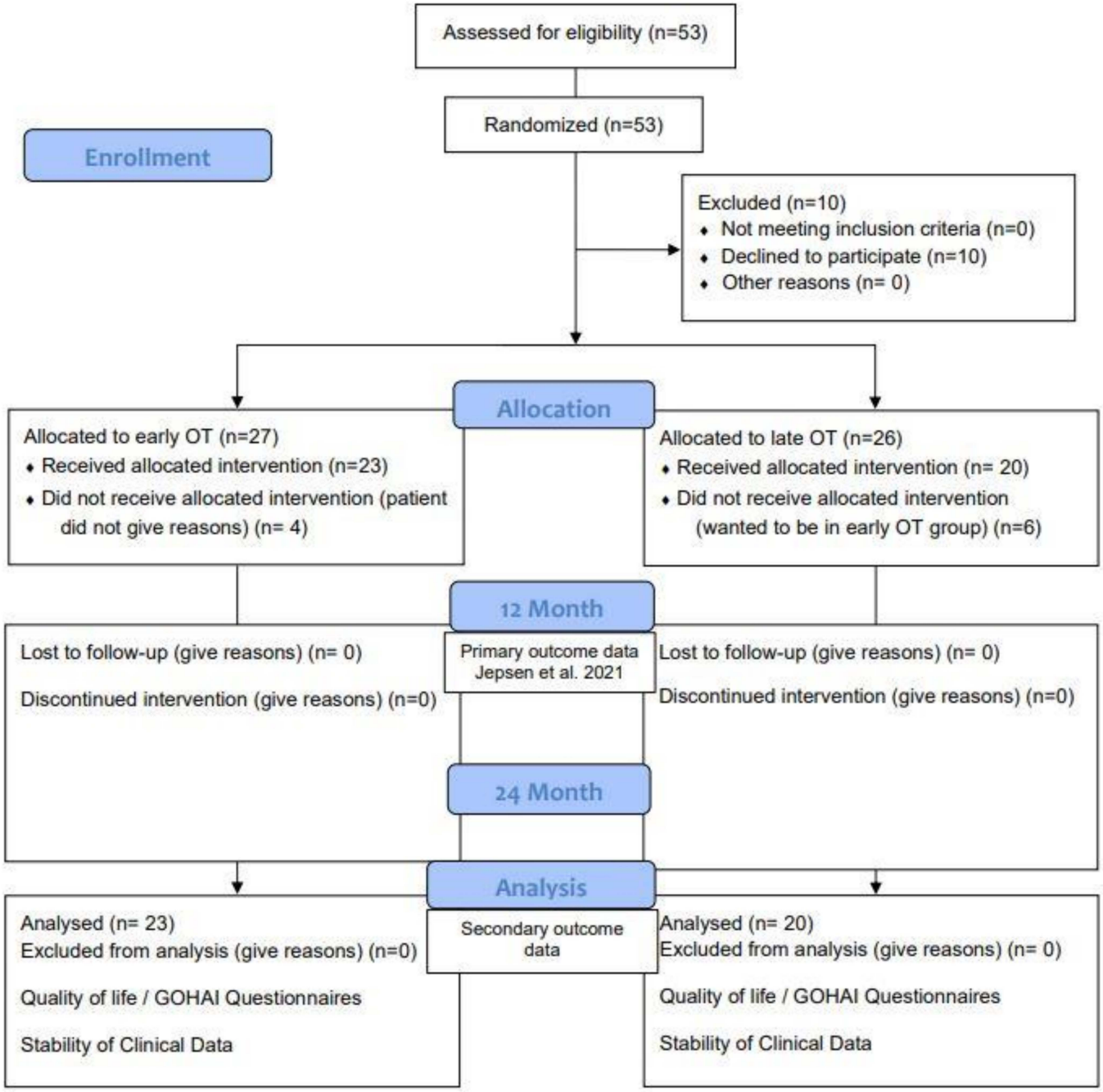


Figure 1. Study flowchart following CONSORT (Consolidated Standards of Reporting Trials) guidelines for clinical trials. Fifty-three patients met the inclusion criteria, 26 patients were allocated to the group with late orthodontic therapy (OT) after regenerative periodontal surgery, and 27 to the group with early OT after regenerative periodontal surgery. A total of 10 patients withdrew from the study, 6 expected to be part of the early and withdrew after allocation to the late treatment group. The other 4 patients allocated to the test group did not want to continue the study without giving any reason. All patients of the study completed their 24-month examination.

The details of the study protocol were presented in a previous paper reporting 12-month clinical results [10].

2.2. Minimally Invasive Regenerative Periodontal Surgery

Microsurgical approaches, adapted to the treatment algorithm by Cortellini and Tonetti (2015), were applied to access the defects. A bone substitute (DBBMc, Bio Oss® Collagen; Geistlich, Wolhusen, Switzerland) was used to fill the defect and to prevent a soft tissue collapse. In non-contained defects, a collagen membrane (Bio Gide®Perio; Geistlich, Wolhusen, Switzerland) was applied. An enamel matrix derivative (EMD, Emdogain®; Straumann, Basel, Switzerland) was used for contained defects. Suturing was accomplished with non-resorbable 6-0 and 7-0 monofilament material (e-PTFE, W. L. Gore & Associates, Flagstaff, AZ, USA) by internal offset vertical mattress sutures, interrupted single sutures, double sling sutures, or a combination of these for achieving primary closure.

2.3. Orthodontic Therapy

Individual treatment objectives were defined and visualized for each subject. In cases of increased tooth mobility (>grade 1), passive fixed appliances were inserted prior to periodontal therapy for stabilization. Orthodontic tooth movement was carried out using fixed orthodontic appliances and individualized segmented arch mechanics in pre-adjusted 0.022-inch slot-sized brackets. Orthodontic movement was started with a 0.012 nickel–titanium (Ni–Ti) wire, followed by the alignment with the sequence of 0.014 Ni–Ti, 0.016 Ni–Ti, 0.018 Ni–Ti and 0.016 × 0.016 stainless steel wire. Up to the sequence of 0.016, Ni–Ti wire teeth were "secured" by a figure eight ligature in order to provide continuous transmission of orthodontic forces. Maximum emphasis was put on applying low forces and moments. Bone-borne temporary anchorage devices were used in some cases for anchorage reinforcement. Once treatment goals were achieved, orthodontic appliances were removed, and teeth were stabilized with bonded fixed retainers or fiber-reinforced restorations. In all cases, target teeth were moved toward the defect.

2.4. Supportive Care

Frequent recall visits were scheduled at 2 days, 2 weeks and 4 weeks post-surgery. Subsequently, all patients were enrolled in a regular supportive care program every 2 months for the duration of the study. In case of recurrent periodontal inflammation, OT was interrupted until inflammation could be controlled by gentle biofilm removal and oral hygiene reinforcement.

2.5. Periodontal Parameters

For each center, the same expert periodontists performed RPS, expert orthodontists performed OT and the same calibrated examiners collected all clinical parameters. In addition to the previously reported data at baseline, 6 and 12 months, the following periodontal outcome variables were recorded at 24 months:

(1) Clinical attachment level (CAL),
(2) Probing pocket depth (PPD),
(3) Bleeding on probing (BOP),
(4) Full-mouth bleeding scores (FMBS),
(5) Full-mouth plaque scores (FMPS).

2.6. Patient-Reported Outcomes

After thorough explanation of the information to be collected, perceptions of OHrQoL were assessed with a questionnaire given to all participants regarding their oral status at baseline, 6, 12 and 24 months. The twelve-question general oral health assessment index (GOHAI), originally developed by Atchinson and Dolan [42], was used as a tool of measurement in validated translations of the GOHAI questionnaire into the native language of the participants [43–45]. Each of the twelve questions referred to their personal

experience in the previous 3 months and was answered independently by the patient using a Likert scale (0 = "never" to 4 = "very often") (Table S1).

For the evaluation, the answer scores for the twelve questions were summed up after coding [25], and for questions 3, 5 and 7, scoring was inverted and the scale thus ranged from 0–48 [28]. A high value indicates impairments of oral health-related quality of life, and low values indicate only a few problems.

2.7. Data Analysis

Computerized chairside periodontal data entry into a periodontal electronic database [Parostatus, Berlin, Germany or Florida Probe data base, USA] allowed for an export, via excel, into the statistical software program.

Descriptive statistics were summarized as means and standard deviations for quantitative data and frequencies and percentages for qualitative data. Means for each treatment group and differences between treatment groups were presented, along with associated 95% confidence intervals.

The comparison of clinical CAL changes after 24 months between treatment groups was based on a two-sided two-sample *t*-test, at the 5% level of significance. Statistical analysis of the clinical data was performed by an independent biostatistician (RF) using the software IBM® SPSS® Statistics 29 (Software version: 29.0.0).

3. Results

All 43 patients (mean age: 45.4 ± 11.9 years (early OT), 52.0 ± 9.4 years (late OT), 26 females, 17 males) were followed up until the time of their 24-month visit (until January 2022) and when they had completed all of their follow-up examinations (Figure 1). At 24 months, thirty patients had finished the combined treatment with 18 patients (78%) in the early group and 12 patients (60%) in the late group.

3.1. Periodontal Outcomes

Comparing the two treatment protocols, mean clinical attachment level gain (ΔCAL ± SD) after 24 months was statistically significantly higher for early OT (5.96 ± 2.1; CI: 6.8, 5.1 mm) versus late OT (4.65 ± 1.76; CI: 5.4, 3.9 mm) ($p = 0.034$). When compared to 12 months, CAL showed further improvements at 24 months with an intergroup difference from the baseline of 1.31 mm in favor of early OT (Table 1).

Table 1. Changes in clinical parameters CAL and PPD compared to baseline at 12 and 24 months (mean ± SD) for target sites in early and late treatment group. Differences between both groups in CAL change after 24 months (secondary outcome) were tested by unpaired *t*-test.

		Early OT *n* = 23		**Late OT *n* = 20**		**Early vs. Late OT**	
		BL-12 mo	**BL-24 mo**	**BL-12 mo**	**BL-24 mo**	**ΔChange BL-24 mo**	
ΔCAL (mean ± SD)	mm	5.39 ± 2.2	5.96 ± 2.10	4.45 ± 1.7	4.65 ± 1.76	1.31	$p = 0.034$
Estimate	95% CI	[6.3, 4.4]	[6.81, 5.10]	[5.3, 3.6]	[5.42, 3.88]	[2.5, 0.1]	
ΔPPD (mean ± SD)	mm	4.21 ± 1.9	4.43 ± 1.62	3.90 ± 1.5	3.90 ± 1.33	0.53	$p = 0.248$
Estimate	95% CI	[5.0, 3.4]	[5.1, 3.7]	[4.6, 3.2]	[4.5, 3.3]	[1.46, 0.39]	

BL: Baseline, CAL: Clinical Attachment Level, PPD: Probing Pocket Depth, CI: Confidence Interval.

Table 2 depicts descriptive statistics for clinical parameters at baseline (BL), 12 and 24 months. Both groups were well-balanced at baseline with regard to CAL and PPD and showed statistically significant improved outcomes after 12 and 24 months ($p < 0.0001$): Baseline CAL had changed from 9.8 to 3.9 (early OT) and from 9.2 to 4.5 mm (late OT) at 24 months, respectively. Mean probing pocket depths (PPD) remained stable between 12 and 24 months with 2.9 mm (SD: 0.9) in the early OT group and 3.2 mm (SD: 0.9) in the late OT group. Pocket closure (PPD ≤ 4 mm) was obtained in 91% of defects with early OT compared to 90% with late OT. Over the course of treatment, patients maintained their good level of adherence to a strict 2-month performed supportive care protocol and full-mouth

plaque scores were consistently low (FMPS well under 20%). This was accompanied by low full-mouth bleeding scores (FMBS) of 10.5 ± 4.8% vs. 12.7 ± 6.8% (early vs. late) at baseline, 10.6 ± 4.9% vs. 7.7 ± 4.9% at 6 months, 14.7 ± 13.1% vs. 11.3 ± 9.1% at 12 months and 9.2 ± 8.2% vs. 7.2 ± 4.1% at 24 months (Table 3).

Table 2. Clinical parameters (mean ± SD) for target sites in early and late orthodontic treatment (OT) group at baseline, 12 months and 24 months. Differences between follow-up visits in CAL or PPD after 24 months (secondary outcome) were tested by paired *t*-test.

Variable		Early OT (*n* = 23)				Late OT (*n* = 20)			
		Baseline	**12 mo**	**24 mo**	**BL vs. 24 mo**	**Baseline**	**12 mo**	**24 mo**	**BL vs. 24 mo**
CAL (mean ± SD)	mm	9.8 ± 2.5	4.4 ± 1.7	3.9 ±1.9	p <0.0001	9.2 ± 2.5	4.7 ± 2.4	4.50 ± 2.19	p < 0.0001
Estimate	95% CI	[8.8, 10.9]	[3.7, 5.2]	[3.1, 4.7]	[5.0, 6.7]	[8.0, 10.4]	[3.6, 5.8]	[3.5, 5.5]	[3.9, 5.5]
PPD (mean ± SD)	mm	7.3 ± 1.6	3.1 ± 0.9	2.9 ± 0.9	p < 0.0001	7.1 ± 1.7	3.2 ± 1.1	3.2 ± 0.9	p < 0.0001
Estimate	95% CI	[6.6, 8.0]	[2.7, 3.5]	[2.5, 3.3]	[3.7, 5.1]	[6.3, 7.9]	[2.7, 3.7]	[2.7, 3.6]	[3.1, 5.4]
PI	n (%)	4 (17%)	3 (13%)	2 (8%)		1 (5%)	2 (10%)	2 (10%)	
BOP	n (%)	13 (53%)	7 (30%)	4 (17%)		9 (45%)	3 (15%)	0 (0%)	
PUS	n (%)	1	0	0		2	0	0	
Pocket closure (PPD ≤ 4 mm)	n (%)	n/a	21 (91%)	21 (91%)		n/a	17 (85%)	18 (90%)	
Pocket closure (PPD ≤ 4 mm, no BOP)	n (%)	n/a	16 (69%)	18 (78%)		n/a	15 (75%)	15 (75%)	

BL: Baseline, CAL: Clinical Attachment Level, PPD: Probing Pocket Depth, PI: Plaque Index, BOP: Bleeding on Probing, PUS: Suppuration, CI: Confidence Interval.

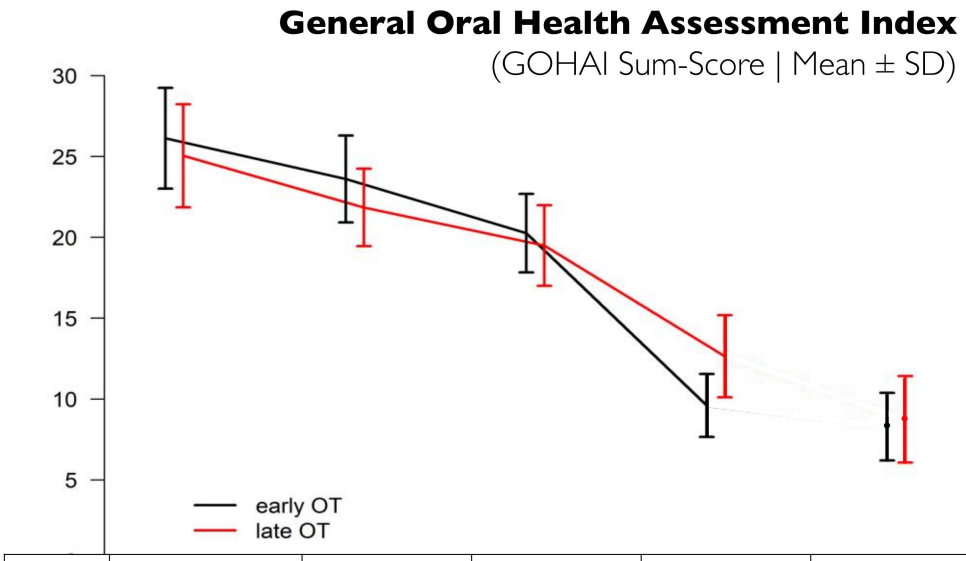
Table 3. Changes of patient-based plaque (FMPS) and bleeding scores (FMBS) over time: at baseline, 6, 12 and 24 months and numbers of patients in the different phases of orthodontic therapy (1 = active, 2 = retention phase, 3 = finished).

Variables		Early OT (*n* = 23)				Late OT (*n* = 20)			
		Baseline	**6 Months**	**12 Months**	**24 Months**	**Baseline**	**6 Months**	**12 Months**	**24 Months**
Orthodontic therapy	Number of patients								
active	n		23	12			20	17	2
retention	n			9	5			3	6
finished	n			2	18			0	12
Full-mouth plaque scores & bleeding scores									
FMPS * (mean ± SD)	(%)	12.9 ± 4.9	15.0 ± 6	16.9 ± 10.1	13.2 ± 7.3	15.2 ± 6.2	15.0 ± 7.0	17.1 ± 8.6	13.4 ± 6.7
	95% CI	[11, 15]	[12, 18]	[13, 21]	[10, 16]	[12, 18]	[12, 18]	[13, 21]	[10, 16]
FMBS ** (mean ± SD)	(%)	10.5 ± 4.8	10.6 ± 4.9	14.7 ± 13.1	9.2 ± 8.2	12.7 ± 6.8	7.7 ± 4.9	11.0 ± 9.0	7.2 ± 4.1
	95% CI	[8, 13]	[9, 13]	[9, 21]	[5, 13]	[10, 16]	[6, 10]	[7, 15]	[5, 9]

* FMPS = full-mouth plaque score [O'Leary-1972], ** FMBS = full-mouth bleeding score (out of 6 sites per tooth).

3.2. Oral Health-Related Quality of Life (OHrQoL)

The OHrQoL of the patients, as measured by GOHAI sum-scores, improved continuously over the course of the study from 26.1 ± 7.5 to 9.6 ± 4.7 for early OT and from 25.1 ± 7.1 to 12.7 ± 5.6 for late OT (Figure 2) without relevant differences between the two treatment groups. In a subgroup of patients that had already completed the combined perio-ortho treatment at 24 months (n = 18/23 for early OT and n = 12/20 for late OT), the final GOHAI scores showed to be very similar (8.1 ± 4.4 vs. 8.8 ± 4.7).



	Baseline Surgery n=43	6 months n=43	12 months n=43	24 months n=43	OT completed within ≤ 24 months, n=30
Late OT	**25.1±7.3**	**21.9±5.5**	**19.5±5.7**	**12.7±5.8**	**8.8±4.7**
Early OT	**26.1±7.6**	**23.6±6.6**	**20.3±5.9**	**9.6±4.8**	**8.1±4.4**

Figure 2. Patient-reported oral health-related quality of life (OHrQoL) as assessed by GOHAI sum-scores recorded at baseline (before surgery), at 6, 12, and 24 months. Mean GOHAI scores (± SD) in subjects (n = 43) treated with late OT (red line) and early OT (black line). Mean GOHAI scores (±SD) for subjects (n = 30) with OT completed in less or equal to 24 months are presented separately. GOHAI scores are expressed as total sum scores with all 12 questions included (values ranging from 0 to 48) with higher scores indicating greater negative impact on oral health-related quality of life [28].

4. Discussion

The results of this 24-month follow-up of a multicenter RCT provide evidence that early stimulation of periodontal wound healing with biomechanical forces has a favorable impact on the clinical outcomes of regenerative periodontal procedures in stage IV periodontitis patients with pathologic tooth migration. The present findings also support the hypothesis that a combined periodontal regenerative and orthodontic treatment could significantly improve the oral health-related quality of life of these patients. Both of the above findings are novel and of high clinical relevance.

The scientific rationale for our previous study [10] was the limited information available on the treatment of patients with stage IV periodontitis with intrabony defects and pathologic tooth migration in need of orthodontic therapy. The optimal interval between regenerative periodontal surgery and orthodontic therapy (OT) had been a matter of ongoing debate. The principal findings after 12 months were that significant periodontal improvements of a similar magnitude were observed following early (after 4 weeks) or late (after 6 months) initiation of OT.

So far, to the best of our knowledge, no other randomized clinical study has evaluated the effect of the timing of OT on periodontal outcomes over a period of 24 months. These findings confirm a suspected "stimulating" effect of early OT on regenerative outcomes [17–19,23]. Both healing after RPS and healing after OT are highly coordinated processes in which various cells, such as immune, bone and periodontal ligament (PDL) cells, cytokines and signals/pathways, are involved. The whole periodontal attachment apparatus, including the alveolar bone, exhibits biological responses and changes, including a modification of the local vascularization. As known from wound healing studies, cells can respond to mechanical signals and micromechanical forces, where micro-deformations on the cellular level can stimulate cell proliferation and division [46]. In particular, PDL fibroblasts are mechano-sensing cells responsible for a complex immune response associated with

the initiation of bone remodeling [47]. Fibroblasts can react to micro-deformational forces with increased proliferation and expression of collagen type I, basic fibroblast growth factor and transforming growth factor beta [48]. Mechanosensitive cells of the periodontium possess the ability to respond to a mechanical load by changing their cellular functions, including, among others, cytoskeletal rearrangement [47,49,50]. Mechanical stress of an appropriate amount which is applied to the cell membrane is detected, among others, by integrins and focal adhesion molecules, and, in this way, it triggers the assembly of specified "stress fibers" of the cytoskeleton. The latter is connected to the nuclear lamina by the linker of nucleoskeleton and cytoskeleton (LINC) complex [51]. In this way, the rearrangement of the cytoskeleton is transduced to the nucleus, leading to transcriptional changes affecting pathways that regulate cell proliferation, differentiation, motility, as well as the production of cytokines and growth factors [52].

In periodontal disease [stage III or IV], the wound associated with intrabony periodontal defects remains in the inflammatory phase and fibroblasts cannot perform their tasks due to the inflammatory environment. It is known that, in the initial phase of tooth movement, mechanical forces distort the interstitial space within the PDL and alveolar bone [53,54]. By application of micro-mechanical forces applied shortly after regenerative surgery, wound micro-deformations may induce cellular proliferation and migration [46] and enhance periodontal regeneration as well as tissue remodeling [55]. However, it has to be realized that the biological mechanisms underlying orthodontic tooth movement are still not fully understood [56]. More well-designed preclinical experiments have to be performed in order to elucidate the synergy between regenerative medicine and biomechanical force application in periodontal defects to explain the favorable clinical outcomes of the present study.

To the best of our knowledge, no other prospective study has investigated the impact of a combined periodontal–orthodontic therapy on the quality of life of patients with stage IV periodontitis affected by pathologic tooth migration. The finding of significant improvements in OHrQoL, as measured by a continuous reduction in GOHAI scores, confirms that the combined treatment not only improved the objectively assessed periodontal conditions of the patients but also their subjective perception of regained oral health, due to improved esthetics and function.

Earlier studies have already demonstrated that periodontal therapy has a positive impact on OHrQoL in patients affected by periodontitis, as measured by various accepted scoring systems [57–60]. These effects were mainly reported between 1 week and up to 12 months following the non-surgical periodontal treatment. No significant differences in the positive impact on OHrQoL were seen when comparing quadrant-wise scaling and root planing versus one-stage full-mouth disinfection [61]. Patients treated by periodontal surgery reported a worse OHrQoL in the first post-operative week [62]. With regard to the impact of periodontal surgery compared to non-surgical treatment, in some studies a low impact was observed [58,63–65] whereas others reported more pronounced additional improvements following surgery [66]. It has also been shown that orthodontic therapy has a positive impact on OHrQoL in patients affected by malpositioned teeth/malocclusion. Most of these studies, however, were conducted in children and adolescents [67]. Little, if any, information is available on adults [68]. Based on these reports of positive impacts on OHrQoL of orthodontic therapy in patients with malocclusion and of periodontal therapy in patients with periodontitis it can be assumed that the significant improvements observed in the present study can be attributed to both components of the combined therapy.

GOHAI sum scores, in the way they were calculated in the present study, can range between 48 (worst OHrQoL) and 0 [28,69]. The GOHAI rather than the alternative OHIP scoring system was chosen for the present study based on the findings by Öhrn and Jönsson [28]. With regard to the magnitude of the effect observed, already at 12 months after periodontal surgery mean GOHAI scores were reduced by about 6 points and decreased by another 7 (late OT) and 10 points (early OT) at 24 months, respectively. Interestingly, in the subgroup of patients in whom orthodontic treatment was completed at 24 months,

the mean GOHAI scores were below 9, with no difference between the groups. In the absence of a meaningful benchmark for comparison between mean scores, Tsakos [70] proposed to employ minimally important differences (MID) instead to assist data interpretability. Following this suggestion, Jönsson and Öhrn [69] established a MID of 3 for improvements in GOHAI scores in 87 patients before, and at 12 months after, non-surgical periodontal therapy.

At present, no such MID values have been reported for the treatment of stage IV periodontitis patients. However, the significant improvements in OHrQoL (>15 GOHAI score points) in the present study compare favorably with a reduction of 5.4 points, as reported in a recent systematic review with meta-analysis, following prosthetic rehabilitation of fully/partially edentulous with previous periodontitis [71].

The present 24-month follow-up of an RCT has several strengths, such as the prospective well-controlled design, the length of follow-up, the high adherence of the patients to supportive care and compliance with a high level of self-performed oral hygiene, and the multi-center, multi-national approach, among others. On the other hand, the limited number of subjects and the fact that patients were treated in specialist settings may limit the generalizability of the results.

Future interdisciplinary studies with close cooperation between periodontics and orthodontics are warranted. A further exploration of the synergy between regenerative periodontal medicine and biomechanical orthodontic forces and their impact on the patients' OHrQoL is of high clinical relevance because it is well-known that many adult patients affected by severe periodontitis are interested in seeking orthodontic treatment for oral rehabilitation due to the esthetic and functional changes caused by pathologic tooth migration [72].

5. Conclusions

Within the limitations of this study, taken together, the findings of the present 24-month follow-up show that a combined periodontal regenerative and orthodontic treatment for patients with good adherence to supportive care protocols resulted in:

(1) significantly improved periodontal conditions,
(2) significantly higher CAL-gain for early initiation of OT,
(3) an overall significantly improved OHrQoL.

From the perspective of oral rehabilitation, orthodontic therapy plays an important role in the comprehensive treatment of stage IV periodontitis patients. More well-designed preclinical studies are warranted to further elucidate the mechanisms underlying the observed synergy between periodontal regenerative medicine and orthodontic biomechanical force application in advanced periodontitis.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/bioengineering10060695/s1, Table S1: Questionnaire for patient reported outcomes (impact on patients' OHrQoL).

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee, University of Bonn (code 034/16) for the centers Bonn and Aachen and by the competent local authorities for the centers in Torino (code PROT 04-2017) and Madrid (code 16/492-E).

Informed Consent Statement: Written informed consent for publication was obtained from all participating patients involved in the study and to publish this paper.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest with regard to this study.

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Zielsetzung der Arbeit

Die kieferorthopädische Therapie mittels Multibandapparaturen ist bei der Behandlung von Erwachsenen häufig mit ästhetischen, funktionellen und phonetischen Beeinträchtigungen verbunden. Nachdem in den vorherigen Studien festgestellt werden konnte, dass die kombinierte regenerativ-parodontalchirurgische Therapie mit anschließender kieferorthopädischer Zahnbewegung mittels Multibandapparaturen bei Stadium IV Parodontitis erfolgreich zum Zahnerhalt und zur Verbesserung der parodontalen Parameter eingesetzt werden kann, sollte in der vorliegenden Arbeit untersucht werden, ob diese kombinierte Therapie auch mit neueren, kaum sichtbaren Clear Alignerschienen (CA) möglich ist.

Methoden und Ergebnisse

Zehn Patienten mit Stadium IV Parodontitis und pathologischer Zahnwanderung (PTM) und insgesamt 103 intraossären Defekten wurden nach erfolgreicher antiinfektiöser Therapie (AIT) parodontalchirurgisch regenerativ mit DBBMc mit oder ohne CM oder EMD in einer parodontologischen Fachzahnarztpraxis behandelt. Die kieferorthopädische Zahnbewegung durch Clear Alignerschienen wurde erst begonnen, wenn die Zahnmobilität < 2 betrug, was im Mittel nach 4,5 Monaten der Fall war. Die Patienten wurden angewiesen, die Clear Alignerschienen mindestens 22 Stunden pro Tag zu tragen und alle zwei Wochen durch die nachfolgende Schiene auszutauschen. Während der kieferorthopädischen Therapie wurden die Patienten in kurzen Intervallabständen in der UPT betreut.

Die Veränderung des radiologischen Knochenniveaus (rBL) und der Sondierungstiefen (PPD) wurde ein Jahr nach regenerativer Therapie und nach Abschluss der kieferorthopädischen Therapie nachuntersucht. Es zeigte sich ein statistisch signifikant mittlerer radiologischer Knochengewinn von 2,13 ± 1,64mm ein Jahr nach regenerativer Therapie und 3,02 ± 2,00mm nach Beendigung der kieferorthopädischen Zahnbewegung. PC wurde in 73% aller Defekte ein Jahr nach regenerativer Therapie erreicht, was mit 76% PC bei Beendigung der kieferorthopädischen Zahnbewegung stabil blieb.

Schlussfolgerung

Durch diese Studie konnte erstmalig aufgezeigt werden, dass der Einsatz von Clear Alignern in der kombinierten regenerativ-parodontalchirurgischen und kieferorthopädischen Therapie bei Patienten mit Stadium IV Parodontitis und PTM eine mögliche alternative Option ist.

Clinical effectiveness of regenerative periodontal surgery and orthodontic tooth movement with clear aligners in stage IV periodontitis: a case series

Christina Tietmann, Dr med dent/Søren Jepsen, Prof, Dr med, Dr med dent, MS/Roxana Kauer/Karin Jepsen, PD, Dr med dent

Objectives: To evaluate the clinical effectiveness of regenerative treatment of intrabony defects in combination with consecutive orthodontic therapy with clear aligners in stage IV (type 2) periodontitis. **Method and materials:** Ten patients with a total of 103 intrabony defects were analyzed after regenerative surgery using collagen-deproteinized bovine bone mineral with or without collagen membrane or enamel matrix derivative followed by orthodontic therapy with clear aligners. Changes in radiographic bone level and probing pocket depths were evaluated after 1 year (T_1) and at final splinting (T_2) after orthodontic tooth movement. **Results:** Mean radiographic bone level gain was significant, with 2.13 ± 1.64 mm at T_1 and 3.02 ± 2.00 mm at T_2. Mean probing pocket depth was significantly reduced from 5.40 ± 1.80 mm at baseline to 3.78 ± 1.73 mm at T_1, and remained stable with 3.73 ± 1.70 mm at T_2. Pocket closure (≤ 4 mm probing pocket depth) was accomplished in 76% of all defects. Tooth loss amounted to 2.9%. **Conclusion:** Within the limitations of the retrospective study design, the findings suggest that the interdisciplinary treatment of periodontitis stage IV by regenerative periodontal surgery and consecutive orthodontic therapy with clear aligners can lead to favorable results. *(Quintessence Int 2024;55:348–357; doi: 10.3290/j.qi.b5213521)*

Keywords: bovine bone mineral, clear aligner, orthodontic tooth movement, pathologic tooth migration, regenerative periodontal therapy, stage IV periodontitis

The complexity of severe periodontal attachment loss, high prevalence of intrabony defects, pathologic tooth migration (PTM), bite collapse, and secondary occlusal trauma in stage IV periodontitis may require the combination of periodontal regenerative and orthodontic treatment, according to the recently published clinical practice guideline (CPG).[1-3] This interdisciplinary approach of periodontal regenerative and consecutive orthodontic therapy (OT) aims at controlling periodontal infection, reconstructing vertical defects, and realigning migrated teeth to restore function and esthetics for a good long-term prognosis of the dentition of the patients.

While it is well known that the combination of periodontal and orthodontic tooth movement with fixed appliances is not on average associated with any significant adverse effects in periodontitis patients once successful steps 1 and 2 have been achieved,[3-6] a considerable benefit for enhanced periodontal parameters of the combined periodontal and orthodontic therapy in comparison to periodontal therapy alone has been documented in a recent systematic review.[7] If periodontal regenerative therapy of intrabony defects is combined with orthodontic tooth movements in stage IV periodontitis, an even more pronounced improvement of periodontal outcomes and long-term stability was observed in retrospective studies with a large number of defects.[8,9] In addition, early timing of OT – by 1 month after regenerative therapy – did not lead only to similar outcomes of clinical periodontal parameters at 12 months, but also to significantly greater clinical attachment level (CAL) gain and improved quality of life in patients with stage IV periodontitis at 24 months after regenerative treatment, as a recent multi-center randomized clinical trial revealed.[10,11]

Impaired function and esthetics are the major interests of adult patients diagnosed with periodontitis to seek orthodontic treatment, with the majority of patients indicating a preference for clear aligners. They expressed that visibility of the orthodontic appliance would be a matter of concern.[12] Although the use of transparent aligner therapy seems to give an advantage in terms of the patient preference for esthetics, objective outcomes, such as occlusion or the condition of periodontal tissues, are the prime matter of concern. The impact of clear aligners on periodontal health versus fixed orthodontic appliances in the long term have been discussed controversially.[13-21] While the benefit of the combined regenerative periodontal and consecutive orthodontic therapy with fixed orthodontic appliances in the treatment of stagy IV periodontitis is well documented,[8-11] only limited data exist on the interdisciplinary concept with clear aligners in patients diagnosed with stage IV periodontitis.[22]

The aim of this retrospective analysis was to evaluate the clinical effectiveness with regard to radiographic bone level (rBL) gain of regenerative periodontal surgery of intrabony defects in combination with subsequent orthodontic tooth movement by clear aligners in patients with stage IV periodontitis and PTM.

Method and materials

Study design and patients

This retrospective analysis included data of ten patients presenting with severe periodontitis and PTM (stage IV periodontitis, case type 2,[3] treated by an interdisciplinary approach in a periodontal specialty practice (CT) in Aachen, Germany. The interdisciplinary treatment consisted of a comprehensive periodontal therapy including regenerative periodontal surgery and subsequent orthodontic tooth movement with clear aligners, between 2016 and 2023.

The study was conducted in accordance with the Helsinki Declaration (version 2008) and approved by the Ethics committee of the University of Bonn (#16/23). All patients had given their written informed consent for a retrospective evaluation of their clinical and radiographical data.

Inclusion criteria for the analysis were:

- successfully completed steps 1 and 2 of periodontal therapy as exhibited by an adequate oral hygiene and control of inflammation (full-mouth plaque score [FMPS] of ≤ 20% and full-mouth bleeding score [FMBS] of ≤ 20%)
- one- or two-wall intrabony defects (3 mm or deeper) with indication for periodontal regenerative surgery and PTM requiring OT
- clinical and radiographic data of a continuous follow-up from 1 year after regenerative surgery up to final splinting after OT
- aligner therapy was delayed until tooth mobility was < 1.[23]

Exclusion criteria were:

- noncompliance with supportive periodontal therapy
- incomplete probing or radiographic data
- additional surgical or maxillofacial treatment in the areas of interest.

Patients with systemic diseases (ie, controlled diabetes) were not excluded. All patients were nonsmokers.

Based on these criteria, ten patients with a total of 103 regeneratively treated intrabony defects and subsequent OT by clear aligners were included in the analysis.

Treatment

Regenerative periodontal surgery

Regenerative surgery of teeth with intrabony defects was performed by a single experienced periodontist (CT) after successful step 1 and 2 periodontal therapy and orthodontic consultation in the period of 2016 to 2022. After block and/or infiltration anesthesia, a minimally invasive microsurgical approach for incisions and release of the flap for regenerative procedures was used as previously described.[8,9,24,25] Depending on the configuration of the intrabony defect, the biomaterial for grafting of the intrabony defect was chosen. A bone filler was used (collagenous demineralized bovine bone mineral, DBBMc; BioOss Collagen, Geistlich) to prevent a soft-tissue collapse into the defect. If the graft material was at risk for dislocation in noncontained defects, a collagen membrane (CM; Bio Gide Perio, Geistlich) was applied without pin or suture fixation. Enamel matrix derivative (EMD; Emdogain, Straumann) was used in contained defects to enhance periodontal wound healing. Primary tension-free closure of the coronally positioned flap was achieved by modified horizontal mattress sutures and additional single interrupted sutures for papilla adaptation (6-0 monofilament single sutures, Premilene USP6/0-DS13, B. Braun; Seralene USP6/0-DS12 SeragWiessner; Seralene USP6/0-DS15, SeragWiessner). Apical split-flap preparation was only performed if needed for coronal positioning and tension-free flap closure for healing on primary intention.

Postoperatively, a strict anti-infective protocol was administered to the patient including the use of 0.2% chlorhexidine

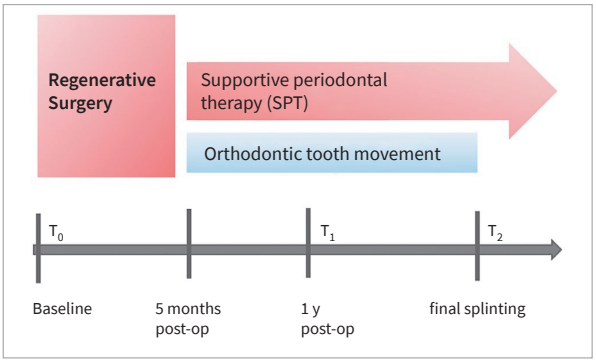

Fig 1 Chronologic sequence of treatment and examinations (T_0, T_1, T_2).

solution three times a day and refraining from mechanical tooth cleaning in the surgically treated areas for 4 weeks or until complete wound healing. After 10 to 14 days, sutures were removed.

Orthodontic therapy

After successful step 1 and 2 of periodontal therapy, orthodontic consultation was performed to define and visualize the individual interdisciplinary treatment options. In cases with increased tooth mobility (> grade 1),[23] removable acrylic splints were inserted to facilitate stabilization of the clot and graft after regenerative therapy. If needed for additional stabilization during surgery, semi-permanent lingual splints were inserted prior to regenerative surgery.

After complete wound healing, intraoral scans of the maxilla and the mandible were taken for concise orthodontic treatment planning by aligner therapy. Tooth movements and endpoints were defined with regard to existing PTM. Depending on tooth mobility, active orthodontic tooth movements with low forces and moments started in mean 4.5 months (range 2 to 12 months) after periodontal regenerative surgery, using clear aligners in all patients performed by two experienced orthodontists (PW, LS). Attachments were bonded if needed with regard to planned tooth movements (mean number 7.4). All patients were instructed to wear the aligners full-time except during meals and oral hygiene, and to change the aligners every 2 weeks. When the predefined treatment goals for esthetic and function in each patient had been accomplished, active OT was considered completed. In six cases, scans for minimal refinements by additional clear aligners were necessary to optimize occlusal contacts. The individual duration of OT determined the time span of active orthodontic tooth movements, from delivery of the first aligner to final splinting, and varied from 8 to 21 months with a mean duration of 12.6 months.

The number of aligners varied from 18 to 42 aligners. Treatment outcomes were stabilized by fixed retainers and removable splints.

Supportive periodontal therapy

Following regenerative therapy, supportive therapy started with a strict interval of 4 weeks up to 3 months during the whole duration of OT.[26] If inflammation reoccurred, OT was discontinued until oral hygiene reinforcement and cautious professional tooth cleaning displayed control of inflammation.

Table 1 Patient and defect characteristics

Parameter		Baseline (N = 10)	T_2
Patients (n)		10	
Sex, n (%)	Female	6 (60)	
	Male	4 (40)	
Mean age, y (range)		51.5 (26–61)	NA
Smokers (%)		0.0	
Defects (n)		103	100
Single-rooted teeth, n (%)		58 (56)	57 (57)
Multi-rooted teeth, n (%)		45 (44)	43 (43)
Mean bone level (mm)		8.41 ± 2.40	8.45 ± 2.38
DBBMc + EMD, n (%)		29 (28.16)	
DBBMc + CM + EMD, n (%)		49 (47.57)	
EMD, n (%)		25 (24.27)	

CM, collagen membrane; DBBMc, collagenous demineralized bovine bone mineral; EMD, enamel matrix derivative.

Outcomes

Clinical and radiographic measurements

The primary outcome measure was change in rBL; change in PPD and frequency of pocket closure (sites with PPD ≤ 4 mm) served as secondary outcomes after 12 months (T_1) and at final splinting (T_2) after active OT. During surgery, the tooth site with the most advanced bone loss mesially or distally (distance between the cementoenamel junction or restoration to the bottom of the defect) was defined as target site. For calibration of the preoperative periapical radiograph, the intraoperative bone level (BL) was applied by using the overall tooth length as

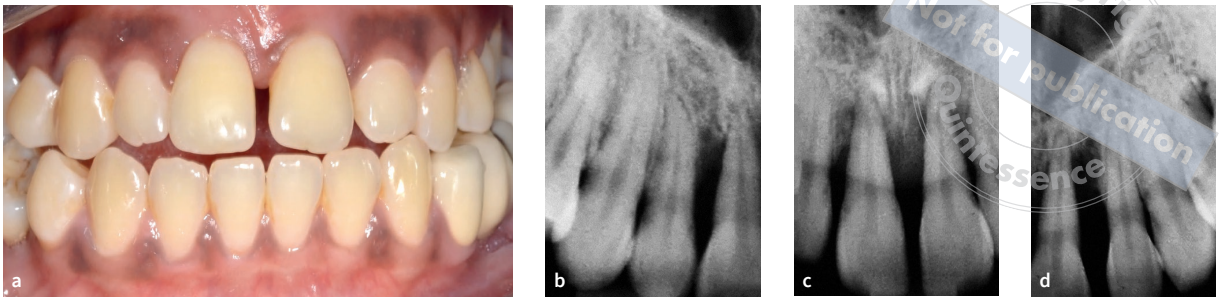

Fig 2a to d Clinical and radiographic situation of a 25-year-old patient diagnosed with stage IV periodontitis with pathologic tooth migration (spacing and flaring). At initial exam before step 1 and 2 of periodontal therapy (T_0 = baseline) *(a)*.

a reference length, as previously described.[24] The radiographs were then analyzed using ImageJ software (Version 1.43u, National Institutes of Health) by a trained and calibrated examiner (RK) who was not involved in the surgeries. For all timepoints, baseline (T_0), 1 year (T_1), and at final splinting (T_2) after active OT, complete clinical and radiographic data were obtained for all 100 defects in ten patients as previously described (Fig 1).[8,9]

Statistical analysis

The statistical analysis was performed using the statistical software R, version 4.2.3,[27] with a significance level of 5%. rBL and PPD, and its change over time, were summarized descriptively for three time points (T_0, T_1, and T_2) at the defect and patient level, and for the most severe defect per patient by means and standard deviations (SDs).

For the comparison of change in rBL and PPD between time points, a Wilcoxon signed-rank test was used. To take into account a possible clustering at the patient level, a Wilcoxon signed-rank test for clustered data was applied.[28] A logistic regression with time as fixed and patient and defect as random effects was run to compare the pocket closures between time points.

To explore the effect of explanatory variables FMBS and FMPS at T_2 on the change of rBL from baseline to T_2, a multilevel analysis was performed using a linear mixed effect regression with the patient as the random factor. To control for the influence of "rBL at baseline" this was included as an additional covariate. *P* values were derived with the Satterthwaite degrees of freedom method.[29] The level of significance of each test was set to .05.

Statistical analysis of the clinical and radiographic data was performed by an independent expert biostatistician (UW).

Results

Patient and defect characteristics

Ten patients with a total of 103 defects diagnosed with stage IV periodontitis grade C (n = 8) and grade B (n = 2) were included in this retrospective analysis. Data collection was completed by December 2023. Prior to OT, all patients had received steps 1, 2, and 3 of periodontal therapy,[30] and showed full adherence to the scheduled appointments of supportive therapy during OT. The number of regeneratively treated defects per patient ranged from 2 to 22 with an average of 10.3 defects.

Mean rBL of the 103 defects was 8.42 ± 2.40 mm. Complete observation data at T_2 were available for 100 defects with a mean rBL at baseline of 8.45 ± 2.38 mm. Tooth loss at T_2 amounted to 2.9 % at T_2 (two teeth in two patients at T_1, one tooth at T_2) as a result of root fracture.

A combination of DBBMc + EMD was used in 28.16% of all defects, and a CM was added to this combination therapy in 47.57%. EMD alone was applied in 24.27% of the defects.

Patient and defect characteristics at baseline are presented in Table 1.

Outcomes

Surgeries and soft tissue healing were generally uneventful, and none of the patients presented with any major complications. No allergic reactions, suppuration, or abscesses were observed. Signs of minor complications such as postoperative swelling and pain in the surgically treated area resolved within a few days after surgery. In the rare case of wound dehiscences,

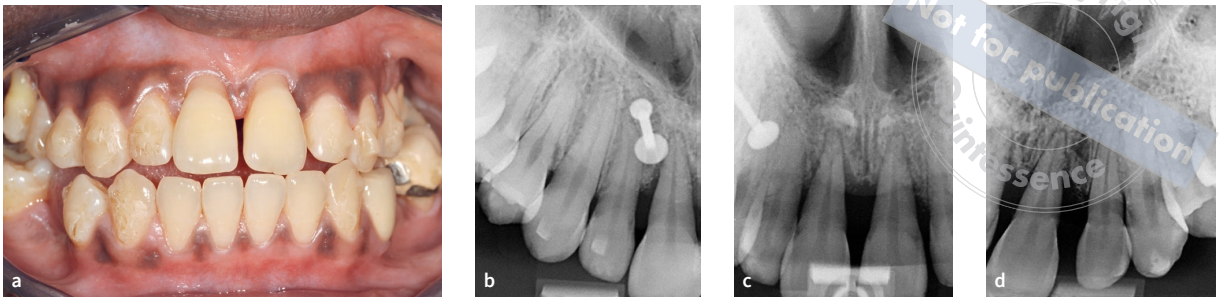

Fig 3a to d One year after regenerative surgery (T_1), 1 month after start of orthodontic tooth movements by clear aligner therapy with attachments in place.

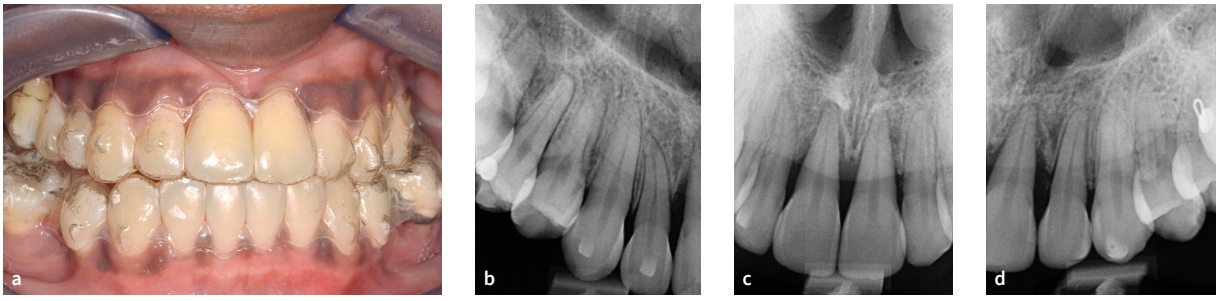

Fig 4a to d After 8 months of start of orthodontic tooth movements with clear aligners in place.

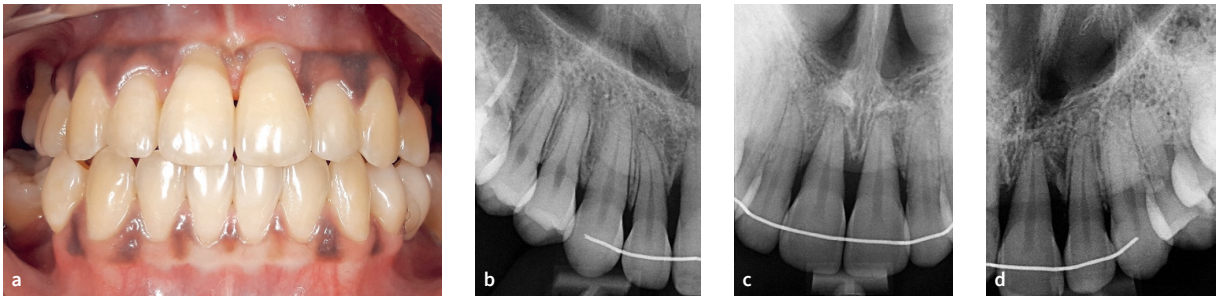

Fig 5a to d At final splinting (T_2) at completion of orthodontic therapy (OT) and insertion of resin bonded retainer.

reinforcement of postoperative intensive clinical care was administered with no further complications of wound healing or inflammation. A representative example of a treated patient included in the present analysis is illustrated in Figs 2 to 5.

Analysis of the primary outcome (change in rBL over time) of 100 defects revealed a significant gain in rBL of 2.13 ± 1.64 mm ($P < .0027$) at T_1, and 3.02 ± 2.00 mm at T_2 ($P < .0025$). Similar changes in rBL were observed when data were compared to the data analyzed at the patient level. rBL gain was even more pronounced, with 3.45 ± 2.33 mm at T_1, and 5.01 ± 2.68 mm at T_2 ($P < .002$ at both time points) when the deepest defect per patient was analyzed (Tables 2 and 3; Fig 6a to c).[31]

Different treatment modalities did not affect the change of rBL over time, as previously described (Fig 6d).[8,9]

Mean PPD was significantly reduced from 5.40 ± 1.80 mm at baseline to 3.78 ± 1.73 mm at T_1, and remained stable, with 3.73 ± 1.70 mm at T_2. When looking at the deepest defect, mean PPD reduction was even more pronounced, but only statistically significant for T_1 ($P < .0094$). Pocket closure (PPD ≤ 4 mm) was accomplished in all defects, with complete observations in 73% at T_1 and with further improvement of 76% at T_2 ($P < .0001$) (Tables 4 and 5).

A multilevel analysis revealed that only plaque ($P = .0068$) was significant when added as a single variable to the minimal model only containing rBL at baseline. With regard to change in PPD, neither plaque nor bleeding on probing had a significant effect at T_2.

The data of the final model for rBL are available on request.

Table 2 Mean rBL ± standard deviation (mm) over time

Parameter	N	T_0	T_1	T_2
rBL per defect (n = 103)	103	8.42 ± 2.40	NA ± NA	NA ± NA
rBL per defect in complete cases (n = 100)	100	8.45 ± 2.38	6.32 ± 2.10	5.43 ± 1.91
rBL per patient (n = 10)	10	8.71 ± 1.13	6.49 ± 1.07	5.61 ± 0.97
rBL deepest defect per patient (n = 22)	22	12.40 ± 3.10	8.95 ± 2.41	7.39 ± 2.12

T_0, baseline; T_1, 1 year; T_2, final splinting; calculated for patients and defects.

Table 3 *P* values* for testing bone level between time points

Parameter	T_0.T_1	T_1.T_2	T_0.T_2
rBL per defect, complete cases (n = 100)	.0027	.0116	.0025
rBL per patient (n = 10), complete cases	.0020	.0098	.0020
rBL deepest defect per patient (n = 10)	.0020	.0488	.0020

*Wilcoxon signed-rank test from the R-library coin version 1.4.3.[31]

Discussion

The present data show the clinical effectiveness of regenerative periodontal therapy and consecutive OT by clear aligners in patients with stage IV periodontitis. This combined treatment modality resulted in significant improvements of teeth severely compromised by intrabony defects and PTM, as exhibited by a mean rBL gain of 3.02 mm at final splinting of OT and pocket closure (PPD ≤ 4 mm) in a considerable number of treated defects.

The data compare well with the results of the present authors' previous publications of periodontal regenerative and consecutive OT, with fixed orthodontic appliances leading to a successful retention of the natural dentition in an adequate state of health and function.[8,9] However, although significant bone level gain was achieved by both orthodontic treatment modalities, the mean rBL after 1 year (T_1, 2.13 ± 1.64 mm; $P < .0001$) and at final splinting T_2 (3.02 ± 2.00 mm; $P < .0001$) was less than with fixed orthodontic appliances (T_1, 4.63 ± 2.43 mm; T_2, 4.19 ± 2.61 mm) in the same setting of a private periodontal practice and orthodontic specialists. Similar findings are observed in terms of PPD reduction: PPD reduction with aligner therapy was less than with fixed orthodontic appliances at T_1 (1.62 ± 1.96 mm vs 2.65 ± 1.90 mm) and at T_2 (1.67 ± 2.26 mm vs 2.77 ± 1.56 mm). The same applies to pocket closure at T_1 and T_2 (73% to 76% vs 87% to 86%).

As already stated in previous reports,[8,9] the additional application of orthodontic forces after regenerative therapy led to an improved mean rBL gain and PPD reduction compared to regenerative surgery alone.[24] A good long-term prognosis by this combined treatment can be achieved even for severely periodontally compromised patients if compliant with supportive periodontal therapy and adequate oral hygiene.[9,32]

The results of the present study cannot be easily compared to those of previously published studies due to terms of differences in study protocols, severity of periodontal disease, choice of periodontal therapy (with or without regenerative procedures), and choice of outcome measures.

Previous studies have evaluated the periodontal health status during the application of fixed orthodontic appliances versus clear aligner therapy. A randomized controlled clinical trial and two systematic reviews with meta-analysis found no statistically significant differences between the two possibilities of fixed orthodontic appliances and clear aligners,[15,20,33] while some reports have stated a slight tendency in favor of aligner therapy with regard to plaque indices and bleeding on probing.[17,19,34] However, these latter studies did not include patients diagnosed with periodontal disease. So far, there is only one study comparing the combined periodontal and orthodontic treatment with fixed appliances and clear aligners in patients with a history of periodontitis to find no differences between fixed appliances versus clear aligners concerning periodontal health (periodontal probing depth [$P = 1.00$] or alveolar bone levels [$P = .69$]).[22]

The present study is, to the authors' best knowledge, the first study analyzing rBL gain following regenerative periodontal surgery and OT by clear aligners. In contrast, the study of Han[22] mainly covered patients without regenerative surgery (only five patients out of 35 patients were treated regeneratively) prior to OT, with only minor incisor malalignment. Therefore, change of

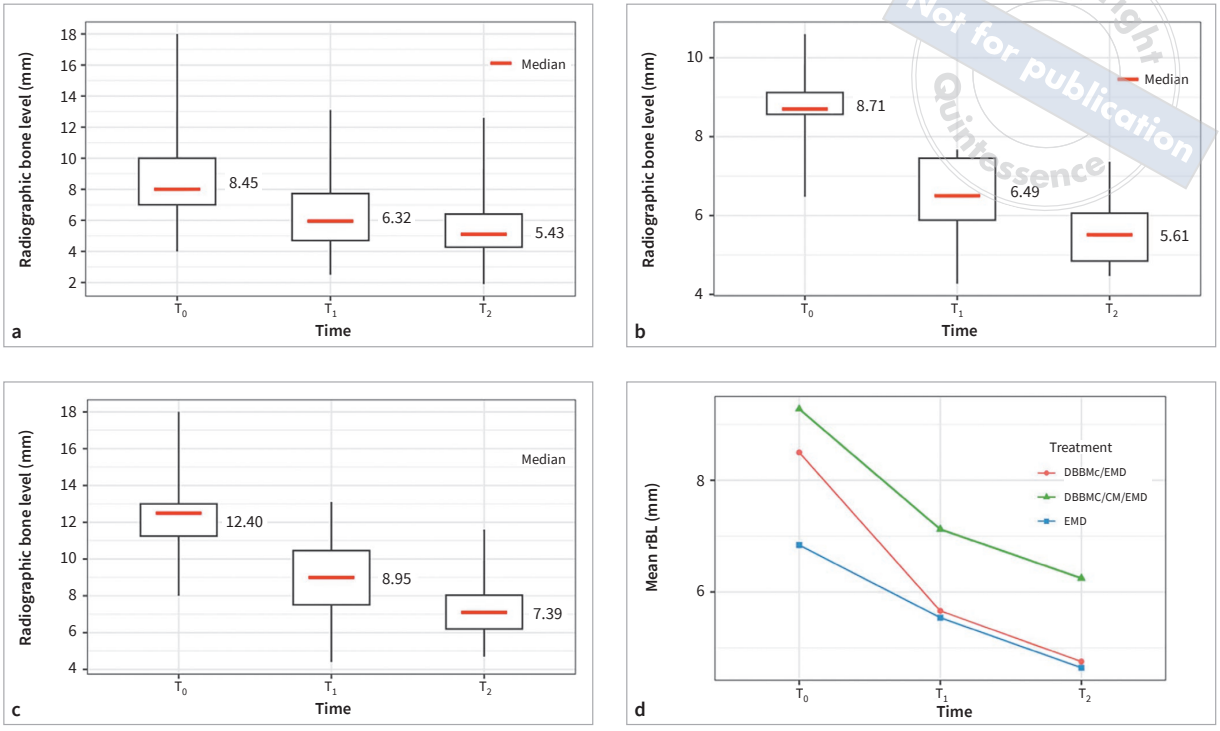

Fig 6a to d Changes in rBL over time (mean + SD) (100 defects in 10 patients, complete observations): at defect level (n = 100) *(a)*; at patient level (n = 10) *(b)*; average over all defects *(c)*; at deepest defect per patient (n = 10) *(d)* for different treatment modalities. CM, collagen membrane; DBBMc, collagenous demineralized bovine bone mineral; EMD, enamel matrix derivative.

rBL at final splinting of orthodontic tooth movement by clear aligner therapy after regenerative periodontal surgery in the present study is higher (3.02 ± 3.05 mm) than with periodontal therapy without regenerative procedures (0.22 ± 0.49 mm).[22] In addition, the severity of periodontal disease with regard to mean alveolar bone level (4.02 ± 1.48 mm to 3.48 ± 1.10 mm) and PPD (3.01 ± 0.77 mm to 2.08 ± 0.43 mm) at baseline was less pronounced than in the present study. The same applies to change in PPDs (1.67 ± 2.26 mm vs 0.20 ± 0.29 mm).

Thus, due to less severity of periodontal disease and PTM, duration time of orthodontic tooth movement with a mean of 6 months was much shorter than in the present study. As the authors stated, assessment of radiographs after 6 months of orthodontic tooth movement was not long enough to observe alveolar bone change.[22]

However, a recent systematic review by Papageorgiou et al[35] found in a re-analysis of the dataset of Han[22] differences with smaller benefits for aligners in comparison with fixed orthodontic appliances concerning periodontal health.

Early timing of orthodontic tooth movement (4 weeks after regenerative therapy) leads to a significantly greater CAL gain and better quality of life in patients with stage IV periodontitis at 24 months after regenerative treatment, as a recent multicenter randomized clinical trial revealed.[10,11] However, the protocol of that study included fixed orthodontic appliances, enabling splinting of severely periodontally compromised teeth after regenerative periodontal surgery. In the present study, due to advanced pathologic tooth mobility > 1,[23] the start of orthodontic tooth movements by clear aligner therapy was delayed by a mean of 4.5 months after regenerative periodontal surgery. The lack of the stabilizing effect by fixed orthodontic appliances, less accuracy of aligner therapy to realize a prescribed tooth movement,[36,37] ordering additional corrective sets of aligners (refinements), and the delayed start

of OT might explain the lower gain in rBL and PPD reduction in comparison to the present authors' former reports.[8,9]

Although rBL gain and PPD reduction were less with aligner therapy than with fixed orthodontic appliances after regenerative periodontal surgery, the observed tooth retention by this combined periodontal-regenerative and orthodontic treatment are in line with and in support of the European Federation of Periodontology (EFP) S3 clinical practice guideline (CPG) on the treatment of stage IV periodontitis.[3,35,38] The evidence-based CPG gives a clear recommendation for orthodontic treatment of regeneratively treated intrabony defects since the combined treatment significantly improves periodontal outcomes and significantly reduces inflammation as long as guidelines of regenerative periodontal treatment and sequences of therapeutic interventions are followed.[3,30] Inflammation has to be under control before, during, and after OT based on the recommendation of the evidence-based EFP-S3 level CPG for the treatment of stage IV periodontitis.[3]

Taking into account the superior functional outcomes of fixed orthodontic appliances,[15,17] the splinting effect of severely periodontally compromised teeth and earlier start of orthodontic tooth movements,[8-10] early aligner therapy after regenerative therapy can only be considered as a treatment choice either in mild or moderate malocclusions associated with periodontitis. Therefore, orthodontic tooth movements by aligner therapy can only begin directly after periodontal therapy when pathologic tooth moblity is less than grade II[23] or has to be delayed until tooth mobility is < grade II.

As a first study focusing on rBL change after regenerative periodontal therapy and consecutive orthodontic tooth movements by aligner therapy in the treatment of stage IV periodontitis, the present study exhibits new data on this combined therapy. The number of defects treated by the same periodontist and orthodontic specialists and the setting of a private practice strengthen the generalizability of the results. Adding to the strengths, the radiographs were evaluated by the same blinded examiner, and data analysis was performed by an independent expert statistician, both not being involved in the clinical phases of the study. Moreover, the study was conducted independently and not funded by industry.

The present study has also some inherent limitations, primarily due to its retrospective study design, low number of patients, and a missing comparison group. Therefore, it has to be regarded as feasibility study for further prospective randomized clinical trials. Possible sources of bias, such as, measurement errors of rBL due to change of tooth position as well as orthodontically induced root resorption and the use of radiopaque bone fillers have been previously discussed in detail.[8]

Table 4 Frequency distribution of residual PPD for all defects (N = 100), complete observation time

PPD (mm)	Baseline (T_0)	T_1	T_2
≤ 4	34 (34.00%)	73 (73.00%)	76 (76.00%)
5	18 (18.00%)	10 (10.00%)	10 (10.00%)
6	25 (25.00%)	9 (9.00%)	7 (7.00%)
7	8 (8.00%)	3 (3.00%)	7 (7.00%)
8	11 (11.00%)	4 (4.00%)	0 (0.00%)
9	3 (3.00%)	0 (0.00%)	0 (0.00%)
10	0 (0.00%)	1 (1.00%)	0 (0.00%)
11	1 (1.00%)	0 (0.00%)	0 (0.00%)

Table 5 *P* values* for testing proportion of pocket closure (pc) between time points

Comparison	*P*
pc0 – pc1	< .00001
pc0 – pc2	< .00001
pc1 – pc2	.571

*Logistic regression with time as fixed and patient and defect as random effects.

Conclusion

Within the limitations of the retrospective study design, the present results suggest that the combination of regenerative treatment and consecutive orthodontic tooth movement by clear aligners as patient preference is a viable option for favorable results in the treatment of patients diagnosed with stage IV periodontitis and mild to moderate malocclusion (PTM).

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Disclosure

The authors declare no conflict of interest with regard to this study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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4. DISKUSSION

Parodontitis Stadium IV mit pathologischer Zahnwanderung (PTM) erfordert eine komplexe interdisziplinäre Therapie zur Rehabilitation von Funktion und Ästhetik.

Die Ergebnisse der ersten Studie (*Tietmann et al., 2021*) der vorliegenden Arbeit zeigten, dass die kombinierte regenerative Therapie intraossärer Defekte mit anschließender kieferorthopädischer Zahnbewegung auch in einer großen Kohorte von Patienten mit Parodontitis im Stadium IV möglich ist. Die Studie konnte nachweisen, dass bei einer großen Anzahl schwer parodontal vorgeschädigter Zähne mit intraossären Defekten und PTM der Einsatz von bovinem Knochenersatzmaterial mit oder ohne Kollagenmembran oder EMD mit anschließender kieferorthopädischer Zahnbewegung zu einem signifikanten radiologischen Knochengewinn und Reduktion der Sondierungstiefen führt. Der mittlere radiologische Knochengewinn von 4,67 $\pm$ 2,5mm ein Jahr nach regenerativer Therapie stimmt mit den Ergebnissen von 1,3 bis 4,4mm zuvor veröffentlichter Fallserien der kombinierten Therapie überein bzw. übertrifft diese (*Corrente et al., 2003, Cardaropoli et al., 2006, Ogihara & Wang, 2010, Attia et al., 2012a und 2019, Ghezzi et al., 2013*).

Die vorliegende Arbeit ist die Studie mit der bisher größten dokumentierten Anzahl von Patienten und Defekten (48 Patienten mit insgesamt 526 Defekten) dieses interdisziplinären Therapieansatzes zur Behandlung von Parodontitis im Stadium IV mit PTM. Das mit 0,57% geringe Ausmaß an Zahnverlusten sowie die Tatsache, dass die Studie in einer parodontologischen Fachzahnarztpraxis durchgeführt wurde, unterstreicht die Generalisierbarkeit der Ergebnisse dieser kombinierten Therapie bei Parodontitis im Stadium IV, wenn bestimmte Parameter der regenerativen und kieferorthopädischen Therapie berücksichtigt werden (*Jepsen et al., 2023 b und c*).

Die vorliegende Studie (*Tietmann et al., 2021*) hat aufgrund der Ergebnisse der kombinierten Therapie in Bezug auf Gewinn an radiologischem Knochenniveau (rBLg) und „Pocket closure" (PPD $\leq$4mmin) von 87% ein Jahr nach regenerativer Therapie zur evidenzbasierten Empfehlung

R7.5 der S3-Leitlinie bei der Therapie der Parodontitis im Stadium IV (*Kloukos et al., 2022, Martin et al., 2022, Papageorgiou et al., 2022, Herrera et al., 2022*) beigetragen (s. Abbildung 3).

PAR- UND KFO-THERAPIE BEI VERTIKALEN DEFEKTEN	Empfehlungs-grad
Evidenzbasierte Empfehlung (R7.5): Bei Patienten mit Stadium IV Parodontitis, bei denen vertikale Defekte entsprechend der Empfehlungen der Leitlinie ([Sanz et al., 2020] mit den geeigneten regenerativen Interventionen behandelt worden sind, 1. **soll** eine KFO-Therapie durchgeführt werden, gestützt auf die Evidenz, dass diese kombinierte Behandlung die parodontalen Parameter signifikant verbessert (erhöhte KAL-Gewinne, TST-Reduktionen, und RKN-Gewinne) und die gingivale Entzündung (BOP) signifikant reduziert. **Konsensstärke:** Konsens	
2. **sollte nicht** auf eine verlängerte Ausheilung nach der regenerativen Intervention gewartet werden, bevor die KFO-Therapie begonnen wird, weil es Evidenz dafür gibt, dass ein kurzes (1 Monat) und ein längeres Zeitintervall (6 Monate) zwischen der parodontal-regenerativen und der kieferorthopädischen Therapie zu vergleichbaren Ergebnissen führt. **Konsensstärke:** Konsens	

Abb. 3: Quelle: Treatment of stage IV periodontitis: The EFP S3 level clinical practice guideline der European Federation of Periodontology. (*Herrera et al. 2022*)

Diese Ergebnisse waren Anlass für die zweite Studie, in der die Langzeitstabilität der kombinierten regenerativen und kieferorthopädischen Therapie bei Parodontitis Stadium IV mit PTM nach 10 Jahren in der gleichen parodontologischen Fachzahnarztpraxis nachuntersucht wurden. Diese retrospektive Arbeit ist mit 256 Defekten nicht nur die Studie mit der größten Anzahl an nachuntersuchten Defekten der kombinierten Therapie und mit dem längsten Beobachtungszeitraum, sondern auch die erste Studie, die Langzeitergebnisse über 10 Jahre in Bezug auf den Gewinn an radiologischem Knochenniveau berichtet. Die Ergebnisse der ersten Studie (*Tietmann et al., 2021*) bezüglich mittlerem radiologischem Knochengewinn konnten auch in der Langzeituntersuchung 10 Jahre nach regenerativer Therapie bestätigt werden und waren mit 4,48 + 2,62mm statistisch signifikant. Die Wirksamkeit der kombinierten Therapie zeigte sich auch in Bezug auf die Taschenelimination und Zahnverlust. So konnten nach 10 Jahren 90 % aller

parodontalen Taschen eliminiert (PPD ≤4mm) und 95,5% aller Zähne erhalten werden. Vergleichbare Ergebnisse wurden in der einzigen bisher veröffentlichten Langzeitstudie der kombinierten regenerativen und kieferorthopädischen Therapie über 10 Jahre nur in Bezug auf Taschenelimination und Reduktion der Sondierungstiefen von *Roccuzzo et al.* (*2018*) gezeigt, allerdings mit einer deutlich geringeren Anzahl an Defekten (n=36). Eine weitere Studie von *Aimetti et al. (2020*) beobachtete zwar ähnliche Langzeitergebnisse der kombinierten PA/KFO Therapie bezüglich der Taschenelimination (87%), allerdings flossen in diese Langzeituntersuchung sowohl resektiv als auch regenerativ therapierte Defekte ein und daher kann diese nicht als direkte Vergleichsstudie herangezogen werden. Dies erklärt auch die geringere Reduktion der Sondierungstiefen in der Studie von *Aimetti et al. (2020)* im Vergleich zu unserer Studie.

Die Ergebnisse dieser Langzeitstudie *(Tietmann et al., 2023)* beruhen auf einer Patientenkohorte, die in den Jahren 2001-2010 mit der kombinierten regenerativen und kieferorthopädischen Therapie behandelt wurde (*Tietmann et al., 2021*). Sie bestätigen im nach hinein die Empfehlungen der europäischen S3-Leitlinie für die Therapie von Parodontitis im Stadium IV (*Herrera et al., 2022*) bezüglich Zahnerhalt und Erhalt der geschlossenen Zahnreihe als primäre Behandlungsstrategie.

Die stabilen Langzeitergebnisse nach10 Jahren, die in der zweiten Studie der vorliegenden Arbeit beobachtet wurden, wurden durch eine intensive unterstützende Parodontitistherapie (UPT), wie sie auch in den S-3 Leitlinien für die Therapie der Parodontitis im Stadium I-III verankert ist (*Sanz et al., 2020*), während und nach der kieferorthopädischen Therapie erreicht. Die Patienten wurden während der kieferorthopädischen Therapie engmaschig mit einem maximalen Abstand von 3 Monaten parodontal betreut wie es durch die prospektive Studie von Jiang *et al. (2021)* belegt ist. Bei erneut auftretenden Entzündungszeichen wurde die kieferorthopädische Zahnbewegung unterbrochen, die betreffenden Zähne reinstrumentiert und der Patient bezüglich der Intensivierung der häuslichen Mundhygiene remotiviert. Die kieferorthopädische Therapie wurde erst wieder aufgenommen, wenn die parodontalen Verhältnisse wieder stabil waren. In gleicher Weise erfolgte auch nach Abschluss der kieferorthopädischen Therapie eine lebenslange

unterstützende Parodontitistherapie und kieferorthopädische Retention durch passiv fixierte Lingualretainer und herausnehmbare kieferorthopädische Apparaturen sowie regelmäßige kieferorthopädische Konsile zur Überprüfung der Retention (*Han et al., 2020*) wie es in den 2022 veröffentlichten S3-Leitlinien für die Therapie der Parodontitis im Stadium IV empfohlen wird (*Herrera et al., 2022*).

Die Ergebnisse der beiden ersten Studien weisen auch darauf hin, dass die regenerative Therapie intraossärer Defekte mit anschließender kieferorthopädischer Zahnbewegung einen größeren Gewinn an radiologischem Knochenniveau (rBLg) und Reduktion der Sondierungstiefen hat als die alleinige regenerative Therapie wie ein „historischer" Vergleich mit einer früheren Nachuntersuchung von über 1000 regenerativ behandelten Defekten über 10 Jahre (*Bröseler et al., 2017*) in der gleichen parodontologischen Fachzahnarztpraxis zeigte. Da die parodontalen Ausgangsparameter der Defekte ähnlich waren, wurde ein möglicher „stimulierender Effekt" der kieferorthopädischen Zahnbewegung in der frühen Wundheilungsphase auf die parodontale Regeneration vermutet wie es in Tierstudien zuvor beobachtet worden war (*Nemcovsky et al, 2004, Vardimon et al., 2001, Diedrich et al., 2003*). Diese Thematik greift auch ein inzwischen neu erschienenes Review mit Meta-analyse auf (*Papageorgiou et al., 2024*). Die Autoren konnten zeigen, dass die kombinierte parodontale und kieferorthopädische Therapie bei Stadium IV Parodontitis deutlich bessere Ergebnisse in Bezug auf Attachmentgewinn, Taschenreduktion, Entzündungsparameter, Knochenniveau und Behandlungserfolg erzielt als die parodontale Therapie alleine.

Der bestmögliche Zeitpunkt für den Beginn der kieferorthopädischen Zahnbewegung nach regenerativer Parodontitistherapie bei Stadium IV Parodontitis mit PTM wurde bis vor kurzem noch als „Grauzone" (*Pini Prato & Chambrone, 2020*) diskutiert. Während einige Autoren bevorzugten, die Ergebnisse der parodontalen Regeneration bis zu 12 Monaten abzuwarten

(*Ghezzi et al., 2008, Roccuzzo et al., 2018, Aimetti et al., 2020, Pini Prato & Chambrone, 2020*), spekulierten andere, dass der frühe Beginn kieferorthopädischer Zahnbewegung keine negativen Effekte oder sogar positive Effekte auf die parodontalen Parameter haben könnte (*Cardaropoli et al., 2001und 2006, Ogihara & Wang, 2010, Ghezzi et al., 2013*).

Daher war es Ziel der dritten Studie, erstmalig vergleichend im randomisierten Studiendesign zu untersuchen, welche Auswirkungen ein früher (4 Wochen) oder später (6 Monate) Beginn der kieferorthopädischen Therapie nach regenerativer Therapie vertikaler Defekte hat. Die Ergebnisse ein Jahr nach regenerativer Therapie zeigten, dass keine statistisch signifikanten Unterschiede zwischen der frühen oder späten KFO-Therapie in Bezug auf Attachmentgewinn (5,4mm vs. 4,5mm), Reduktion der Sondierungstiefen (4,2mm vs. 3,9mm) und Taschenelimination (91% vs. 85%) beobachtet werden konnten.

Die einzige Studie, die bisher den Effekt unterschiedlicher Zeitpunkte der kieferorthopädischen Zahnbewegung verglich, ist die nicht-randomisierte Studie von *Attia et al. (2012a).* Bei 15 Defekten wurden im Split-Mouth-Design die Effekte der kombinierten Therapie mit Beginn der kieferorthopädischen Zahnbewegung unmittelbar oder 2 Monate nach regenerativer Therapie sowie ohne kieferorthopädische Therapie nachuntersucht. Nach einem Jahr zeigten sich hinsichtlich Attachmentgewinn (5,4mm vs. 4,3mm) und Reduktion der Sondierungstiefen (4,0mm vs. 3,7mm) ähnliche, statistisch nicht signifikant bessere Ergebnisse für den unmittelbaren Beginn der kieferorthopädischen Zahnbewegung nach regenerativer Therapie wie in der vorliegenden Studie.

Die vorliegende Arbeit ist die erste Studie, die im Rahmen einer prospektiven, randomisierten klinischen Multicenterstudie zeigt, dass ein früher Beginn der kieferorthopädischen Zahnbewegung bereits 4 Wochen nach regenerativer Therapie von vertikalen Defekten einen vergleichbar positiven Effekt auf die parodontalen Parameter wie ein später Beginn hat. Ein weiteres wichtiges Ergebnis dieser Studie war, dass deshalb die Gesamtbehandlungszeit für den Patienten deutlich reduziert werden kann. Die Erkenntnisse dieser Studie trugen maßgeblich zur Empfehlung der S3-

Leitlinie für die Therapie der Parodontitis im Stadium IV bei, dass nicht auf eine verlängerte Ausheilung nach regenerativer Therapie gewartet werden sollte, bevor die KFO-Therapie begonnen wird (Evidenzbasierte Empfehlung (R7.5) (siehe Abbildung 3) (*Herrera et al., 2022*).

Basierend auf den Ergebnissen der prospektiven multizentrischen randomisierten Studie nach 12 Monaten (*Jepsen et al., 2021*) wurden als weitere Parameter erstmalig die Auswirkung der kombinierten regenerativen parodontalchirurgischen und kieferorthopädischen Therapie auf die Mundgesundheitsbezogene Lebensqualität (OHrQL) sowie die klinische parodontalen Parameter nach 24 Monate überprüft.
Wurden nach 12 Monaten keine statistisch signifikanten Unterschiede bezüglich der parodontalen Parameter im Vergleich zum Beginn der kieferorthopädischen Therapie beobachtet (*Jepsen et al., 2021*), so zeigte sich nach 24 Monaten ein weiterer, statistisch signifikant größerer Attachmentgewinn (CALg) von 1,31mm für den frühen Beginn der kieferorthopädischen Zahnbewegung im Vergleich zu spätem Beginn (5,96mm vs. 4,65mm). Die Reduktion der Sondierungstiefen und die Taschenelimination blieb nach 24 Monaten stabil und war bei frühem oder spätem Beginn der KFO-Therapie gleich. Die frühe kieferorthopädische Zahnbewegung wirkte sich positiv auf die parodontale Wundheilung aus und scheint als „stimulierender" Effekt zu größerem Attachmentgewinn zu führen, was auch schon in frühen Tierstudien (*Nemcovsky et al., 2004, Vardimon et al., 2001, Diedrich et al., 2003*) vermutet wurde.

Gleichzeitig wurde in dieser Studie festgestellt, dass die Patienten eine signifikante Verbesserung ihrer Mundgesundheitsbezogenen Lebensqualität (OHrQL) durch die kombinierte Therapie angaben. Dies zeigte sich in einem deutlich verbesserten GOHAI (general oral health assessment index) 24 Monate nach Beginn der kombinierten regenerativen und kieferorthopädischen Therapie aber ohne statistisch signifikante Unterschiede zwischen frühem oder spätem Beginn der kieferorthopädischen Zahnbewegung. Die Patienten, die nach 24 Monaten die

kieferorthopädische Therapie beendet hatten, berichteten über eine weitere Verbesserung ihrer OHrQL. Bisherige Studien beobachteten positive Auswirkungen auf die OHrQL aufgrund alleiniger parodontaler (*Wong et al., 2012, Brauchle et al., 2013, Shanbhag et al., 2012, Botelho et al., 2020*) oder kieferorthopädischer (*Ribeiro et al., 2023, Kara-Boulad et al., 2022*) Therapie. Daher kann vermutet werden, dass die in dieser Studie beobachtete signifikante Verbesserung der Mundgesundheitsbezogenen Lebensqualität (OHrQL) sowohl auf die parodontale als auch auf die kieferorthopädische Therapie bei Stadium IV Parodontitis mit pathologischer Zahnwanderung zurückzuführen ist.

Viele Patienten mit Parodontitis Stadium IV mit PTM berichten über starke ästhetische und funktionelle Einschränkungen ihrer Lebensqualität und zeigen daher Interesse an kieferorthopädischer Therapie (*Hirschfeld et al., 2019*). In der Regel wird die Einordnung pathologisch gewanderter Zähne durch eine festsitzende Multibandapparatur erreicht. Vor allem erwachsene Patienten empfinden sichtbare Multibandapparaturen beeinträchtigend und präferieren herausnehmbare und möglichst kaum sichtbare kieferorthopädische Apparaturen. Die in den zuvor beschriebenen Studien der vorliegenden Arbeit gezeigten sehr guten Ergebnisse waren mittels Multibandapparaturen erzielt worden.

Daher sollte in der fünften Studie der vorliegenden Arbeit untersucht werden, ob die kombinierte Therapie auch mit neueren kieferorthopädischen Apparaturen, transparenten Clear Alignerschienen (CA) möglich ist bzw. zu ähnlichen Ergebnissen wie mit Multibandapparaturen führen kann. Die retrospektive Analyse von 103 Defekten ergab einen signifikanten Gewinn an radiologischem Knochenniveau von 2,13 $\pm$ 1,64mm ein Jahr nach regenerativer Therapie, der sich bei Abschluss der kieferorthopädischen Therapie noch geringfügig auf 3,02 $\pm$ 2,00mm verbesserte. Eine statistisch signifikante Taschenelimination $\leq$4mm (PC) wurde in 76% aller Defekte bei Beendigung der kieferorthopädischen Zahnbewegung beobachtet.

Diese Arbeit ist die erste Studie, die den Gewinn an radiologischem Knochenniveau durch die kombinierte regenerative und kieferorthopädische Zahnbewegung mittels Clear Aligner anhand

einer großen Defektzahl untersucht hat. Nur eine Studie (*Han et al., 2015*) hat den Gewinn an radiologischem Knochenniveau mittels Clear Aligner bisher nachuntersucht, allerdings war der Hauptanteil der Defekte (30 von 35 Defekten) ohne regenerative Therapie behandelt worden und der Beobachtungszeitraum mit 6 Monaten deutlich kürzer. Daher fielen der Gewinn an radiologischem Knochenniveau und die Reduktion der Sondierungstiefen deutlich geringer aus.

Sowohl der Gewinn an radiologischem Knochenniveau als auch die Taschenelimination sind in dieser Clear Aligner-Studie im Vergleich zu den Ergebnissen mittels Multibandapparatur in unseren vorherigen Studien geringer. Dies kann zum einen durch den fehlenden Stabilisierungseffekt durch die Multibandapparatur der schwer parodontal vorgeschädigten Zähne nach regenerativer Therapie erklärt werden. Zum anderen konnte die kieferorthopädische Zahnbewegung durch Clear Aligner erst dann begonnen werden, wenn die unphysiologischen Lockerungen < Grad 2 betrugen. Aufgrund der schweren parodontalen Vorschädigung bei Parodontitis im Stadium IV ist dies direkt nach regenerativer Therapie in der Regel nicht der Fall, so dass der Beginn der kieferorthopädischen Therapie im Vergleich zu den vorherigen Studien verzögert war. Daher konnte der „stimulierende" Effekt der frühen kieferorthopädischen Bewegung -wie in den multizentrischen, randomisierten Studien von *Jepsen et al., 2021 und 2023* beobachtet - nicht genutzt werden. Ebenso ist die Wahl der kieferorthopädischen Apparatur in Bezug auf die Vorhersagbarkeit der kieferorthopädischen Zahnbewegung und die Auswirkung auf die parodontalen Parameter komplex wie ein inzwischen erschienenes Review mit Meta-analyse (*Papageorgiou et al., 2024*) ausführt. Dies scheint die geringere Reduktion der Sondierungstiefen durch Alignertherapie im Vergleich zu festsitzenden Multibandapparaturen zu erklären wie es auch in der Studie von *Han et al., (2015)* beobachtet wurde.

Hingegen ist der geringe Zahnverlust von 2,9% ähnlich zu den Ergebnissen der beiden ersten Studien der vorliegenden Arbeit (*Tietmann et al., 2021 und 2023*) und unterstreicht die Effektivität

der kombinierten regenerativen und kieferorthopädischen Therapie wie sie in der S3-Leitlinie für die Therapie von Parodontitis im Stadium IV, Typ 2 (*Herrera et al., 2022*) empfohlen wird.

Zwei Studien der vorliegenden Arbeit (*Tietmann et al. 2021*, *Jepsen et al. 2021*) haben maßgeblich zur Entwicklung eines Behandlungsalgorithmus für die Therapie der Parodontitis im Stadium IV mit pathologischer Zahnwanderung (PTM) beigetragen, der für die Planung und Durchführung einer kombinierten parodontologischen und kieferorthopädischen Therapie zur Orientierung dienen soll (s. Abbildung 4).

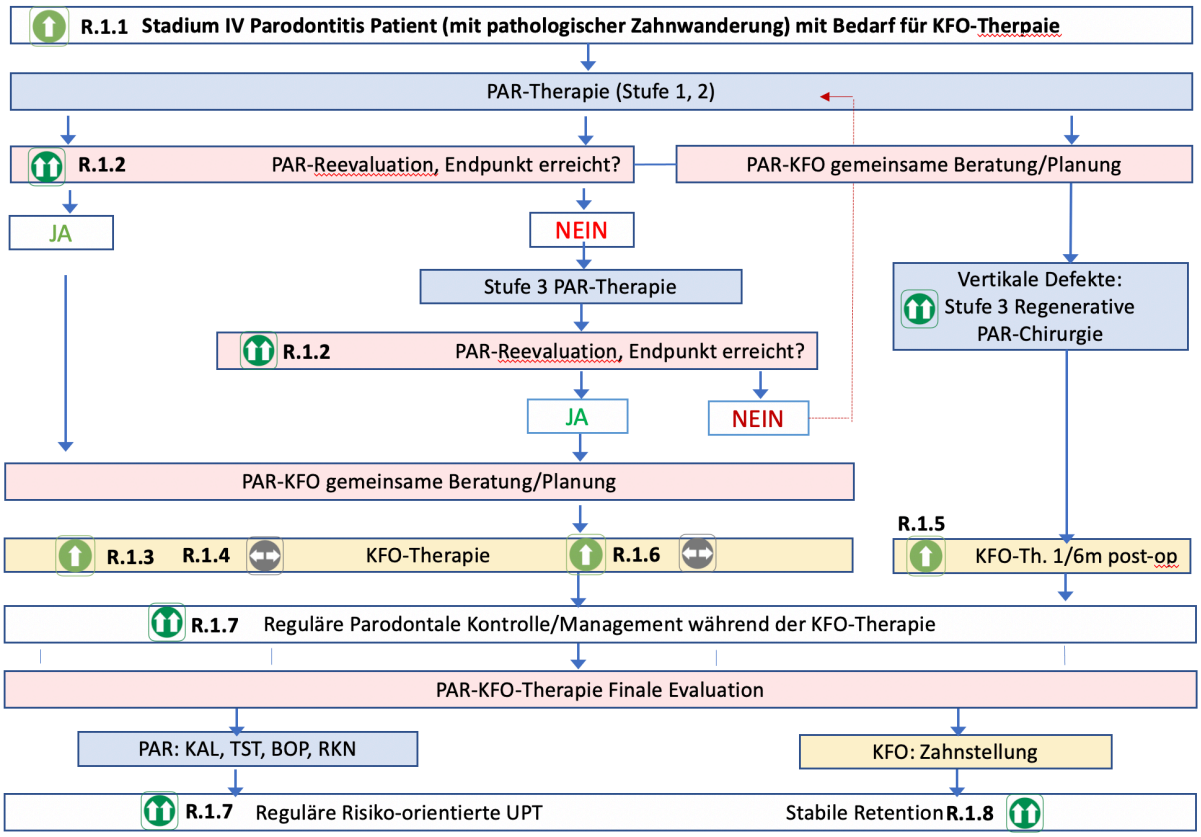

Abb. 4: Flussdiagramm zur Illustrierung wie eine kieferorthopädische Therapie (KFO-Therapie) bei Patienten mit Stadium IV Parodontitis in den parodontalen Behandlungsplan integriert werden kann unter Bezugnahme auf die Empfehlungen R7.1–R7.8 der S3-Leitlinie zur Behandlung der Stadium IV Parodontitis. Die Stufen der parodontalen Therapie wurden in der S3-Leitlinie zur Behandlung der Stadium I – III Parodontitis beschrieben (*Sanz et al., 2020*). KAL: Klinischer Attachment Level; TST: Taschensondierungstiefe; BOP: Sondierungsblutung; RKN: Röntgenologisches Knochenniveau; 1/ 6 m: 1 oder 6 Monate; post-op: post-operativ.
(Quelle: Søren Jepsen, *Herrera et al., 2022*)

5. ZUSAMMENFASSUNG

Eine Parodontitis im Stadium IV ist charakterisiert durch schweren Verlust an parodontalem Attachment, vertikale Knochendefekte und pathologische Zahnwanderung (PTM). Die Komplexität des Krankheitsbildes aufgrund von PTM - gekennzeichnet durch Elongationen, Auffächerungen und Lückenbildungen in Verbindung mit sekundärem okklusalem Trauma, bis hin zu Bisskollaps und mastikatorischer Dysfunktion - erfordert eine interdisziplinäre Therapie, um Funktion und Ästhetik sowie Lebensqualität der Patienten wiederherzustellen.

Bis vor Kurzem gab es viele offene Fragen, ob eine kombinierte regenerativ-parodontalchirurgische und kieferorthopädische Therapie vorhersagbar und vor allem langzeitstabil möglich ist. Ebenso war der optimale Zeitpunkt des Beginns der kieferorthopädischen Therapie unklar. Eventuell synergistische Effekte und ein möglicher Benefit durch frühen Beginn der kieferorthopädischen Zahnbewegung bei der kombinierten Therapie – belegt durch frühe Tierstudien – wurden vermutet. Die Auswirkung einer kombinierten Therapie auf die Mundgesundheitsbezogene Lebensqualität war bisher ebenfalls nicht untersucht.

Die alleinige parodontale Therapie oder regenerative Therapie vertikaler Defekte, wie sie in den S3-Leitlinien für die Therapie der Parodontitis im Stadium I-III aufgrund der Evidenzlage inzwischen als etabliertes Therapieverfahren gilt, reicht bei Patienten mit Parodontitis im Stadium IV aufgrund des komplexen Krankheitsbildes bedingt durch pathologische Zahnwanderung (PTM) nicht aus. Die in 2022 veröffentlichte S3-Leitlinie für die Therapie von Stadium IV Parodontitis (*Herrera et al., 2022*) stellt klar heraus, dass Zahnerhalt und Erhalt der geschlossenen Zahnreihe als primäre Behandlungsstrategie gelten sollte. Ebenso sollte eine kieferorthopädische Therapie nach erfolgreich behandelter Stadium-IV-Parodontitis durchgeführt werden, um Zähne mit pathologischer Zahnwanderung wieder in die Zahnreihe einzugliedern. Vor Veröffentlichung der S3-Leitlinie für die Therapie von Parodontitis im Stadium IV im Jahr 2022 stützte sich die Literatur auf Fallberichte und Fallserien, die nur unzureichende Dokumentationen hinsichtlich Art der

Parodontaltherapie, Einfluss der kieferorthopädischen Therapie auf die parodontalen Verhältnisse und Langzeitstabilität sowie optimaler Zeitpunkt der kieferorthopädischen Zahnbewegung nach regenerativer Parodontaltherapie enthielten.

Die erste der hier vorgelegten Arbeiten fokussierte sich daher darauf, ob eine kombinierte regenerative parodontalchirurgische Therapie mit anschließender kieferorthopädischer Zahnbewegung auch bei einer großen Patientenkohorte in der Praxisrealität einer parodontologischen Fachzahnarztpraxis möglich ist. In der retrospektiven Studie wurde eine statistisch signifikante Verbesserung des radiologischen Knochenniveaus und Taschenelimination ein Jahr und bis zu vier Jahre nach regenerativer Therapie gezeigt. Diese Ergebnisse führten zur nachfolgenden Arbeit, die die Langzeitstabilität der Ergebnisse der kombinierten regenerativen und kieferorthopädischen Therapie anhand der gleichen Patientenkohorte nach 10 Jahren nachuntersuchte. Es konnte gezeigt werden, dass die kombinierte regenerative Therapie vertikaler Knochendefekte mit anschließender kieferorthopädischer Zahnbewegung auch nach 10 Jahren zu langzeitstabilen parodontalen Verhältnissen und langfristigem Zahnerhalt von mehr als 95 % der ehemals schwer parodontal vorgeschädigten Zähne führte, wenn die Patienten an einer engmaschigen UPT teilnahmen. Die Ergebnisse dieser ersten Studie, durchgeführt in den Jahren zwischen 2001-2010, haben maßgeblich zu evidenzbasierten Empfehlungen der europäischen S3-Leitlinie zur Therapie der Parodontitis im Stadium IV (*Herrera et al., 2022*) beigetragen.

Der optimale Zeitpunkt des Beginns der kieferorthopädischen Zahnbewegung nach regenerativer Therapie wurde lange Zeit in Fallserien diskutiert und als „grey zone" (*Pini Prato & Chambrone, 2020*) beschrieben. Daher wurde im Rahmen einer multizentrischen randomisierten Studie die Auswirkung des Zeitpunktes des Beginns der kieferorthopädischen Zahnbewegung nach regenerativer Therapie auf die parodontale Heilung untersucht. Die positiven Ergebnisse zeigten, dass ein Jahr nach regenerativer Therapie keine statistisch signifikanten Unterschiede bei frühem (4 Wochen) oder verzögertem (6 Monate) Beginn der kieferorthopädischen Zahnbewegung in

Bezug auf CAL-Gewinn oder Taschenelimination beobachtet werden konnten. Da ein früher kieferorthopädischer Behandlungsbeginn keine negativen Auswirkungen auf die parodontalen Parameter hat, sollte nicht auf eine verlängerte Ausheilung nach der regenerativen Therapie gewartet werden. Die Ergebnisse dieser randomisierten prospektiven multizentrischen Studie zur Therapie der Parodontitis im Stadium IV waren maßgeblich verantwortlich für die Therapieempfehlung R7.5 der europäischen S3-Leitlinie (*Herrera et al., 2022*) für die kombinierte parodontalchirurgische und kieferorthopädische Therapie von vertikalen Defekten bei Parodontitis im Stadium IV, Typ 2 (siehe Abbildung 3).

Der positive Einfluss auf die parodontalen Parameter durch die kombinierte Therapie in Form von höherem Attachmentgewinn, höherer Taschentiefenreduktion, und Reduktion der parodontalen Entzündung ist nicht nur ein Jahr nach regenerativer Therapie zu beobachten. Wie in der vierten Studie der vorliegenden Arbeit gezeigt, führt der frühe Beginn der kieferorthopädischen Zahnbewegung nach regenerativer Therapie nach 24 Monaten zu weiterem höheren Attachmentgewinn und scheint in Kombination mit der vorherigen regenerativen Therapie vertikaler Defekte als „stimulierender" Effekt in der frühen Phase der parodontalen Wundheilung zu wirken. Ebenso werden Zahnerhalt und Wiedereinordnung pathologisch gewanderter Zähne in die Zahnreihe zur Rekonstruktion von Funktion und Ästhetik von Patienten mit Parodontitis im Stadium IV als deutliche Verbesserung ihrer Mundgesundheitsbezogenen Lebensqualität (OHrQL) wahrgenommen.

Das Interesse von Patienten an kieferorthopädischer Therapie bei Parodontitis Stadium IV zur Stellungskorrektur pathologisch gewanderter Zähne und zum Zahnerhalt ist groß. Gleichzeitig wird eine festsitzende Multibandapparatur oft als Einschränkung empfunden. Die letzte Studie gibt daher einen Ausblick auf den möglichen Einsatz neuerer kieferorthopädischer transparenter Clear Aligner im Rahmen der kombinierten Therapie. Die Ergebnisse zeigen, dass auch Clear Aligner eine mögliche Option für die kombinierte Therapie bei Stadium IV Parodontitis sind. Allerdings

ist der Gewinn an radiologischem Knochenniveau und Taschenelimination (PC) nach Abschluss der kieferorthopädischen Therapie geringer als mit festsitzenden Multibandapparaturen.

Zusammenfassend haben die Ergebnisse der vorliegenden Arbeit zu wichtigen neuen Erkenntnissen in der Therapie von Parodontitis Stadium IV mit PTM geführt. Zwei Studien der vorliegenden Arbeit waren maßgeblich an den Empfehlungen der europäischen S3-Leitlinie zur Therapie der Parodontitis im Stadium IV der kombinierten regenerativ-parodontalchirurgischen Therapie intraossärer Defekte mit anschließender kieferorthopädischer Zahnbewegung beteiligt. Es wurde außerdem gezeigt, dass die kombinierte Therapie bei Stadium IV Parodontitis mit pathologischer Zahnwanderung (PTM) erfolgreich und langzeitstabil angewendet werden kann. Die kieferorthopädische Zahnbewegung nach regenerativer Therapie sollte frühzeitig nach regenerativer Therapie erfolgen, da ein „stimulierender" Effekt während der frühen parodontalen Wundheilung sich langfristig positiv auf die parodontalen Parameter auswirkt. Durch die kombinierte Therapie kann nicht nur das Ziel des langfristigen Zahnerhalts und Erhalts der geschlossenen Zahnreihe erreicht werden, sondern auch die Lebensqualität der Patienten durch die Rekonstruktion von Funktion und Ästhetik langzeitstabil verbessert werden.

6. DARSTELLUNG DER ÜBERLAPPUNG DURCH ANDERE GETEILTE AUTORENSCHAFTEN

Die vorliegende Habilitationsschrift hat fünf publizierte Originalarbeiten zur Grundlage.

Drei der Arbeiten habe ich als Erstautorin (Tietmann et al., J Clin Periodontol 2021; Tietmann et al., J Periodontol 2023; Tietmann et al., Quintessence Int 2024) veröffentlicht.

Eine Arbeit habe ich in geteilter Erstautorenschaft mit Frau PD Dr. Karin Jepsen publiziert (Jepsen und Tietmann et al., Bioengineering 2023). Frau PD Dr. Jepsen ist Oberärztin in der Abteilung für Parodontologie, Zahnerhaltung und Präventive Zahnheilkunde des Universitätsklinikums Bonn, mit der eine enge Kooperation besteht. Sie hat die Arbeit konzipiert. Gemeinsam mit Frau Dr. Jepsen war ich für die Ausführung der Studie (klinische Phase, Datenerhebung), Analyse und Interpretation der Ergebnisse verantwortlich. Entsprechend der gleichwertigen Beiträge wurde die Erstautorenschaft geteilt.

Als Koautorin war ich an der prospektiven multizentrischen randomisierten Studie beteiligt (Jepsen et al., J Clin Periodontol 2021).

Eine Überlappung mit anderen Habilitationsschriften ist nicht gegeben.

Dr. Christina Tietmann

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9. PUBLIKATIONEN

I. Originalarbeiten

1. *Tietmann, C., Jepsen, S., Kauer, R., and Jepsen, K. (2024). Clinical effectiveness of regenerative periodontal surgery and orthodontic tooth movement with clear aligners in stage IV periodontitis: a case series. Quintessence Int. 2024 May 30;55(5):348-357.doi:10.3290/j.qi.b5213521.PMID:38619257 (IF: 1,9).

2. *Tietmann, C., Jepsen, S., Heibrok, H., Wenzel, S., Jepsen, K. (2023). Long-term stability of regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis: 10-year data of a retrospective study. J Periodontol Oct;94(10),1176-1186. doi: 10.1002/JPER.23-0081. Epub 2023 Apr 22. PMID: 37010261
(IF: 4,3)

3. *Tietmann, C., Tezer, I., Youssef, E., Jepsen, S., Jepsen, K. (2023). Management of Teeth with Grade 3 Endo-Periodontal Lesions by Combined Endodontic and Regenerative Periodontal Therapy. J Clin Med Dec 23;13(1),93. doi: 10.3390/jcm13010093. PMID: 38202100 4.
(IF: 3,9)

4. *Jepsen, K., Tietmann, C., Martin, C., Kutschera, E., Jäger, A., Wüllenweber, P., Gaveglio, L., Cardaropoli, D., Sanz-Sánchez, I., Fimmers, R., Jepsen, S. (2023). Synergy of Regenerative Periodontal Surgery and Orthodontics Improves Quality of Life of Patients with Stage IV Periodontitis: 24-Month Outcomes of a Multicenter RCT. Bioengineering (Basel) Jun 7;10(6),695. doi: 10.3390/bioengineering10060695. PMID: 37370626
(IF: 4,6) geteilte Erstautorenschaft

5. *Tietmann, C., Bröseler, F., Axelrad, T., Jepsen, K., Jepsen, S. (2021). Regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis: A retrospective practice-based cohort study. J Clin Periodontol May;48(5),668-678. doi: 10.1111/jcpe.13442. Epub 2021 Mar 25. PMID: 33555608
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6. *Jepsen, K., Tietmann, C., Kutschera, E., Wüllenweber, P., Jäger, A., Cardaropoli, D., Gaveglio, L., Sanz-Sanchez, I., Martin, C., Fimmers, R., Jepsen S. (2021). The effect of timing of orthodontic therapy on the outcomes of regenerative periodontal surgery in patients with stage IV periodontitis: A multicenter randomized trial. J Clin Periodontol Oct;48(10),1282-1292. doi: 10.1111/jcpe.13528. Epub 2021 Aug 12. PMID: 34312872
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7. *Bröseler, F., Tietmann, C., Bommer, C., Drechsel, T., Heinzel-Gutenbrunner, M., Jepsen, S. (2020). Randomised clinical trial investigating self-assembling peptide P_{11}-4 in the treatment of early caries. Clin Oral Investig Jan;24(1),123-132. doi: 10.1007/s00784-019-02901-4. Epub 2019 Apr 29. PMID: 31037343
(IF:3,4) geteilte Erstautorenschaft

8. *Bröseler, F., Tietmann, C., Hinz, A.K., Jepsen, S. (2017). Long-term results of periodontal regenerative therapy: A retrospective practice-based cohort study. J Clin Periodontol May;44(5),520-529. doi: 10.1111/jcpe.12723. Epub 2017 Apr 27. PMID: 28303584
(IF: 6,7) geteilte Erstautorenschaft

9. *Franke, M., Bröseler, F., Tietmann C. (2015). Patient-related evaluation after systematic periodontal therapy - a clinical study on periodontal health-related quality of life (PHQoL). Oral Health Prev Dent 13(2),163-8. doi: 10.3290/j.ohpd.a32340. PMID: 25019103
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10. Tietmann, C., Bröseler F. (2006). Long-term Clinical Outcome after Reconstruction of Periodontal Defects Using a Bovine-Derived Xenograft:A Retrospective Cohort Study. PERIO 3/2,79-86.
(IF: 0)

II. Fallberichte

1. Wenzel, S., Tietmann, C., Bröseler, F. (2017). Zahnerhalt durch forcierte Magnetextrusion. Schweizerische Monatsschrift f. Zahnheilkunde,9:759-765.
   (IF: 0)

2. Wenzel S., Heck, J., Tietmann, C., Bröseler, F. (2014). Therapie einer aggressiven Parodontitis mit anschließender KFO-Therapie - ein Fallbericht. PARODONTOLOGIE 25(1):49-64
   (IF: 0)

3. *Tietmann, C., Bissada, N.F. (2006) Aggressive periodontitis in a patient with chronic cutaneous lupus erythematosus: a case report. Quintessence International May;37(5),401-8. PMID: 16683689
   (IF:1,9)

4. Bröseler, F., Tietmann, C. (2005). Die Therapie isolierter 2- bis 3-wandiger Parodontalläsionen unter Erhaltung der interdentalen Papillen mittels regenerativer Technik – Eine Falldarstellung. (2005). PARODONTOLOGIE 16/2: 137-143
   (IF: 0)

5. *Tietmann, C., Bröseler F. (2002). Enhanced periodontal response and esthetics of implant-supported bridge by the use of galvanoforming technique: case report. Clin Implant Dent Relat Res 4(1), 53-6. doi: 10.1111/j.1708-8208.2002.tb00152.x. PMID: 11938639 1
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III. Videopapers: keine

IV. Übersichtsartikel

1. *Jepsen, K., Tietmann, C., Jepsen, S. (2024). Stadium IV Parodontitis - Falltyp2 Extraktion und Implantat oder Zahnerhalt von Zähnen mit pathologischer Zahnwanderung durch kombinierte PAR- und KFO-Therapie? IMPLANTOLOGIE, accepted: 27. März 2024
   (IF:0,1)

2. Jepsen, K., Tietmann, C., Jepsen, S. (2023). Stadium-IV-Parodontitis – Falltyp 2, Kombinierte PAR- und KFO-Therapie bei Patienten mit pathologischer Zahnwanderung aufgrund einer weit fortgeschrittenen Parodontitis, PARODONTOLOGIE 34 (1), 33-52
   (IF: 0)

3. Franke, M., Tietmann, C., Bröseler, F. (2013). Periimplantitis - eine neue Herausforderung Diagnostik, Präventionsstrategien und Nachsorge. PARODONTOLOGIE 24(1), 69-75.
   (IF: 0)

4. Tietmann, C. (2011). Synergieeffekte durch interdisziplinäre Ansätze im Rahmen regenerativer Maßnahmen – von der Zahnmobilität zur Zahnstabilität. PARODONTOLOGIE 22 (2),135-14.
   (IF: 0)

5. Franke, M., Tietmann, C., Sadr, N., Meisen, D., Bröseler, F. (2011) Patientenbezogene Beurteilung nach durchgeführter systematischer Parodontitis-Therapie. Multifall-Studie, Langzeit-Untersuchung zur Veränderung der Lebensqualität nach PA-Therapie PARODONTOLOGIE 22 (3),309-338.
   (IF: 0)

6. Tietmann, C., Wüllenweber P. (2010. Interdisziplinäre Therapiekonzepte zum Erhalt stark parodontal vorgeschädigter Zähne. Quintessence Team-Journal 40, 67-75.
   (IF:0)

7. Bröseler, F., Tietmann, C. (2009). Regenerative Parodontalchirurgie - Integration in die Praxis. PARODONTOLOGIE 20(1),31-36.
(IF: 0)

8. Tietmann, C., Bröseler, F. (2007). Langfristige Betreuung parodontal erkrankter Patienten – der Schlüssel zum Erfolg- Ein Praxiskonzept. PARODONTOLOGIE 18(1),21-28.
(IF: 0)

V. Letters: keine

VI. Abstracts

*Gedruckte Vorträge und Poster-Präsentationen auf wissenschaftlichen Tagungen
=Publizierte Abstracts von Vorträgen und Postern
+Nicht gedruckte Vorträge

1. Langzeitprognose kombinierter regenerativer und kieferorthopädischer Therapie bei Stadium IV Parodontitis, (Frühjahrstagung DG PARO, 2024, Berlin)*

2. Regenerative periodontal surgery and orthodontic tooth movement in stage iv periodontitis: 10-year data of a retrospective clinical cohort study. (Research Networking Day, Osteology Symposium Barcelona, 2023)*

3. Interdisziplinäre Therapiekonzepte zum Zahnerhalt. (DG PARO Master, Dresden 2023)+

4. Long-term effectiveness of regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis:10-year data of a retrospective clinical cohort study. (Osteology Symposium 2023, Barcelona)*

5. Einsatz von Hyaluronsäure und Octenidin bei Rezidiven in der UPT. (Deutscher Zahnärztetag 2023, Hamburg)+

6. Regenerative periodontal surgery and orthodontic tooth movement in stage IV periodontitis:10-year data of a retrospective clinical cohort study. (EUROPERIO, 2022, Kopenhagen) *

7. Die systematische parodontale Therapie – ein Leitfaden für den Praktiker. (Berliner Zahnärztetag 2021)+

8. Therapie der Parodontitis Stadium IV mit vertikalen Defekten und pathologischer Zahnwanderung durch kombiniert paro-regenerative und kieferorthopädische Therapie - Ergebnisse einer retrospektiven Kohortenstudie (ARPA 2021, Wiesbaden)+

9. Kombination von regenerativer PA-Therapie und Kieferorthopädie. (HARANNI Akademie, 2021, Herne)+

10. A-10-year retrospective analysis of transalveolar sinus floor elevation and simultaneous implant placement using DBBM. (Osteology Symposium 2019, Barcelona)*

11. One stage bone augmentation at implants using GBR with demineralized bovine bonemineral and collagen membrane in patients with or without a history of periodontitis – 10- year results. (Osteology Symposium 2019, Barcelona)*

12. Regenerative Procedures and Orthodontics in the Treatment of Severe Intrabony Defects. (Osteology Symposium 2019, Barcelona) *

13. Funktioniert parodontale Regeneration immer? (Frühjahrstagung DG PARO, Frankfurt, 2019)+

14. Parodontitis, wenn es chronisch wird… (Frühjahrstagung DG PARO Berlin, 2018)+

15. Weichgewebemanagement mit einer neuen Kollagenmatrix. (DGI-Tagung, Köln, 2018)+

16. Langzeitergebnisse kombiniert parodontalchirurgisch-kieferorthopädischer Therapie (ARPA 2016, Bonn)+

17. Orthodontic and regenerative periodontal therapy in the treatment of severe intrabony defects. (European Orthodontic Society Conference, 2015, Venedig)*

18. Orthodontic tooth movements and regenerative periodontal procedures in the treatment of severe intrabony defects. (SIDO, Mailand 2015)*

19. Regenerative therapy using bovine bone mineral shows stable long-term results: a retrospective clinical cohort study. (Osteology Symposium 2015, Monaco)*

20. A long-term retrospective analysis of osteotome sinus elevation and simultaneous implant placement. (EUROPERIO, 2015, London)*

21. Interdisziplinäre Therapiekonzepte: regenerative parodontologische und kieferorthopädische Therapie. (Jahrestagung DG PARO 2014, Münster)+

22. Langfristiger Zahnerhalt durch regenerative Therapie. (DGZMK 2014, Düsseldorf)+

23. Effect of CurodontTM Repair in Patients with Buccal Caries Lesions: a mono-center RCT, intermediate report. (CONSEUR0 2013, Paris)*

24. Regenerative Procedures and Orthodontics in the Treatment of Severe Intrabony Defects. (Osteology Symposium 2013, Monaco)*

25. Patient related quality of life evaluation after therapy of severe periodontitis – consecutive retrospective cohort study. (EUROPERIO 2012, Wien)*

26. Increased implant success in periodontally compromised subjects. (EAO 2012, Kopenhagen)*

27. Residual Periopathogens after Access Flap and two different antibiotic Therapies – 1-year clinical results. (EUROPERIO 2012, Wien)*

28. Regenerative Procedures and Orthodontics in the Treatment of Severe Intrabony Defects -Oral Presentation (EUROPERIO-7, Wien 2012)*

29. Ridge Augmentation using bovine-derived Xenograft prior to Implant Placement in the Esthetic Zone. (EUROPERIO, 2009, Stockholm)*

30. Increased Implant Success in periodontally compromised subjects: Retrospective clinical and radiographical 5 year-evaluation of patients with and without a history of periodontitis. (EAO, 2012, Athen)*

31. Therapie multipler Rezessionen. (Osteology Symposium, 2010, Baden-Baden)+

32. Synergieffekte durch interdisziplinäre Ansätze im Rahmen regenerativer Maßnahmen – von der Zahnmobilität zur Zahnstabilität. (NAgP, 2010, Aachen)+

33. Implant Success in Patients with a History of Chronic Periodontitis. (EUROPERIO, 2009, Stockholm)*

34. Reconstruction of periodontal defects using a bovine-derived xenograft. (EUROPERIO, 2006, Madrid)*

35. Clinical guidelines improving the outcome of regenerative procedures using deproteinized bovine derived xenograft (BDX). (EUROPERIO, 2006, Madrid)*

36. Regenerative Therapie in der Praxis. (Jahrestagung DG PARO, 2006 Erfurt)+

37. Covering of Full Arch Recessions by the Use of Enamel Matrix Derivative. Forum for Innovation. (2004 AAP Annual Meeting, San Diego, CA, USA)*