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주소 04802 서울특별시 성동구 광나루로 257
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REVIEW ARTICLE

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Intraoral scanning versus conventional impressions for working time and patient discomfort: A systematic review and meta-analysis

구강 스캐닝과 전통적 인상 채득의 작업 시간 및 환자 불편감 비교: 체계적 문헌 고찰 및 메타분석

Suin Shin[1], Jaehoon Cho[2,*]

[1]Department of Computer Graphics Technology, Polytechnic Institute, Purdue University, West Lafayette, USA
[2]Edeun Union Dental Clinic, Busan, Korea

ABSTRACT

Purpose: Intraoral scanning (IOS) is increasingly used as a digital alternative to conventional impressions, yet reported benefits for chairside efficiency and patient experience vary across studies. This review quantified differences in working time and patient-reported discomfort and explored effects by age and conventional impression material.

Materials and Methods: PubMed, the Cochrane Library, Google Scholar, and RISS were searched in accordance with PRISMA 2020 for randomized or prospective comparative studies. Random-effects meta-analyses pooled mean differences (MD) for working time and Hedges' g standardized mean differences (SMD) for discomfort on visual analog scales. Prespecified subgroup analyses were conducted by age group and conventional impression material.

Results: Fifteen studies were included. IOS shortened working time (MD −3.39 min; 95% CI −5.16 to −1.62), with larger time savings versus polyvinyl siloxane and polyether than alginate. IOS also reduced discomfort (SMD −1.24; 95% CI −1.53 to −0.94), with consistent benefits across materials and across adult and pediatric populations.

Conclusion: IOS improves patient comfort and modestly reduces chairside time compared with conventional impressions. These findings support IOS use in routine clinical practice and suggest that time reductions are more pronounced when conventional impressions use polyvinyl siloxane or polyether rather than alginate *(J Korean Dent Assoc 2026; 64(7): 223-234)*

Key words : Dental Impression Technique; Computer-Aided Design; Patient Satisfaction; Meta-Analysis

서론

최근 치과 진료 환경은 CAD/CAM 기술의 발전과 함께 디지털 워크플로를 중심으로 빠르게 변화하고 있다. 이러한 변화의 핵심 요소 중 하나인 구강 스캐닝(intraoral scanning, IOS)은 전통적인 인상 채득 과정을 디지털 데이터로 대체함으로써, 보철 및 수복 치료 전반에서 활용 범위를 지속적으로 확대해왔다. 구강 스캐너는 구강 내 구조를 직접 촬영하여 3차원 디지털 인상을 획득할 수 있게 하며, 이는 인상재와 트레이를 사용하는 기존 방식에서 발생할 수 있는 물리적·기계적 한계를 보완하는 기술로 평가받고 있다.

기존의 전통적인 인상 채득 방식은 alginate나 실리콘 기반 인상재를 사용하여 인상을 채득하고 경화가 완료될 때까지 구강 내에 유지해야 하는 특성상, 환자에게 불편감, 구역 반사, 불쾌한 맛, 호흡 곤란 등의 문제를 유발할 수 있다[1]. 이러한 과정은 환자의 협조도에 영향을 미칠 뿐 아니라, 술자 입장에서도 인상 실패로 인한 재채득, 진료 시간 증가, 작업 효율 저하

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*Corresponding author: Dr. Jaehoon Cho
Edeun Union Dental Clinic, 403, 4F, M-Tower, 469-1, Yeonsan-dong, Yeonje-gu, Busan 47569, Korea
Tel: +82-51-791-0002, E-mail: chojae716@naver.com

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로 이어질 가능성이 있다[2]. 반면 구강 스캐닝은 인상재 사용을 최소화하거나 제거함으로써, 환자의 신체적 부담을 줄이고 보다 간소화된 임상 프로토콜을 제공할 수 있는 대안으로 제시되고 있다[3].

구강 스캐닝과 전통적 인상 채득 방식의 비교에 관한 기존 연구들은 정확도, 정밀도, 변연 적합도 등 기술적 측면을 중심으로 다수 보고되어 왔으며, 두 방법 간 임상적으로 허용 가능한 수준의 결과를 보인다는 점이 반복적으로 제시되어 왔다[4]. 최근에는 환자 선호도, 만족도, 불편감과 같은 환자 보고 결과(patient-reported outcome measures, PROMs)에 대한 관심도 점차 증가하고 있다[5]. 그러나 이러한 연구들은 특정 임상 상황이나 제한된 결과 변수에 초점을 맞춘 경우가 많아, 결과 해석에 있어 일관성이 부족하다는 한계를 지닌다. 또한 연구 설계, 사용된 스캐너와 인상재의 종류, 평가 방식의 차이로 인해 이질성이 크며, 인상 채득 시간과 환자 불편감이 부차적 결과로 다뤄지거나 체계적으로 비교되지 않은 경우도 적지 않다.

이에 본 연구는 기존 문헌에서 제기된 이러한 한계를 보완하고자, 구강 스캐닝과 전통적 인상 채득 방식 간의 차이를 인상 채득 시간과 환자 불편감이라는 임상적으로 중요한 두 가지 변수에 초점을 맞추어 분석하고자 한다. 특히, 체계적 문헌 고찰 및 메타분석을 통해 두 인상 방식의 임상적 특성을 종합적으로 비교함으로써, 임상 환경에서 보다 효율적이고 환자 중심적인 인상 채득 방법 선택에 근거를 제공하는 것을 본 연구의 목적으로 한다.

재료 및 방법

본 연구는 체계적 문헌 고찰 및 메타분석(systematic review and meta-analysis)으로, Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) 2020 가이드라인에 의거하여 수행되었다. 연구의 프로토콜은 사전에 정의된 Population, Intervention, Comparison, Outcome, Study Design(PICOS) 전략에 따라 수립되었다.

문헌 검색은 2025년 11월 1일부터 2025년 11월 30일까지 PubMed, Google Scholar, Cochrane Library, RISS 등의 국내외 데이터베이스를 이용하여 진행되었다. 문헌 검색에는 구강 스캐너, 디지털 인상, 전통적 인상, 작업 시간, 환자 불편감, visual analogue scale(VAS) 등 MeSH 기반 용어를 조합하여 사용하였다. 실제 수행한 상세 검색 전략은 다음과 같다. ("intraoral scanner" or “digital impression”) and ("conventional impression") and ("working time" or "patient discomfort”).

문헌의 선정 및 배제 과정은 PICOS criteria에 기반하여 수행되었다. 이에 따른 구체적인 포함 기준과 배제 기준은 Table 1에 상세히 기술하였다.

본 연구는 사람을 대상으로 구강 스캐닝과 전통적 인상채득을 직접 비교한 무작위 대조 임상시험 및 전향적 대조 비교 임상연구를 포함하였다. 대상자 포함 기준은 진단 또는 고정성 보철물 제작을 위해 인상 채득이 필요한 환자로 설정하였다. 증례 보고, in vitro 연구, 종설, 학위논문 등은 제외하였다.

문헌 선택 과정은 두 명의 연구자가 독립적으로 수행하였으며, 1차적으로 제목과 초록을 스크리닝하여 관련 없는 문헌을

Table 1. Inclusion and exclusion criteria (PICOS framework)

	Inclusion criteria	Exclusion criteria
Population	Patients requiring dental impressions for diagnosis or fixed prostheses	In vitro models Animal subjects
Intervention	Digital impression using intraoral scanners (IOS) for direct data acquisition	Extraoral scanning of dental stone casts
Comparison	Conventional impression techniques using alginate, polyvinyl siloxane, polyether	Comparisons between different digital scanners without a conventional control group
Outcome	1) Working time : Total chairside time required for scanning or impression 2) Patient discomfort : Quantified data using visual analogue scale (VAS)	1) Qualitative data only (e.g., preference surveys without scores) 2) Insufficient data for statistical extraction
Study design	Randomized controlled trials (parallel/crossover) and prospective controlled comparative clinical studies	Case reports, reviews, conference abstracts, and theses/dissertations

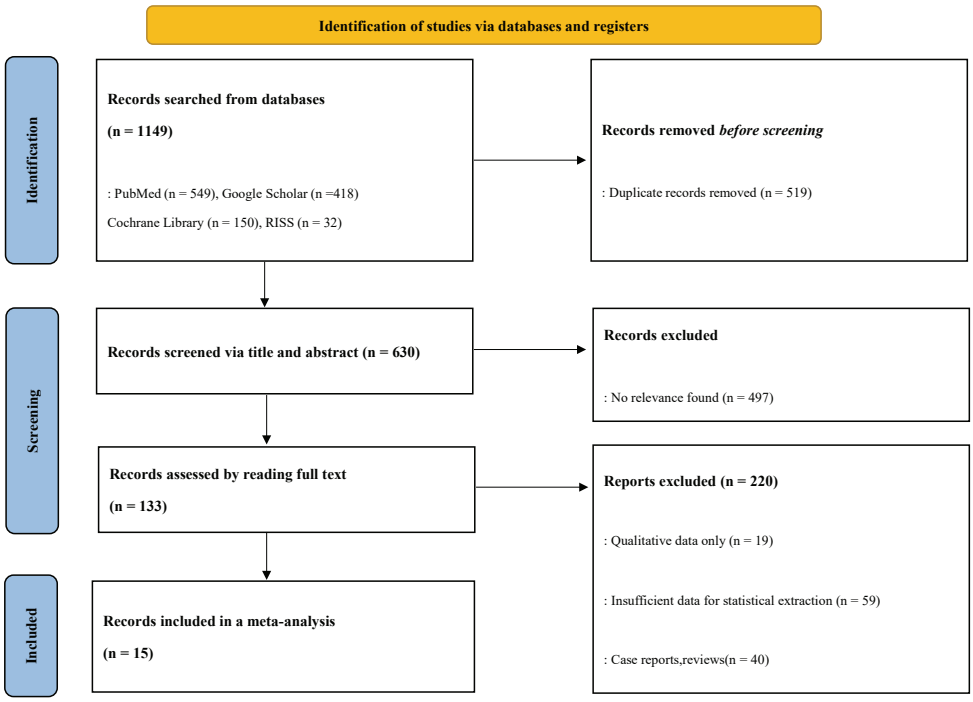

Fig. 1. PRISMA 2020 flow diagram depicts the study identification, screening, eligibility assessment, and inclusion process for the systematic review and meta-analysis comparing intraoral scanning with conventional impression techniques.

배제하였고 2차적으로 원문을 검토하여 최종 포함 여부를 결정하였다. 선정 과정에서 연구자 간의 의견 불일치가 발생한 경우에는, 해당 문헌을 재검토하고 상호 간의 충분한 논의를 거쳐 최종 합의에 도달하였다. 문헌 선택의 전체 과정은 PRISMA flow diagram를 통해 제시하였다(Fig. 1).

최종 선정된 문헌에서는 제1저자, 출판 연도, 대상자 수, 환자의 평균 연령(성인/소아), 사용된 구강 스캐너의 종류, 대조군 인상재의 종류(alginate, polyvinyl siloxane, polyether), 그리고 각 그룹에서 인상채득에 소요된 작업시간 및 VAS의 평균과 표준편차 등을 추출하였다. 본 연구는 인상 채득 방식 자체의 효율성을 비교하기 위해 체어사이드에서 이뤄진 실제 작업 시간만을 분석 범위로 하였다. 따라서 기공 과정을 포함한 denture delivery 등 전체 워크플로우에 사용된 시간은 정량적 합성에서 제외하였다.

포함된 연구의 비뚤림 위험 평가는 Cochrane Risk of Bias(RoB) 2.0의 5가지 도메인 구조를 기반으로 수행하였다. 각 도메인은 D1(무작위 배정 과정에서 발생하는 비뚤림), D2(의도한 중재에서 이탈함으로 인한 비뚤림), D3(결측 결과 데이터로 인한 비뚤림), D4(결과 측정의 비뚤림), D5(보고된 결과 선택의 비뚤림)을 의미한다.

다만 일부 전향적 비교연구(비무작위 연구)의 경우 무작위배정 과정에 관한 도메인 해석에 제한이 있어, 해당 연구 설계에서 기인할 수 있는 교란 및 선택편향 가능성을 결과 해석에서 보수적으로 반영하였다.

메타분석은 R software (ver. 4.5.2, R Foundation for Statistical Computing, Vienna, Austria)의 'meta' 패키지를 사용하여 수행되었다. 작업 시간은 측정 단위가 동일하므로 평균 차(mean difference, MD)를, 환자 불편감은 연구마다 척도의 범위가 다를 수 있음을 고려하여 표준화된 평균 차(standardized mean difference, SMD)를 효과크기로 산출하였으며, 95% 신뢰구간을 함께 제시하였다. 연구 간의 이질성은 I2 통계량과 Cochrane's Q test를 통해 평가하였다. 본 연구에 포함된 문헌들은 구강 스캐너의 종류, 술자의 숙련도, 그리고 대조군 인상재의 물성 등 임상적 이질성이 존재한다고 판단되었기에, 보수적인 추정을 위하여 무작위 효과 모형(random-effects model)을 적용하였다. 또한, 이질성의 원인을 규명하기 위해 환자의 연령과 인상재의 종류에 따른 하위그룹 분석을 시행하였다. 출판 편향은 funnel plot의 시각적 대칭성을 확인하고 Egger's 회귀검정을 통해 통계적 유의성을 검증하였다. 모든 통계적 유의수준은 $p < 0.05$로 설정하였다.

결과

문헌 선정의 전 과정은 PRISMA flow diagram 으로 도식화하였다(Fig. 1). 데이터베이스 검색 및 중복 문헌 제거 후, 제목/초록 선별과 원문 평가를 거쳐 최종적으로 15편의 연구가 메타분석에 포함되었다(Table 2)[6-20]. 최종 선정된 15편의 문헌 중, 체어사이드 작업 시간에 부합하는 정량자료(분 단위, mean ± SD)를 보고하여 메타분석에 포함 가능한 무작위 대조 임상시험(randomized controlled trial, RCT)은 13편이었으며, 나머지 2편은 전향적 대조 비교 연구였다. 한편, VAS를 기반으로 환자 불편감을 정량자료로 보고하여 메타분석에 포함 가능한 문헌은 14편이었다.

ROB 2.0에 따라 15편의 포함 연구를 평가한 결과, 전반적 비뚤림 위험은 Some concerns 11편(73.3%), High risk 4편(26.7%)으로 분류되었다. 도메인별 분포는 다음과 같다. 무작위화 과정(D1)은 Low 3편(20.0%), Some concerns 9편(60.0%), High 3편(20.0%)이었다. 의도한 중재에서의 이탈(D2)은 Low 10편(66.7%), Some concerns 5편(33.3%)으로 분류되었다. 결측 결과자료(D3)는 Low 10편(66.7%), Some concerns 4편(26.7%), High 1편(6.7%)이었다. 결과 측정(D4) 및 보고된 결과 선택(D5)은 모든 연구에서 Some concerns(각 15편, 100%)으로 평가되었다(Figs. 2 and 3).

메타분석 결과: 작업 시간

작업시간은 13편 연구(구강 스캐닝 453명, 전통적 인상채득 473명)를 대상으로 랜덤효과모형으로 분석하였다. 전체 효과는 MD = −3.39 minutes(95% CI, −5.16 to −1.62 ; $p < 0.001$)로, 디지털 구강 스캐닝이 전통적 인상채득에 비해 유의하게 작업시간을 단축시키는 것으로 나타났다. 다만 이질성은 높았으며(I^2 = 99.5%, τ^2 = 10.3519, Q 검정 $p < 0.001$), 이에 따라 환자 연령군과 인상재에 따른 하위그룹 분석을 진행하였다.

환자 연령군에 따른 하위그룹 분석 결과는 Figure 4와 같다. 성인군은 MD = −3.54 minutes(95% CI, −6.14 to −0.94), 소아군은 MD = −3.10 minutes(95% CI, −3.97 to −2.23) 로 두 그룹에서 모두 구강 스캐닝이 전통적 인상채득에 비해 작업시간을 유의하게 단축시키는 것으로 확인되었다. 점추정치 기준으로 성인군에서 소아군 대비 더 큰 효과크기가 관찰되었으나, 연령군에 따른 하위그룹별 효과 크기의 차이는 유의하지 않았다(χ^2 = 0.10, df = 1, p = 0.7523).

인상재 유형에 따른 하위그룹 분석 결과는 Figure 5와 같다. 하위그룹별 효과 크기에 있어 통계적으로 유의한 차이가 확인되었다(χ^2 = 10.06, df = 2, p = 0.0065). 구체적으로, 구강 스캐닝은 polyvinyl siloxane과 비교하였을 때 MD = −5.63 min-

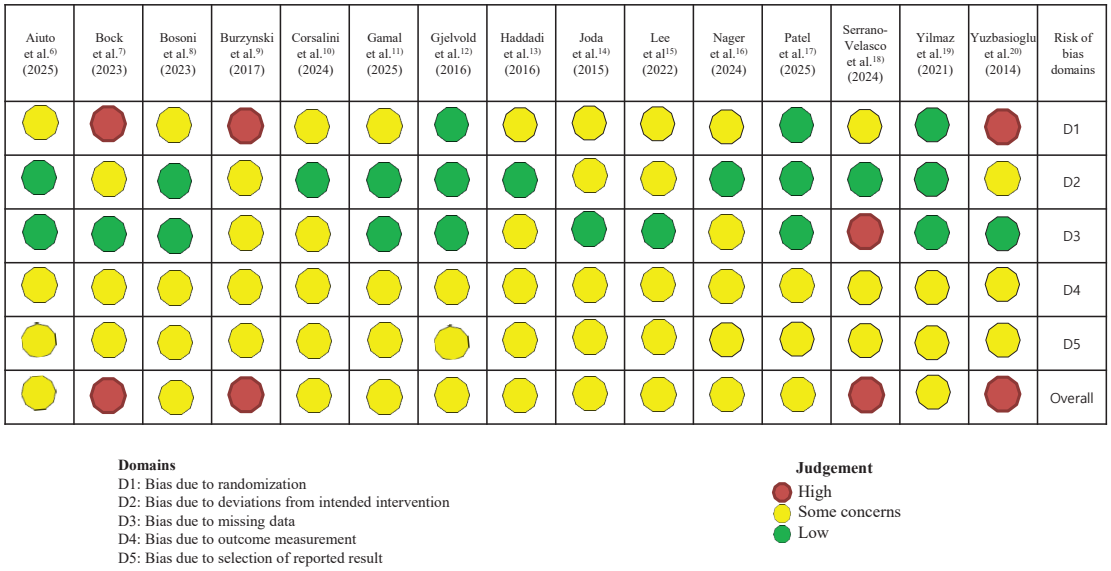

Fig. 2. Risk of bias (RoB 2.0) traffic-light plot for the included studies. Domain-level judgements are presented for D1 (randomization process), D2 (deviations from intended interventions), D3 (missing outcome data), D4 (measurement of the outcome), and D5 (selection of the reported result), along with the overall RoB 2.0 judgement for each study.

Table 2. General characteristics of included studies

Study	Country	Study design	N of participants (IOS/Conventional)	Mean age	Digital scanning system	Conventional impression material	VAS measurement criteria	Working time measurement criteria
Aiuto et al.[6] (2025)	Italy, Spain	Randomized crossover trial	107/107	7.33±1.42	TRIOS 3 (3Shape)	Alginate (CA37 Normal set, Cavex) + wax bite	100-mm VAS evaluating patient's experience	Chairside stepwise acquisition time recorded. IOS: registration → mandibular scan → maxillary scan → bite scan; Conventional (alginate): tray selection → mandibular impression → maxillary impression (± bite as applicable).
Bock et al.[7] (2023)	Germany	Randomized crossover trial	30/30	NR (≥16y)	Primescan; TRIOS 4; Medit i700; Emerald S	Alginate (Cavex Orthotrace)	Not assessed	Chairside acquisition time measured for IOS vs alginate. Additionally, time until model availability was reported separately (conventional metric included impression + plaster casting, excluding setting time).
Bosoni et al.[8] (2023)	Italy	Randomized crossover trial	24/24	8.8±1.0	TRIOS 3 (3Shape)	Alginate (Orthoprint, Zhermack) + wax bite	VAS 0-10 (comfort, pain, gag reflex, breathing difficulty)	Total chairside impression procedure duration recorded for IOS vs alginate, following the predefined protocol (both arches with bite registration as applicable).
Burzynski et al.[9] (2017)	USA	Prospective comparative clinical study	60/60	NR (median = 15)	TRIOS Color (3Shape)	Alginate (NR)	100-mm VAS	IOS: chairside time to complete full-mouth scan + bite registration. Conventional: chairside time to mix alginate and complete maxillary + mandibular impressions.
Corsalini et al.[10] (2024)	Italy	Randomized controlled trial	26/46	NR	TRIOS 3 (3Shape)	PVS (Hydrorise Hydrophobic, Zhermack) + wax bite	Questionnaire with VAS for perceived comfort (scale NR)	Overall chairside impression-taking time reported for each workflow; explicit start/end boundaries were not specified in the extracted report.
Gamal et al.[11] (2025)	Egypt	Randomized crossover trial	30/30	NR (range : 7-11)	TRIOS 4 (3Shape)	PVS (Aquasil Soft Putty, Dentsply Sirona)	VAS 0-10 for comfort & gag reflex	IOS: stopwatch-measured chairside time from start of registration to completion of mandibular scan + maxillary scan + bite scan (excluding verbal explanation/isolation). Conventional (PVS): tray selection → mandibular impression → maxillary impression → wax bite.
Gjelvold et al.[12] (2016)	Sweden	Randomized controlled trial	21/21	56±15	TRIOS Standard-P12 (3Shape)	Polyether (Impregum Penta, 3M ESPE)	VAS 0-100 mm (patient discomfort)	Time was split into preparation time and impression time. For working-time comparison, impression time (prepared teeth + opposing arch + bite registration) was used; remakes were included (preparation time reported separately).
Haddadi et al.[13] (2018)	Denmark	Randomized crossover trial	19/19	NR	NR	PVS (one-step, two viscosity)	100-mm VAS (100=max discomfort)	Total operating time recorded stepwise for IOS and conventional impressions
Joda et al.[14] (2015)	Switzerland	Randomized crossover trial	20/20	55.4	iTero (Align)	Polyether (Impregum Penta, 3M ESPE)	VAS 0-100 for convenience-related factors	Total work time recorded stepwise by an assistant for each method, covering acquisition of the implant site plus opposing arch and bite registration according to predefined sequences.
Lee et al.[15] (2022)	USA	Randomized crossover trial	30/30	53.13	iTero Element (Align)	PVS (Aquasil Ultra Monophase, Dentsply Sirona)	VAS 0-100 comfort questionnaire	Working time defined as chairside acquisition/procedure time. Conventional working time: from material loading to complete setting; Digital working time: per scanning protocol.
Nagar et al.[16] (2024)	Spain	Randomized controlled trial	50/50	65	TRIOS (3Shape)	Alginate primary + zinc oxide eugenol secondary	100-mm VAS	Time outcome reflected overall clinical workflow time from impression stage to denture delivery (not chairside acquisition/procedure minutes); therefore not eligible for chairside working-time pooling.
Patel et al.[17] (2025)	India	Randomized crossover trial	23/23	NR (range : 8-12)	Irific (NeuralHive)	Alginate (NR)	VAS 0-10 post-session	Conventional (alginate): stopwatch from start of mixing to impression removal. IOS: scanning time recorded by software (both arches, ending with bite registration).
Serrano-Velasco et al.[18] (2024)	Spain	Randomized crossover trial	51/51	12.35	iTero Element 5D Plus +Primescan	Alginate (Orthoprint, Zhermack) + wax bite	100-mm VAS adapted for children	Objective chairside working time was not reported; time was assessed primarily as a patient-perceived domain rather than stopwatch-/software-recorded duration; therefore not eligible for chairside working-time pooling.
Yilmaz et al.[19] (2021)	Turkey	Randomized crossover trial	39/39	21.73±7.86	TRIOS 3 (3Shape)	Alginate (Hydrogum 5, Zhermack)	VAS comfort score (scale details NR)	Stepwise chairside acquisition time recorded. IOS: registration → mandibular scan → maxillary scan → bite scan; Conventional: tray selection → mandibular impression → maxillary impression → wax bite.
Yuzbasioglu et al.[20] (2014)	Turkey	Prospective comparative clinical study	24/24	21.87±2.76	CEREC Omnicam (Sirona)	Polyether (Impregum, 3M ESPE)	VAS 0-100 self-administered questionnaire	Stepwise chairside workflow time recorded (seconds). Conventional: tray selection → adhesive application → impressions → bite; IOS: patient data entry/lab prescription → upper-lower scanning → bite scan.

N: number, NR: not reported, MD: mean difference, SMD: standardized mean difference, VAS: visual analogue scale

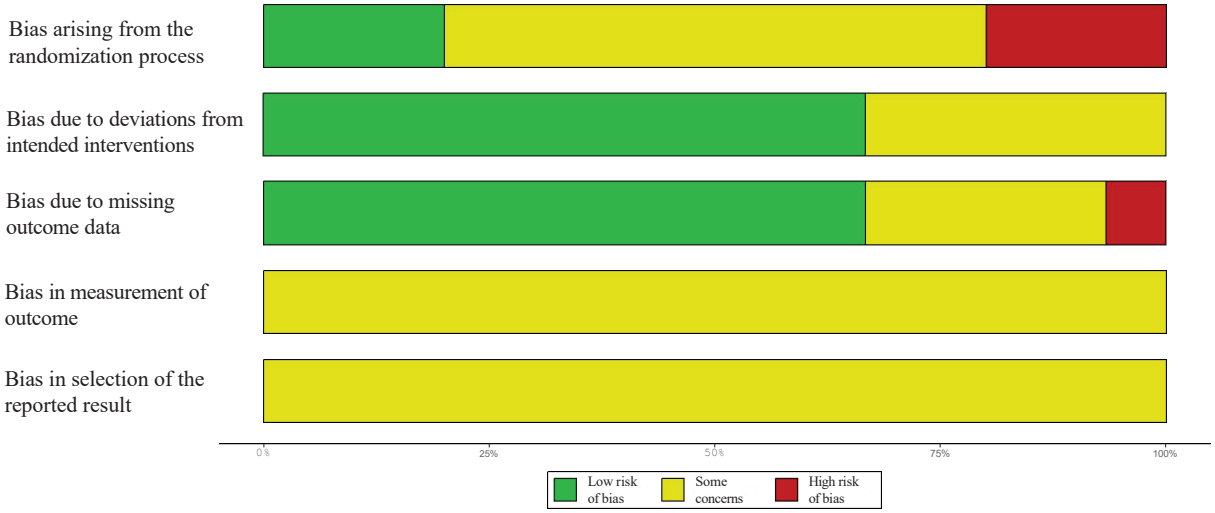

Fig. 3. Summary plot of Risk of bias (RoB 2.0) judgements shows the proportion of included studies rated as low RoB 2.0, some concerns, or high risk of bias for each RoB 2.0 domain (D1–D5) and the overall judgement.

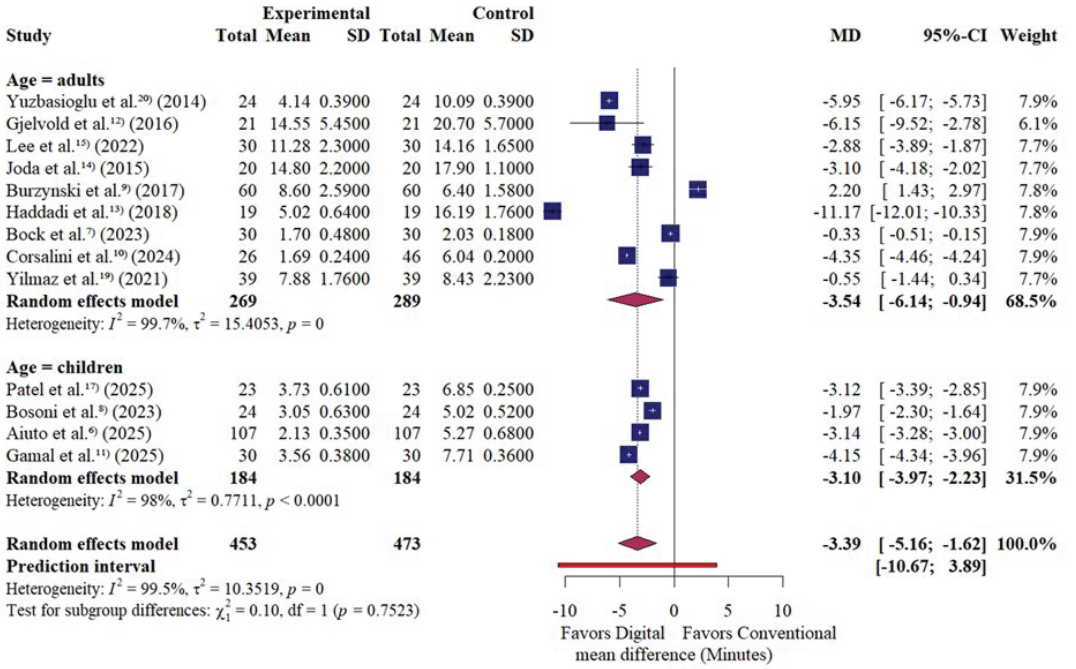

Fig. 4. Forest plot of working time (minutes) comparing intraoral scanning (IOS) versus conventional impression techniques, stratified by age group (adults vs children), using a random-effects model. Effect sizes are presented as mean differences (MDs) with 95% confidence intervals (CIs); negative MDs values favor IOS (shorter working time). Square sizes reflect study weights and diamonds indicate pooled estimates (with a prediction interval where shown).

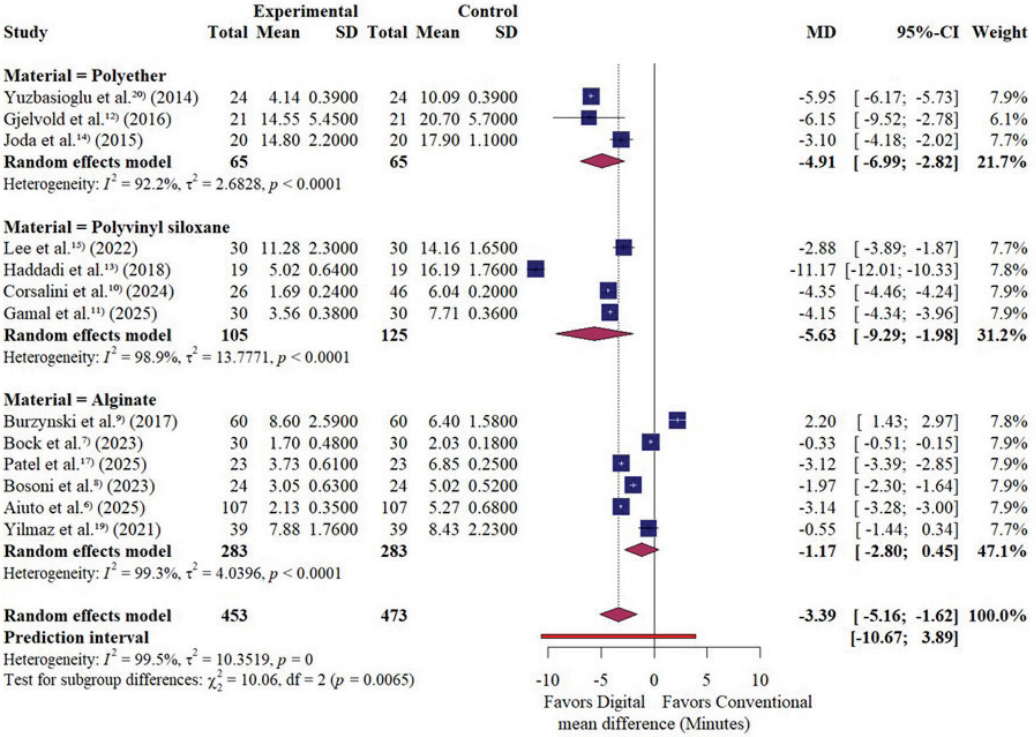

Fig. 5. Forest plot of working time (minutes) by conventional impression material (polyether, polyvinyl siloxane, and alginate) comparing intraoral scanning (IOS) versus conventional impressions using a random-effects model. Effect sizes are presented as mean differences (MDs) with 95% confidence intervals (CIs); negative mean difference values favor IOS. Square sizes reflect study weights and diamonds represent pooled estimates (with a prediction interval where shown).

utes(95% CI, −9.29 to −1.98)로 작업시간에서 가장 큰 단축 효과를 나타냈다. 한편, polyether와 대비해서는 MD = −4.91 minutes(95% CI, −6.99 to −2.82)로 작업시간 단축 효과가 뚜렷하였다.

반면 alginate 하위그룹은 MD = −1.17 minutes(95% CI, −2.80 to 0.45)로 나타났다. 이는 구강 스캐닝이 작업시간을 단축시키는 경향성을 보였으나, 통계적으로 유의미한 차이는 관찰되지 않았음을 의미한다.

메타분석 결과: 환자 불편감

환자 불편감은 14편 연구(구강 스캐닝 524명, 전통적 인상채득 544명)에서 추출되었으며, 연구 간 척도/분산 차이를 고려하여 SMD 기반으로 랜덤효과모형 분석을 수행하였다. 전체 효과는 SMD = −1.24(95% CI, −1.53 to −0.94) 로, 구강 스캐닝이 전통적 인상채득에 비해 환자 불편감을 유의하게 감소시키는 것으로 나타났다. 이질성은 중등도-높은 수준이었다(I^2 = 80.8%, τ^2 = 0.2398, Q 검정 p 〈 0.001). 이에 따라 환자 연령군과 인상재에 따른 하위그룹 분석을 진행하였다.

연령군 하위그룹 분석에서 성인 그룹은 SMD = −1.29(95% CI, −1.70 to −0.87), 소아 그룹은 SMD = −1.16(95% CI, −1.58 to −0.74)으로 두 군 모두 구강 스캐닝이 전통적 인상채득 대비 불편감을 유의하게 감소시키는 것으로 나타났다(Fig. 6). 점추정치 기준으로 성인 그룹에서 더 큰 효과크기가 수치상으로 관찰되었으나, 연령군에 따른 하위그룹별 효과 크기의 차이는 통계적으로 유의하지 않았다(χ^2 = 0.17, df = 1, p = 0.6767).

인상재 기준 하위그룹 분석에서, polyether는 SMD = −1.50(95% CI, −2.04 to −0.96), polyvinyl siloxane은 SMD = −1.49(95% CI, −1.78 to −1.19), alginate는 SMD = −1.03(95% CI, −1.51 to −0.54)로 모든 하위그룹에서 구강 스캐닝이 전통적 인상채득 대비 불편감을 유의하게 감소시키는 것으로 나타났다(Fig. 7). 점추정치 기준으로는 polyether, polyvinyl siloxane, alginate 순으로 높은 효과크기가 수치상으로 관찰되었으나, 인상재에 따른 하위그룹별 효과크기의 차이는 유의하지 않았다(χ^2 = 2.77, df = 2, p = 0.2503).

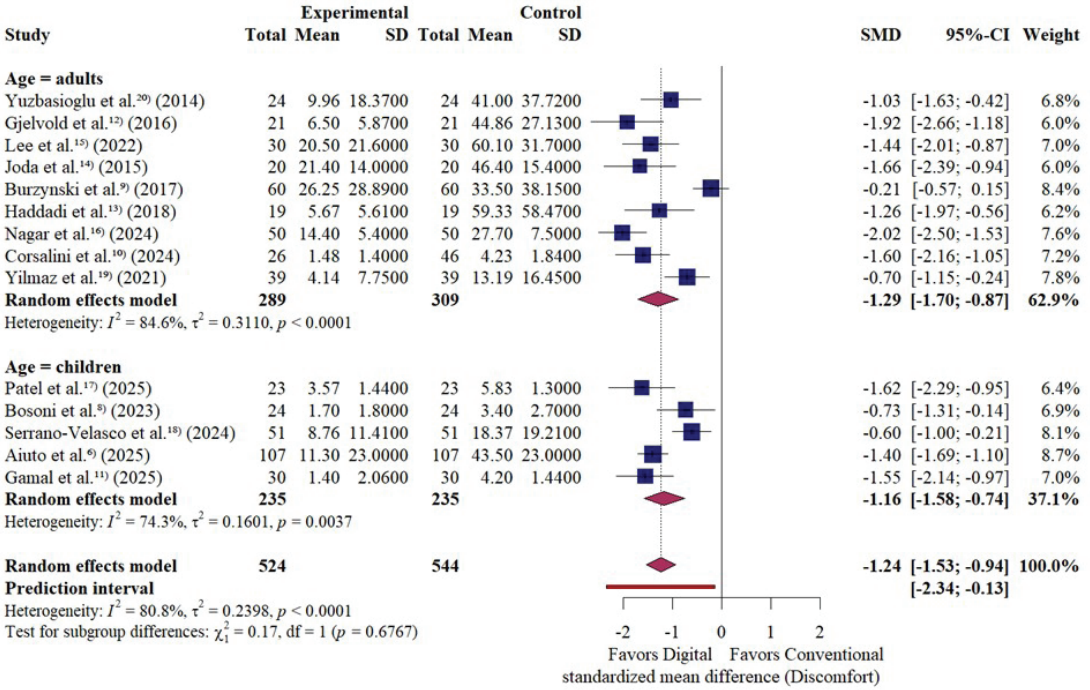

Fig. 6. Forest plot of patient discomfort comparing intraoral scanning (IOS) versus conventional impression techniques, stratified by age group (adults vs children), using an inverse variance (IV) random-effects model. Effect sizes are presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs); negative SMDs values favor IOS (lower discomfort). Square sizes reflect study weights and diamonds indicate pooled estimates (with a prediction interval where shown).

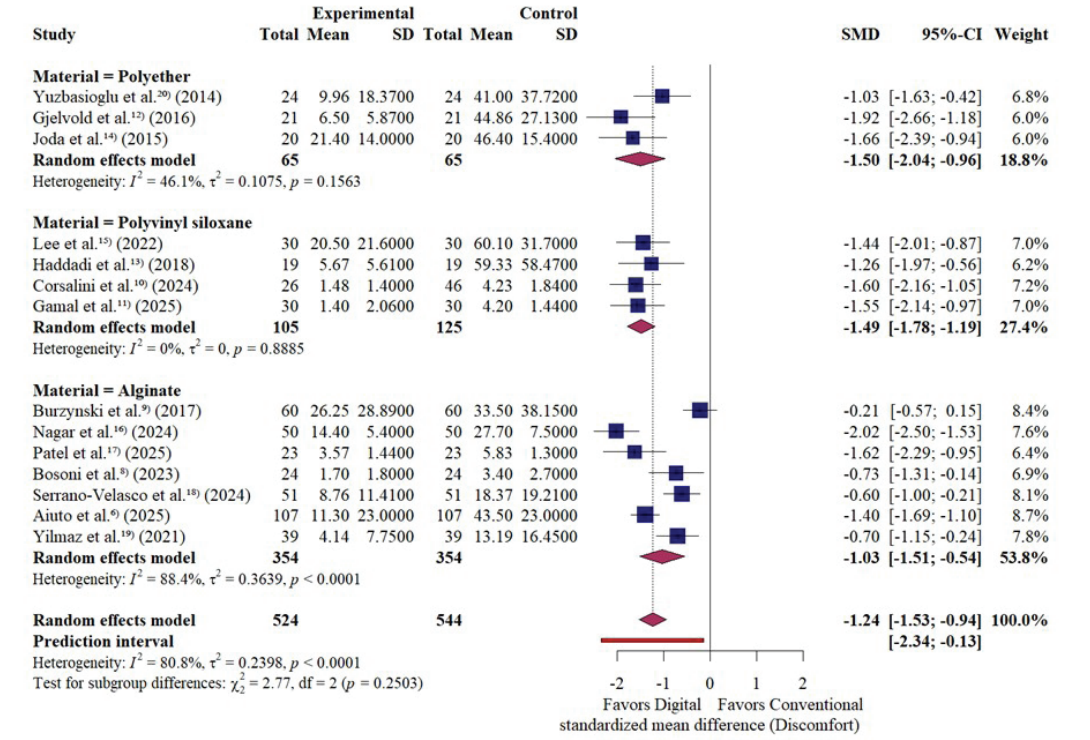

Fig. 7. Forest plot of patient discomfort by conventional impression material (polyether, polyvinyl siloxane, and alginate) comparing intraoral scanning (IOS) versus conventional impressions using an inverse variance (IV) random-effects model. Effect sizes are presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs); negative SMD values favor IOS. Square sizes reflect study weights and diamonds represent pooled estimates (with a prediction interval where shown).

출판편향(publication bias) 평가

funnel plot 시각적 평가에서 작업시간 및 불편감 결과 모두에서 뚜렷한 비대칭은 관찰되지 않았다(Figs. 8 and 9). Egger's 회귀검정 결과, 작업시간은 t = 0.37, df = 11, p = 0.7156, 환자 불편감은 t = −1.49, df = 12, p = 0.1630으로 두 결과 모두에서 funnel plot의 비대칭을 시사하는 통계적 근거는 확인되지 않았다. 다만, 포함된 연구 수가 제한적이므로 출판편향 가능성을 완전히 배제할 수는 없으며, 해석에 주의가 필요하다.

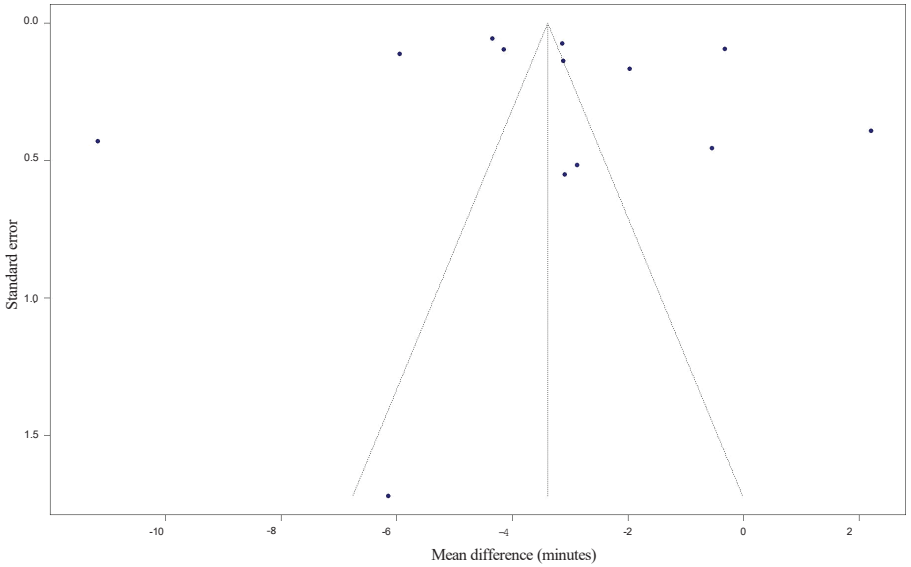

Fig. 8. Funnel plot assessing potential small-study effects/publication bias for the working time outcome comparing intraoral scanning with conventional impression techniques. Each point represents an individual study plotted by effect size (mean difference, minutes) against its standard error; the vertical line indicates the pooled effect estimate and the dashed lines indicate pseudo 95% confidence limits.

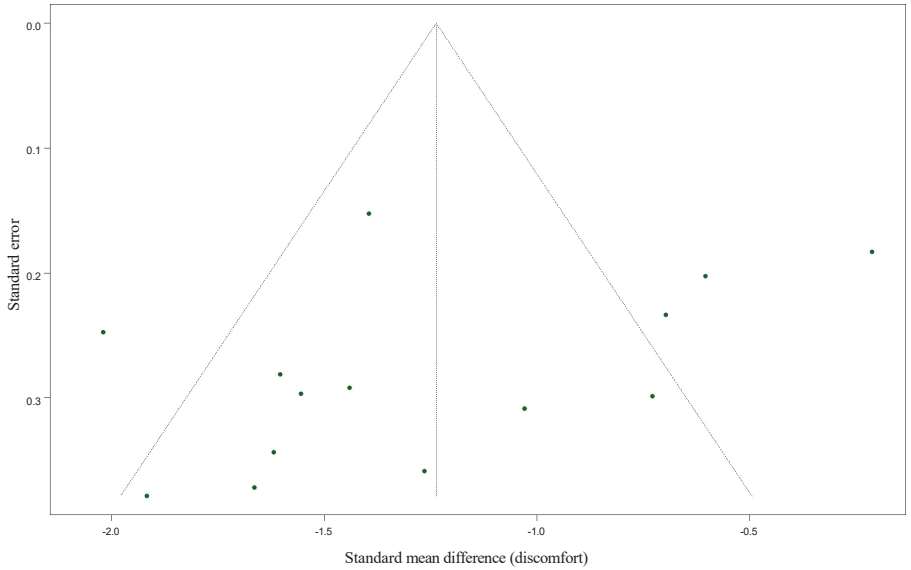

Fig. 9. Funnel plot assessing potential small-study effects/publication bias for the patient discomfort outcome comparing intraoral scanning with conventional impression techniques. Each point represents an individual study plotted by effect size (standardized mean difference) against its standard error; the vertical line indicates the pooled effect estimate and the dashed lines indicate pseudo 95% confidence limits

고찰

본 체계적 문헌고찰 및 메타분석은 구강 스캐닝과 전통적 인상 채득 간의 임상적 차이를 작업시간과 환자 불편감이라는 환자 중심 지표에 초점을 맞추어 종합적으로 평가하였다. 본 연구에서 구강 스캐닝은 전통적 인상 채득에 비해 작업시간을 평균 3.39분 단축시켰으며(MD = −3.39 min), 환자 불편감을 유의하게 감소시키는 것으로 나타났다(SMD = −1.24). 이러한 결과는 디지털 인상 채득이 환자 경험을 개선하면서 임상 효율성을 향상시킬 수 있다는 기존 임상 연구 및 체계적 문헌고찰 연구의 결론과 일치한다[14,21-23].

환자 불편감의 감소는 구강 스캐닝이 인상 트레이와 인상재를 구강 내에 장시간 유지해야 하는 과정을 제거함으로써, 구역 반사, 호흡 불편, 불쾌감(맛·냄새) 및 압박감을 줄이는 기전으로 설명될 수 있다[12,20]. 실제로 다수의 RCT에서 환자들은 디지털 인상 채득을 더 선호하거나 불편감이 더 낮다고 보고하였으며[12-14,20,21], 이는 본 연구의 전체 효과크기와 일치하는 결과라고 할 수 있다. 한편, Cohen은 표준화된 평균차에 대해 0.2/0.5/0.8을 각각 작은/중간/큰 효과로 해석하는 경험적 기준을 제시한 바 있다[24]. 따라서 본 연구에서 관찰된 환자 불편감의 SMD가 0.8을 상회한다는 점은, 구강 스캐닝의 전통적 인상채득 대비 불편감을 감소시키는 효과가 통계적으로 유의할 뿐 아니라 임상적으로도 유의미하다는 가능성을 시사한다.

작업시간의 단축은 구강 스캐닝이 인상재 혼합, 트레이 장착, 경화 대기 및 인상체 제거 과정에 소요되는 시간을 줄일 수 있다는 점에서 타당하다[12,13]. 특히 전통적 인상 채득에서 재인상 발생이나 술자·환자 협조도 문제로 인한 추가 시간이 발생할 수 있다는 점을 고려하면, 단순 평균 시간 차 이상으로 체감 효율성이 확대될 여지도 있다[20,22]. 다만 작업시간은 연구마다 정의가 상이하여(트레이 선택 및 접착제 도포 시간 포함 여부, 스캔 재촬영 포함 여부, 교합 채득 포함 여부 등), 본 연구의 추정치는 평균적인 경향으로 해석하는 것이 적절하리라 사료된다.

본 연구에서 작업시간 결과의 이질성이 매우 높게 관찰되었는데, 이는 작업시간의 정의와 측정 범위가 연구마다 완전히 동일하지 않았기 때문일 가능성이 크다. 이외에도 치과 디지털 장비 연구의 특성상 스캐너 세대/모델, 스캔 전략, 술자 숙련도, 보철·교정 등 임상 상황, 인상 범위(부분/전악) 가 복합적으로 작용하기 때문으로 해석된다[23,25,26]. 특히 구강 스캐닝은 술자 경험에 따라 스캔 품질과 소요 시간이 달라질 수 있고, 초기 러닝커브 구간에서는 오히려 시간이 증가할 수 있다는 점이 보고되어 왔다[26]. 반면, 전통적 인상채득은 재료 특성 및 술자 습관에 따라 비교적 프로토콜 시간이 고정적으로 형성되는 경향이 있어, 연구 간 작업시간 분산이 구강 스캐닝에서 더 크게 나타날 수 있다[25,26].

인상재 종류에 따른 하위그룹 분석에서 구강 스캐닝의 작업시간 단축 효과는 polyvinyl siloxane 및 polyether 대비 더 크게 나타났으나, alginate와 비교시에는 통계적으로 유의한 시간 단축 효과가 나타나지 않았으므로 임상 적용시 이를 고려해야 한다. 이는 polyvinyl siloxane/polyether의 경우 인상 채득 전 준비 단계가 많고(트레이 준비, 혼합 및 주입, 경화 대기 등) 구강 내 유지시간이 길어질 수 있는 반면, alginate는 상대적으로 간단하고 경화 시간이 짧아 시간 격차가 축소되기 때문으로 설명 가능하다[9,12,13]. 실제로 alginate와 구강 스캐닝을 직접 비교한 무작위 교차 연구에서도 시간 단축 효과는 상황, 측정 방식에 따라 결과가 상이할 수 있음이 보고된 바 있다[9,19]. 반면 불편감은 인상재 종류에 관계없이 구강 스캐닝이 일관되게 유리하였는데, 이는 인상재 종류와 무관하게 트레이 및 인상재 자체가 유발하는 구역 반사, 압박감 등의 불편 요인이 공통적으로 존재하기 때문으로 해석된다[22].

연령(성인/소아) 하위그룹 분석에서는 두 결과 모두에서 구강 스캐닝의 효과가 일관되었고, 하위그룹 간 차이는 유의하지 않았다. 이는 소아에서도 구강 스캐닝이 전통적 인상 대비 불편감을 줄이고 환자 선호를 향상시킬 수 있다는 기존 연구 결과와 일치한다[8,19]. 특히 소아·청소년에서는 구역 반사 및 불안이 인상 채득의 주요 장애 요인이 될 수 있는데, 본 연구 결과는 구강 스캐닝이 이러한 장벽을 낮출 수 있다는 임상적으로 중요한 가능성을 시사한다.

기존 연구는 디지털 인상 채득의 정확도, 적합도, 재현성 등 기술적 측면에 집중한 경우가 많았으나, 최근에는 PROMs와 작업 효율성의 중요성이 강조되고 있다[23]. Gallardo 등(2017)[22]은 체계적 문헌고찰을 통해 디지털 인상이 환자 경험 측면에서 우수하며, 작업시간은 연구 조건에 따라 유사하거나 디지털이 유리할 수 있다고 보고한 바 있다. 본 연구는 여기서 한 걸음 나아가, 환자 불편감과 작업시간을 핵심 지표로 설정하여 메타분석을 진행하였으며, 연령 및 인상재 종류에 따른 하위그룹 분석을 통해 임상적 해석 가능성을 확장했다는 점에서 의의를 갖는다. 또한 메타분석에 포함된 연구의 비뚤림 위험을

RoB 2.0으로 체계적으로 평가하고, 출판편향을 함께 검토함으로써 결과의 신뢰도를 다각도로 점검하였다.

본 연구의 한계는 다음과 같다. 첫째, 대상 문헌의 부족으로 인해 연구마다 작업시간의 정의와 측정 범위가 조금씩 상이하였고, 스캐너 모델 · 스캔 범위 · 임상 술식 또한 상이하여 높은 이질성이 잔존한 상태에서 통계 분석이 시행되었다. 둘째, 디지털 워크플로우는 술자 숙련도가 결과와 큰 상관관계를 가지나, 본 연구에서는 데이터의 부족으로 말미암아 이를 메타분석에 반영하지 못하였다. 향후 관련 연구가 축적되어 후속 연구가 이뤄진다면, 작업시간의 정의를 명확히 좁히는 한편, 스캐너 세대/모델과 술자 숙련도(러닝커브)를 층화하여 보고하는 연구가 가능하리라 사료된다. 또한, 인상채득 과정에서 환자가 느끼는 불편감뿐 아니라 불안, 선호도, 재방문의향 등을 핵심 지표로 포함하는 메타분석이 필요할 것이다. 한편, 전통적인 인상채득에 수반되는 작업모형의 제작도 오늘날 디지털 워크플로우를 통해 구현 가능함을 상기해보면, 기공 전에 소요되는 총 작업 시간의 차이를 비교하는 후속 연구 또한 필요하리라 사료된다.

Conflicts of Interest: None

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REVIEW ARTICLE

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Age-friendly oral health care: A scoping review and conceptual framework for integrating dentistry into healthy ageing

Soyeon Kim[1], Young-Seok Park[1,*], Kung-Rock Kwon[2]

[1]Department of Oral Anatomy and Dental Research Institute, School of Dentistry, Seoul National University, Seoul, Korea
[2]Department of Prosthodontics, School of Dentistry, Kyung Hee University, Seoul, Korea

ABSTRACT

Purpose: Oral health is increasingly recognized as a key component of healthy ageing, yet it remains insufficiently integrated into age-friendly health systems. To map existing evidence on oral health in older adults and propose a conceptual framework for age-friendly oral health care.
Methods: A scoping review was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. A PubMed search identified 708 records (April 18, 2026). After applying filters (last 10 years, ≥ 65 years, human studies), 247 records remained. Following thorough screening, 52 studies were included and thematically analyzed.
Results: The included studies showed consistent associations between oral health and functional outcomes, frailty, and quality of life. Functional oral health, particularly mastication and dentition, emerged as a key determinant of healthy ageing. However, the evidence was fragmented, and no study proposed an integrated framework linking oral health to age-friendly health systems.
Conclusion: The concept of age-friendly oral health care is proposed to bridge this gap and align dentistry with broader ageing frameworks. Establishing this concept may support more coherent policy development and integrated care for older adults. ***(J Korean Dent Assoc 2026; 64(7): 235-244)***

Key words : Healthy Ageing; Oral Health; Frailty; Geriatric Dentistry

Introduction

Population aging is a defining demographic transformation of the twenty-first century, placing unprecedented demands on healthcare systems to evolve beyond clinical efficacy toward coordinated, person-centered care[1]. The World Health Organization (WHO) has redefined healthy aging as the preservation of functional ability and well-being rather than the mere absence of disease[2]. This paradigm shift has been operationalized through the Age-Friendly Health Systems (AFHS) initiative and its 4Ms framework (What Matters, Medication, Mentation, and Mobility), which provides a structured approach to aligning care with the needs of older adults[1,3,4].

Despite the rapid adoption of age-friendly principles in general medicine, dentistry remains largely procedure-oriented and fragmented, often isolated from broader geriatric care models[5]. Clinical oral care for older adults, particularly those in long-term care or with functional dependency, is frequently compromised by a lack of integrated routines, time constraints, and insufficient provider confidence[6]. This gap is particularly critical because

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*Corresponding author: Prof. Young-Seok Park
Department of Oral Anatomy, School of Dentistry, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-740-8627, E-mail: ayoayo7@snu.ac.kr

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oral health is closely associated with systemic health, nutrition, and psychological well-being[7]. Furthermore, older adults tend to perceive oral care not merely as a technical service, but in relation to autonomy, trust, and life-course experiences[8,9].

Addressing these challenges requires moving beyond chairside-centered interventions toward a comprehensive system of assessment and support. Persistent barriers—such as mobility limitations, reduced oral health literacy, and cognitive decline—highlight the necessity of multidisciplinary approaches involving caregivers and non-dental professionals[10–12]. In practice, oral care for dependent older adults is often delegated to nursing or caregiving staff; however, such integration remains inconsistent and insufficiently structured[13]. In addition, social and environmental factors, including community structure and access to care, may further influence oral health outcomes in older populations[14]. Nevertheless, many clinicians report uncertainty and insufficient training when managing patients with advanced frailty or cognitive impairment, particularly in relation to the Mentation domain.

In response, the concept of Age-Friendly Oral Health Care (AFOHC) is emerging as a framework to align dental practice with AFHS principles. Rather than defining a new subspecialty, AFOHC emphasizes system-level adaptation, including environmental modification, caregiver engagement, and clinical protocols tailored to varying levels of functional and cognitive capacity. This perspective is consistent with earlier calls for a broader, system-oriented approach to oral health promotion in older adults[15,16].

Accordingly, the aim of this study is to conceptualize an AFOHC framework by adapting AFHS principles to dental settings, with particular consideration of the Korean context. As a society undergoing rapid demographic transition to a super-aged structure, Korea faces a "time-compressed" challenge in which advanced clinical dental capabilities coexist with insufficient system-level readiness for managing frail and cognitively impaired older adults. By proposing a model tailored to such conditions, this study seeks to contribute to a more coherent, equitable, and sustainable oral health care system that recognizes oral health as an essential component of healthy aging.

Materials and Methods

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The study aims to map the evidence on AFOHC and establish its conceptual framework within the broader health system[17].

A systematic literature search was conducted in PubMed on April 18, 2026. The search strategy combined terms related to ageing, oral health, and age-friendly care concepts. The full search string was as follows: ("older adults" OR elderly OR ageing OR aging OR geriatric*) AND ("oral health" OR "oral care" OR dentistry OR "dental care" OR "geriatric dentistry") AND ("healthy ageing" OR "healthy aging" OR "age-friendly" OR frailty OR "intrinsic capacity" OR "Age-Friendly Health Systems"). Filters were applied for human studies, adults aged ≥ 65 years, English language, and publication years 2016–2026. The search initially yielded 708 records. After applying automated filters for human subjects, age ≥ 65, and a 10-year publication window (2016–2026), 247 records remained. Following a title and abstract screening for conceptual relevance to AFOHC, a final total of 52 studies were included for analysis.

Title and abstract screening were independently conducted by two reviewers to evaluate conceptual relevance to AFOHC. Studies with uncertain eligibility underwent full-text assessment. Disagreements regarding study selection were resolved through discussion and consensus among the authors.

Data were extracted using a structured charting framework. The variables captured included: 1) study characteristics: author, year, country, and study design, 2) context: population and setting, 3) clinical and systemic domains: oral health domains (e.g., oral frailty, mastication), aging-related constructs (e.g., intrinsic capacity), care delivery models, and alignment with age-friendly health frameworks.

A thematic synthesis approach was employed to categorize the findings into five core domains: 1) conceptual frameworks and healthy aging, 2) functional oral health, 3) oral frailty and intrinsic capacity, 4) care delivery and system integration, 5) education and workforce development.

In this framework, "functional oral health" refers primarily to the performance-related aspects of oral function, including mastication, dentition status, and chewing ability, whereas "oral frailty and intrinsic capacity" addresses the broader relationship between oral conditions and systemic ageing processes, including physical frailty, cognitive decline, and reductions in intrinsic capacity. These synthesized findings were ultimately integrated to develop a conceptual model that links oral health to the overarching principles of AFHS.

Results

The initial systematic search of PubMed retrieved 708 records. After applying automated eligibility filters for publication date (2016-2026) and population age (≥ 65 years), 247 records were retained for screening. Following title and abstract screening for conceptual relevance to AFOHC, a final total of 52 studies were included in the review. For studies with uncertain or ambiguous relevance, full-text evaluation was conducted by the authors to ensure appropriate inclusion. Among the 52 included studies, 28 were identified as core studies for the thematic synthesis[18-45], while the remaining studies were classified as supportive studies[46-69]. The detailed selection process is illustrated in the PRISMA flow diagram (Fig. 1).

The included studies (n = 52) exhibited significant methodological heterogeneity, comprising cross-sectional studies, longitudinal cohorts, qualitative research, systematic reviews, and conceptual policy papers. Geographically, the evidence base spanned Europe, North America, and Asia, reflecting a burgeoning global interest in the intersection of aging and dentistry.

From a methodological standpoint, the majority of the literature was observational. A notable paucity of research was observed regarding structured, system-level interventions or the implementation of integrated care models within dental settings.

The thematic analysis identified five dominant domains that characterize the current landscape of AFOHC (Fig. 2). A subset of the literature positioned oral health within the broader paradigm of healthy aging. These studies framed oral health not as an isolated clinical outcome but as a determinant of functional ability and quality of life (QoL)[18,27,42]. However, a significant conceptual gap was identified, as no studies proposed a comprehensive framework integrating oral health into AFHS[23,38,39].

A subset of the literature positioned oral health within the broader paradigm of healthy aging. These studies framed oral health not as an isolated clinical outcome but as a determinant of functional ability and quality of life (QoL)[18,27,42]. However, a significant conceptual gap was identified, as no studies proposed a comprehensive framework integrating oral health into AFHS[23,38,39].

A substantial body of evidence focused on clinical-functional correlates such as masticatory efficiency, dentition status, and chewing ability. Masticatory dysfunction was associated with decreased psychological and social well-being[33,44], while tooth loss was identified as a significant risk factor for frailty, disability, and mortality[30,35,45]. In addition, oral function was found to play a critical role in maintaining nutritional homeostasis and overall health status[27,33].

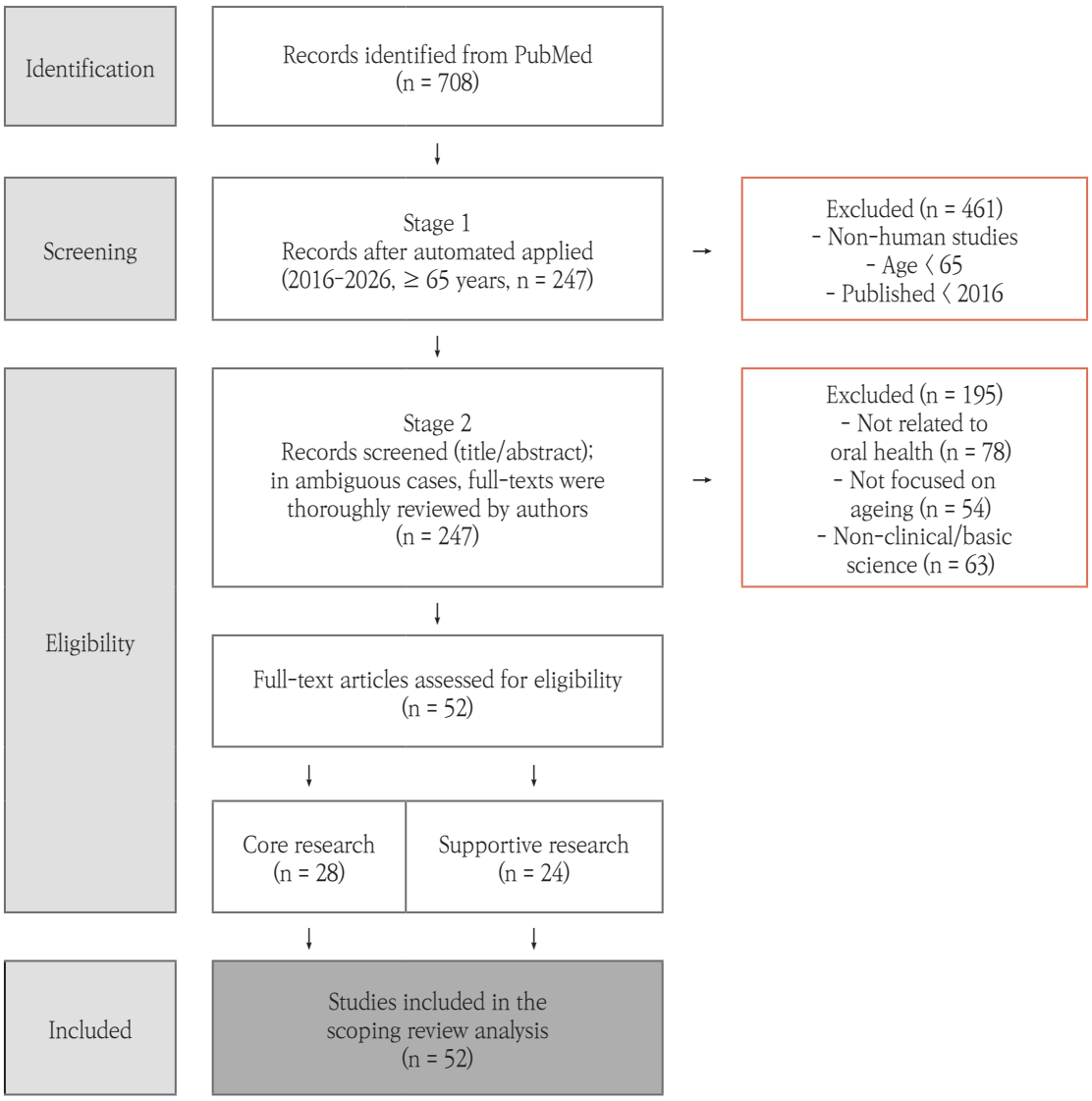

Fig. 1. Selection process of articles by PRISMA guidelines.

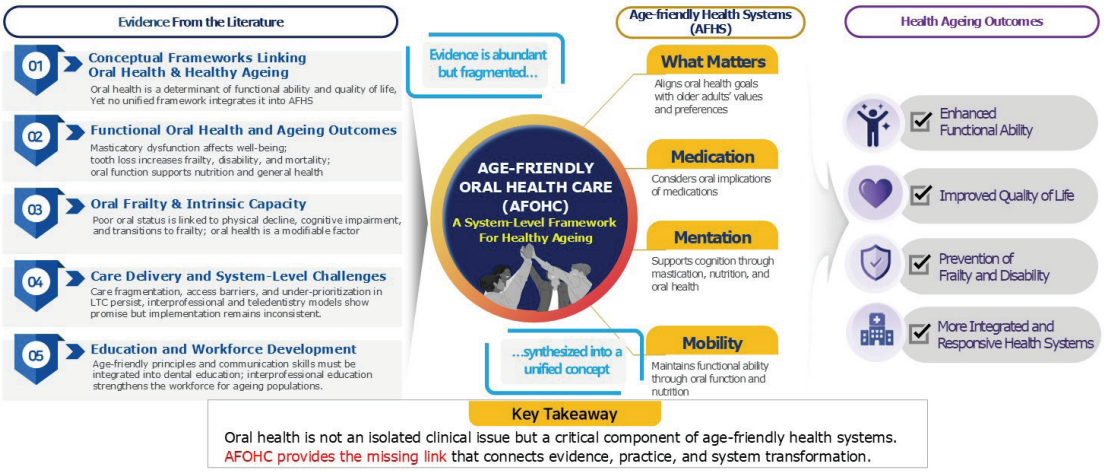

Fig. 2. Thematic Synthesis based on the selection of articles. Five thematic domains identified in the literature highlight both the strength and fragmentation of current evidence. AFOHC is proposed as a unified framework that integrates oral health into the AFHS 4Ms—What Matters, Medication, Mentation, and Mobility—to achieve healthy ageing outcomes.

The literature increasingly links oral health to the constructs of intrinsic capacity and frailty. Poor oral status, often conceptualized as oral frailty, was associated with declines in physical function and increased vulnerability[30,31,35]. Furthermore, studies suggested a bidirectional relationship between masticatory function and cognitive decline[25,27]. Oral health was also identified as a modifiable factor influencing transitions from pre-frailty to frailty[30,35].

The analysis revealed persistent systemic barriers in current dental delivery models. Care fragmentation between dental and general healthcare systems remains a major issue[20,36], while access barriers related to mobility, cognitive impairment, and socioeconomic dependency were consistently reported[41,57]. Oral care is frequently underprioritized in long-term care and community settings[24,31]. Although interprofessional and alternative delivery models such as teledentistry have been proposed, their implementation remains inconsistent[40,41].

The need for an age-friendly dental workforce emerged as a recurring theme. Studies emphasized the importance of integrating age-friendly principles into dental education[21,22], improving communication competencies for cognitively impaired patients[21], and strengthening interprofessional education models to support oral health in aging populations[40].

The synthesis of these domains highlights a critical disconnect. While substantial evidence links oral health to functional aging and frailty, this knowledge remains fragmented across disciplines[18,27,30,35]. Importantly, no study has established a unified framework integrating oral health into AFHS[23,38,39]. This gap suggests that dentistry has yet to fully align with the broader transformation toward age-friendly care, underscoring the need for a system-level conceptual model aligned with the 4Ms framework.

Discussion

This scoping review reveals a paradoxical landscape in geriatric oral health: while the evidence linking oral health to functional aging, frailty, and QoL is robust, its application remains fragmented and isolated. Current research continues to operate within disciplinary silos—geriatric dentistry, epidemiology, and health services—failing to translate clinical findings into a unified, system-level framework. Historically, dentistry has maintained a "procedure-oriented" specialty status, largely disconnected from the broader AFHS movement. This disconnect or evidence system gap suggests that the primary challenge in aging societies is not a lack of clinical evidence, but a lack of systemic integration that aligns oral care with the 4Ms of geriatric care.

The necessity for an AFOHC framework is particularly acute in South Korea, a nation navigating a "time-compressed" transition to a super-aged society. Our analysis highlights three critical structural barriers that characterize the "Korean Paradox". One major challenge is the persistent fragmentation between dental care and the broader systems supporting healthy ageing, including medicine, long-term care, community welfare, nutrition, and functional support services. As a result, oral health is often insufficiently incorporated into multidisciplinary care and public ageing policies, despite its close relationship with frailty, cognition, nutrition, and QoL in older adults[70]. This disconnect may leave frail older adults in a "dental vacuum," where oral health needs are overlooked within comprehensive ageing support systems. The national health insurance structure is heavily weighted toward discrete restorative or surgical interventions. This model provides limited support for the preventive and functional components of AFOHC, such as functional maintenance, caregiver education, and interdisciplinary care coordination, making the adoption of age-friendly models economically unsustainable for practitioners. While clinical expertise is world-class, the dental cur-

riculum has yet to fully embed age-friendly principles. In particular, education related to frailty assessment, communication with cognitively impaired patients, and interdisciplinary geriatric care remains limited, leaving the workforce ill-equipped to lead the shifting demographic reality. In this sense, the Korean paradox reflects not only demographic pressure, but also a structural mismatch between a rapidly ageing society and an oral health delivery system that has yet to be fully integrated into comprehensive healthy ageing and welfare strategies[71].

Given these barriers, the explicit adoption and preemption of the term "Age-Friendly Oral Health Care" is a strategic necessity rather than a mere semantic exercise. In Korea, health policies are often driven by administrative or financial agendas rather than clinical philosophy. By preemptively defining AFOHC through a rigorous academic framework, the dental community can establish a "gold standard," preventing the concept from being diluted into a superficial administrative label or a mere cost-cutting tool. A clearly defined concept serves as a conceptual anchor for aligning research, education, and policy. It provides the dental profession with the intellectual leadership required to ensure that future systemic reforms remain grounded in functional outcomes and patient-centered goals rather than sector-specific interests[72].

While this study provides a comprehensive conceptual framework for AFOHC, the findings should be interpreted within the context of the study design. The literature search was conducted exclusively in PubMed, which may have limited the comprehensiveness of the evidence base by excluding relevant studies indexed in other databases. In addition, the review emphasized conceptual and thematic synthesis rather than quantitative meta-analysis, thereby focusing on framework development rather than statistical evaluation of pooled outcomes. Future research should involve multi-database validation and empirical testing of the proposed AFOHC model in diverse clinical settings.

This scoping review identified five major thematic domains linking oral health and healthy ageing: 1) conceptual frameworks and healthy ageing, 2) functional oral health, 3) oral frailty and intrinsic capacity, 4) care delivery and system integration, and 5) education and workforce development. The findings demonstrate that while substantial evidence supports the association between oral health and ageing-related outcomes, the current evidence remains fragmented and lacks an integrated system-level framework. Based on this synthesis, this study proposes the concept of AFOHC as a person-centered and system-oriented framework that integrates oral health into the broader principles of AFHS. In particular, this study contributes to the field by conceptually distinguishing functional oral health from oral frailty and intrinsic capacity, and by mapping oral health domains onto the 4Ms framework of age-friendly care. Through this approach, AFOHC is positioned not simply as a clinical dental model, but as an essential component of comprehensive healthy ageing and welfare systems for older adults.

Conflicts of Interest: None

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ORIGINAL ARTICLE

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Tas2r108 mediates ligand-specific bitter sensitivity and modulates longevity and metabolic health in mice

Su Young Ki[1,2], In Sun Choi[3], Kyung-Nyun Kim[3,*]

[1]Department of Pharmacology, Korea University College of Medicine, Seoul, Korea
[2]BK21 Graduate Program, Department of Biomedical Sciences, Korea University College of Medicine, Seoul, Korea
[3]Department of Physiology and Neuroscience, College of Dentistry, Kangwon National University, Gangneung, Korea

ABSTRACT

Purpose: This study aims to elucidate the physiological functions of the type 2 taste receptor 108 *(Tas2r108)*, highly expressed in the tongue and exocrine tissues, focusing on its role in bitter taste perception, metabolic homeostasis, and longevity.

Materials and Methods: To identify specific ligands, calcium imaging was performed using CHO-K1 cells transfected with *Tas2r108* and $G_{\alpha 16gust44}$. For in vivo functional analysis, a *Tas2r108* knock-out (*Tas2r108*$^{-/-}$) mouse model was generated using CRISPR/Cas9. Sensory sensitivity was evaluated through two-bottle preference tests, and long-term physiological monitoring assessed body weight, blood pressure, glucose levels, and plasma leptin concentrations.

Results: *In vitro* assays identified cycloheximide as a primary and potent ligand for *Tas2r108* compared to denatonium. In behavioral tests, *Tas2r108*$^{-/-}$ mice showed a significant reduction in bitter sensitivity to cycloheximide, demonstrating this receptor's essential role in detecting specific bitter ligands. Long-term monitoring revealed that *Tas2r108* deficiency significantly extends the average lifespan of mice. While no differences were observed in blood pressure, glucose, or total food intake, *Tas2r108*$^{-/-}$ mice exhibited greater weight gain during adulthood. Notably, plasma leptin levels were higher in the *Tas2r108*$^{-/-}$ group, correlating with this period of significant weight gain.

Conclusion: These findings demonstrate that *Tas2r108* plays a dual role in mediating ligand-specific bitter taste detection and regulating metabolic health and longevity. The results suggest that *Tas2r108* may modulate systemic homeostasis through the leptin signaling pathway, identifying it as a potential target for research into aging and metabolic regulation. ***(J Korean Dent Assoc 2026; 64(7): 245-253)***

Key words : Taste; Cycloheximide; Leptin

Introduction

Taste perception is a critical biological process that guides nutrient intake and reflects the physiological status of an organism. Proper energy and nutrient intake are essential for survival and metabolism. Among the five basic tastes, bitter taste, mediated by type 2 taste receptors (T2Rs), serves as a vital defense mechanism to avoid toxic and harmful substances[1-4]. While T2Rs were initially studied for their role in the tongue, molecular studies have revealed that these receptors are also expressed in various extra-oral tissues, suggesting they play broader physiological roles beyond simple taste detection[5-9].

In the bitter signaling pathway, T2Rs activate alpha-gustducin, leading to a cascade involving PLCβ2 and

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*Corresponding author: Prof. Kyung-Nyun Kim
Department of Physiology and Neuroscience, College of Dentistry, Kangwon National University, Jukheon-gil 7, Gangneung, Gangwon-do 25457, Korea
Tel: +82-33-640-2450, E-mail: knkim@gwnu.ac.kr

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TRPM5[10]. This results in Ca^{2+} release and Na+ influx, which depolarizes the cell and triggers ATP secretion via pannexin and CALHM1/3 to transmit signals to the nervous system[11,12]. Despite having 35 T2Rs in mice, the specific functions of individual receptors in systemic homeostasis remain largely unclarified. Among these, *Tas2r108* is particularly noteworthy due to its exceptionally high expression levels. Previous studies have shown that *Tas2r108* is expressed 2-6 times higher than GAPDH in taste papillae[13] and over 10,000 times higher in exocrine glands, such as the submandibular and lacrimal glands, compared to other T2Rs[8,14]. This unique expression pattern in exocrine tissues suggests that *Tas2r108* may function as a systemic sensor that influences metabolic health and survival.

Furthermore, metabolic homeostasis is closely linked to hormonal regulation. Leptin, a hormone proportional to body fat, acts on the hypothalamus to suppress appetite and increase energy expenditure[15]. Given the high expression of *Tas2r108* in metabolic-related exocrine organs like the pancreas and submandibular gland, it is hypothesized that this receptor may interact with systemic metabolic pathways, potentially affecting lifespan and chronic disease progression.

Therefore, the aims of this study were twofold: first, to identify the specific ligands of *Tas2r108* through intracellular Ca^{2+} activity measurements; and second, to determine its exact physiological role in vivo. Using *Tas2r108*$^{-/-}$ mice generated via CRISPR/Cas9 technology[16,17], we performed two-bottle preference tests to evaluate taste sensitivity and tracked long-term physiological indicators, including lifespan, body weight (BW), blood pressure, glucose levels, and plasma leptin. This comprehensive approach aims to elucidate the essential role of *Tas2r108* in both bitter taste detection and the maintenance of metabolic homeostasis.

Materials and methods

In vitro Ca^{2+} Imaging

CHO-K1 cells (KCLB No. 10061) were cultured in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin at 37 ℃ in 5% CO_2. For *Tas2r108* expression, a chimeric construct was produced by inserting somatostatin receptor 3 and KOZAK sequences at the 5-prime end of the *Tas2r108* gene to enhance membrane localization. The gene fragment was cloned into the pcDNA3.1 expression vector using EcoRI and XhoI

Table 1. Primer sequences and structural components for *Tas2r108* cloning

Component	Sequence (5`→3`)
KOZAK	GCT AGC* GCC ACC
SSTR3	ATG GCC GCT GTT ACC TAT CCT TCA TCC GTG CCT ACG ACC TTG GAC CCT GGG AAT GCA TCC TCA GCC TGG CCC CTG GAC ACG TCC CTG GGG AAT GCA TCT GCT GGC ACT AGC CTG GCA GGA CTG GCT GTC AGT GGC
Tas2r108 Forward primer	GAA TTC† ATG CTC TGG GAA TGT ATG TAT TTG
Tas2r108 reverse primer	CTC GAG‡ CTA CTT GTA GAA ACA GAA AAT CTT CTT TGC

*: Nhe I (vector site), †: Eco R I, ‡: Xho I

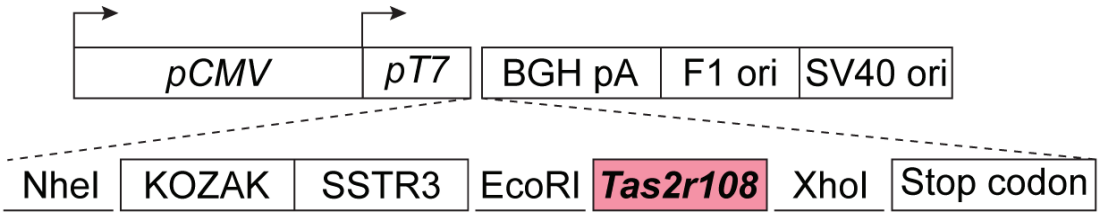

Fig. 1. Molecular cloning and heterologous expression of *Tas2r108*. Schematic shows the *Tas2r108*-inserted pcDNA3.1 expression vector. The *Tas2r108* gene (896 bp) is cloned into the mammalian expression vector pcDNA3.1 (5.5 kb).

restriction enzymes (Fig. 1). The structural components and specific primer sequences used for this cloning process, including restriction sites for *Nhe*I, *EcoR*I, and *Xho*I, are summarized in Table 1. Cells were co-transfected with *Tas2r108* and Gα16gust44 (provided by Yonsei University) using X-treme GENE HP reagent (Roche, Switzerland) at a 1:2 ratio in Opti-MEM. Expression was confirmed by RT-PCR prior to imaging. Cells seeded on cover glasses were loaded with 2mM fura2-AM and pluronic F-127 (Molecular Probes, Inc., Eugene, USA) in Ca^{2+} measurement buffer (pH 7.4) for 30 minutes at room temperature. After washing, cells were stabilized in the dark for 30 minutes. Fluorescence was measured using a CCD camera-based imaging system (Roper Scientific, USA) and MetaFluor 6.1 software. Intracellular Ca^{2+} changes (F340/F380) were recorded during perfusion of CHX (5, 50, 500 uM) and DEN (50, 150, 500 uM) at 2 ml/min. Cell viability was confirmed by 1 mM ATP treatment at the end of each session. All reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) except specifically marked.

Animals and generation of *Tas2r108* knock-out mice

All experimental procedures were approved by the Kangwon National University Animal Care and Use Committee and the Living Modified Organism Commission (GWNU-2020-24-1). C57BL/6 mice were purchased from Orient Bio Inc. (Seongnam, Korea). Mice were maintained in standard plastic cages at 23 ℃ with a 12:12 hour light/dark cycle at the Kangwon National University Animal Care Facility.

Tas2r108$^{-/-}$ mice were generated using the CRISPR/Cas9 system (Macrogen Inc., Seoul, Korea). Single guide RNAs (sgRNAs) targeting exons 1 and 2 were validated in vitro using Cas9 protein (Fig. 2A). Validated sgRNA-Cas9 complexes were microinjected into fertilized embryos obtained from pregnant mare serum gonadotropin (Daesung Microbiological Labs, Inc., Uiwang, Korea) and human chorionic gonadotropin (Daesung Microbiological Labs, Inc.)-treated female mice. F0 mosaic mice were crossed with *Tas2r108*$^{+/+}$ mice to produce F1 heterozygotes (Fig. 2B). F2 homozygotes were obtained through intercrossing F1 mice (Fig. 2B. Genotypes were confirmed by PCR of tail DNA and sequencing. The specific primers used for genotyping were as follows: forward primer (5`- TGC TCT TGG AGG AAC AGA TTC-3`) and reverse primer (5`- GTG GCC TTC ATT CAT GGA CT-3`). The PCR products were analyzed to distinguish between wild-type (1,448 bp) and knock-out (602 bp) alleles based on their respective molecular weights (Fig. 2C).

Behavioral and physiological assessments

Male *Tas2r108*$^{+/+}$ and *Tas2r108*$^{-/-}$ mice were individually housed and tested for 48 hours. Mice were provided with two 10 ml pipettes containing water and a bitter solution (CHX or DEN). Pipette positions were swapped every 24 hours to avoid side preference. Fluid intake was measured every 24 hours. The preference score was calculated as: (Bitter solution intake / Total intake) x 100.

To evaluate the long-term effects of *Tas2r108* deficiency, mice were monitored until natural death. BW, blood pressure, and blood glucose were measured every two weeks. Blood pressure was recorded from the tail artery using a non-invasive system, CODA-HT2 (Kent Scientific, Torrington, CT, USA), and glucose was measured from peripheral blood using a glucometer, Accu-Chek (Roche Diagnostics, Rotkreuz, Switzerland).

Plasma leptin levels were measured at 8, 12, 16, 20, and 24 weeks of age. Blood was collected from the jugular vein into heparin-treated tubes and centrifuged at 12,000 rpm for 25 minutes. Separated plasma was stored at -80 ℃. Leptin concentration was determined using a mouse/rat leptin ELISA kit (Cat. No. M1305, Morinaga Institute of Biological Science, Inc., Yokohama, Japan) following the manufacturer's protocol, with absorbance measured at 450 nm.

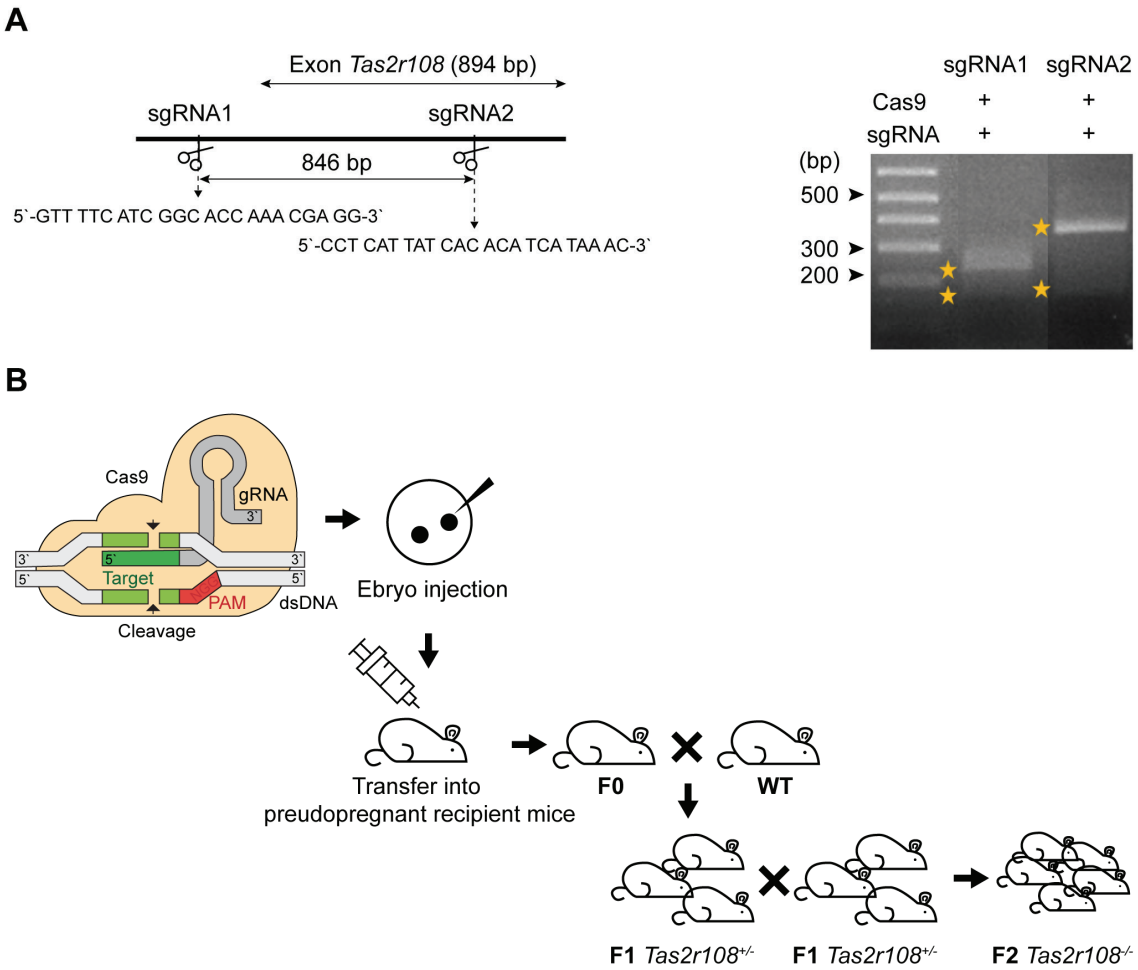

Fig. 2. Generation of *Tas2r108* knock-out mice using the CRISPR/Cas9 system. (A) Schematic represents the target site of *Tas2r108* sgRNA and its evaluation of cleavage efficiency. Electrophoresis validates the effectiveness of the sgRNA targeting the exon of the *Tas2r108* gene. (B) Schematic illustration shows the generation of *Tas2r108* knock-out (*Tas2r108*$^{-/-}$) mice. (C) PCR-based genotyping identifies F2 generation mice. The representative electrophoresis image displays PCR products from F2 mice. *Tas2r108* mosaic (+/−) F0 and wild-type (+/+) mice were crossed to obtain F1. *Tas2r108*$^{+/-}$ F1 hybrids are intercrossed to generate *Tas2r108*$^{-/-}$, *Tas2r108*$^{+/-}$, and *Tas2r108*$^{+/+}$ F2 mice.

Statistical analysis

Data were analyzed using the unpaired t test for comparisons between two groups. For concentration-dependent responses, one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was performed to determine statistical significance. All results are expressed as mean plus or minus SEM, and $p < 0.05$ was considered statistically significant.

Results

Identification of *Tas2r108* ligands via cell transfection and Ca^{2+} imaging

To verify the molecular function of the receptor, we performed in vitro signaling analysis using CHO-K1 cells. RT-PCR confirmed the expression of *Tas2r108* (896 bp) and Gα16gust44 (1,125 bp) in the transfected cells (Fig. 3A). Intracellular Ca^{2+} imaging revealed that *Tas2r108*-transfected cells exhibited robust Ca^{2+} increases in response to 5 uM and 50 uM CHX (Fig. 3B). In contrast, among the tested concentrations of DEN, only 50 uM

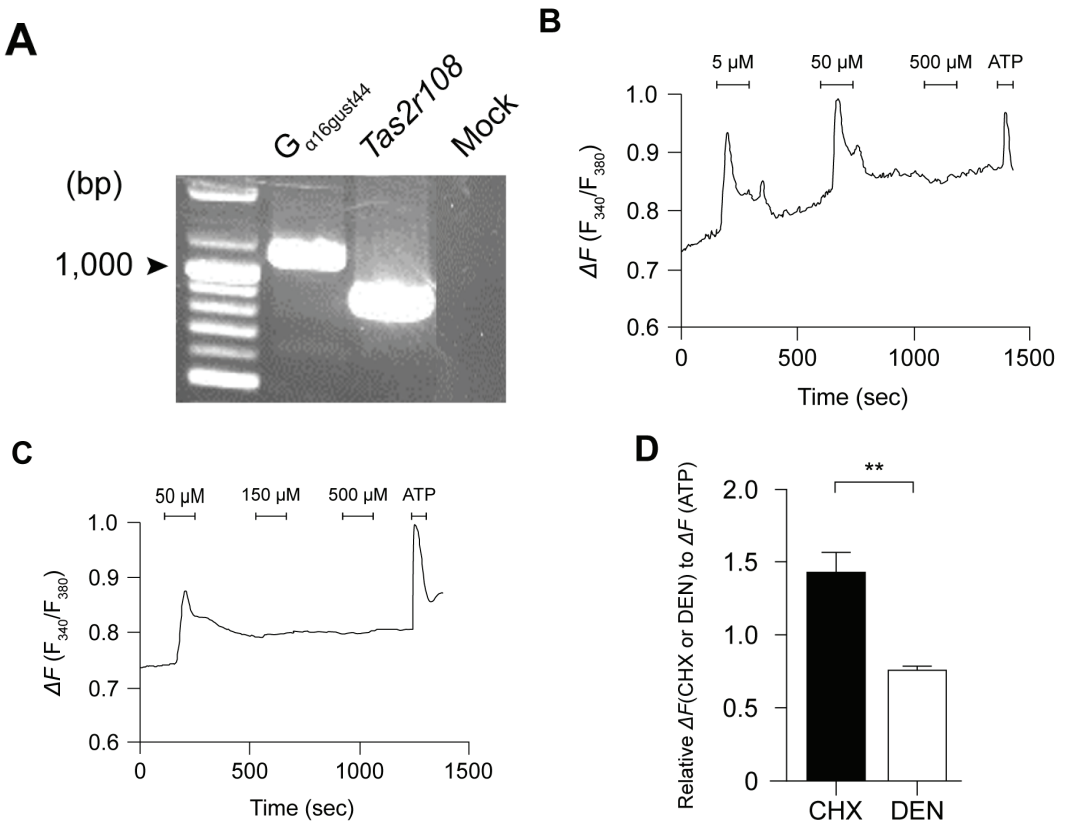

Fig. 3. Functional characterization of *Tas2r108* in a heterologous cell expression system. (A) RT-PCR analysis shows the expression of *Tas2r108* and $G_{\alpha 16gust44}$ expression in CHO-K1 cells. Lane 1, DNA size marker; Lane 2, *Tas2r108* (894 bp); Lane 3, Gα16gust44 (1,125 bp); Lane 4, non-transfected CHO-K1 cells as a negative control (Mock). (B) Representative traces show intracellular Ca^{2+} activity in response to CHX. Transfected CHO-K1 cells are loaded with fura-2 AM and stimulated with varying concentrations of CHX (5, 50, and 500 μM). (C) Representative traces show intracellular Ca^{2+} activity in response to DEN. Experimental conditions were identical to (B), with cells stimulated with 50, 150, and 500 μM DEN. (D) Quantitative analysis represents relative intracellular Ca^{2+} responses. The fluorescence changes are normalized to the response evoked by 1 mM ATP. Data are presented as mean ± SEM (**$p < 0.001$, unpaired *t*-test, n=3).

elicited a significant response (Fig. 3C). When the Ca^{2+} activity for 50 uM CHX and DEN was compared relative to the ATP-induced response, the activity for 50 uM CHX was significantly higher than that for 50 uM DEN ($p < 0.001$) (Fig. 3D). These results identify CHX as a primary and potent ligand for *Tas2r108*.

Generation and genotyping of *Tas2r108* knock-out mice

To investigate the physiological role of *Tas2r108*, we generated *Tas2r108*$^{-/-}$ mice using the CRISPR/Cas9 system. Following the microinjection of the Cas9 protein-sgRNA complex into fertilized embryos, 40 F0 generation mice were obtained. Among them, five mice (two males and three females) were identified as *Tas2r108* mosaic founders. These founders were crossed with *Tas2r108*$^{+/+}$ mice to produce F1 heterozygotes, and subsequent intercrossing of F1 mice yielded F2 offspring. The F2 generation consisted of 4 *Tas2r108*$^{+/+}$, 12 *Tas2r108*$^{+/-}$, and 6 *Tas2r108*$^{-/-}$ mice (Table 2). This distribution followed the expected Mendelian inheritance ratio, confirming the successful establishment of the *Tas2r108*$^{-/-}$ line.

Table 2. Genotype distribution of F2 generation mice generated by CRISPR/Cas9 system

F2	*Tas2r108*$^{+/+}$	*Tas2r108*$^{+/-}$	*Tas2r108*$^{-/-}$
Male	2	3	6
Female	2	9	-

Reduced Bitter Sensitivity in *Tas2r108* knock-out Mice

The effect of *Tas2r108* deficiency on bitter taste perception was evaluated using two-bottle preference tests. Notably, a significant reduction in bitter taste sensitivity was observed in *Tas2r108*$^{-/-}$ mice at a lower concentration of CHX (5 μM), where they exhibited significantly higher preference scores compared to *Tas2r108*$^{+/+}$ mice ($p < 0.001$; Fig. 4A). While both groups exhibited a concentration-dependent avoidance of CHX, the *Tas2r108*$^{-/-}$ group showed significantly higher preference scores for 50 uM CHX compared to the *Tas2r108*$^{+/+}$ group(Fig. 4A). In contrast, no significant differences were observed between 50 μM CHX and DEN within the *Tas2r108*$^{-/-}$ group (Fig. 4B), suggesting that the loss of *Tas2r108* specifically impairs the detection threshold for CHX. These findings demonstrate that *Tas2r108* is essential for maintaining high sensitivity to specific bitter ligands like CHX.

Long-term monitoring of BW and lifespan extension

Long-term physiological monitoring until natural death revealed that *Tas2r108* deficiency significantly extends the lifespan of mice. The average lifespan of *Tas2r108*$^{+/+}$ mice was 472 ± 20 days (67.4 weeks), whereas *Tas2r108*$^{-/-}$ mice survived for an average of approximately 81.0 weeks(Fig. 5A and B). This represents a statistically significant lifespan extension of about 14 weeks

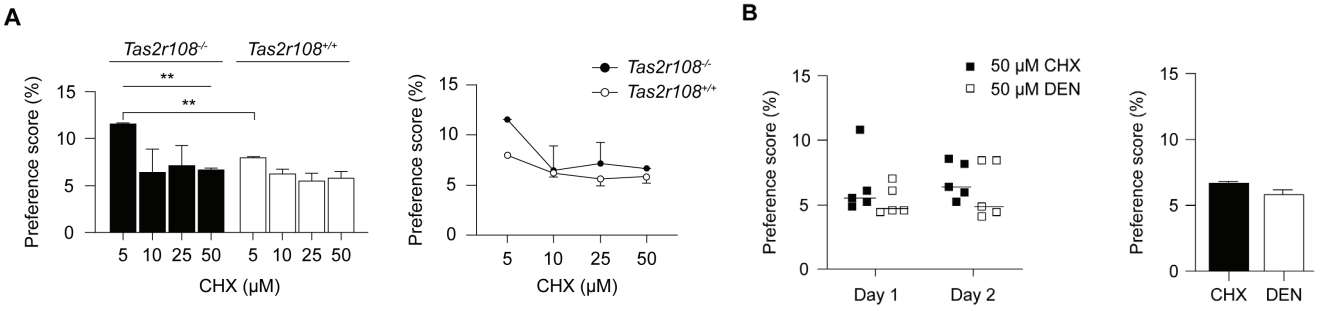

Fig. 4. Two-bottle taste preference assays for CHX and DEN in *Tas2r108*$^{-/-}$ mice. (A) Average preference scores represent 5, 10, 25, and 50 μM CHX in *Tas2r108*$^{-/-}$ and *Tas2r108*$^{+/+}$ mice. Data are presented as mean ± SEM (**$p < 0.001$, unpaired t-test; *$p < 0.01$, ANOVA). (B) Daily and average preference scores show behavior toward 50 μM CHX and DEN in *Tas2r108*$^{-/-}$ mice. Bars represent median (left) and mean ± SEM (right).

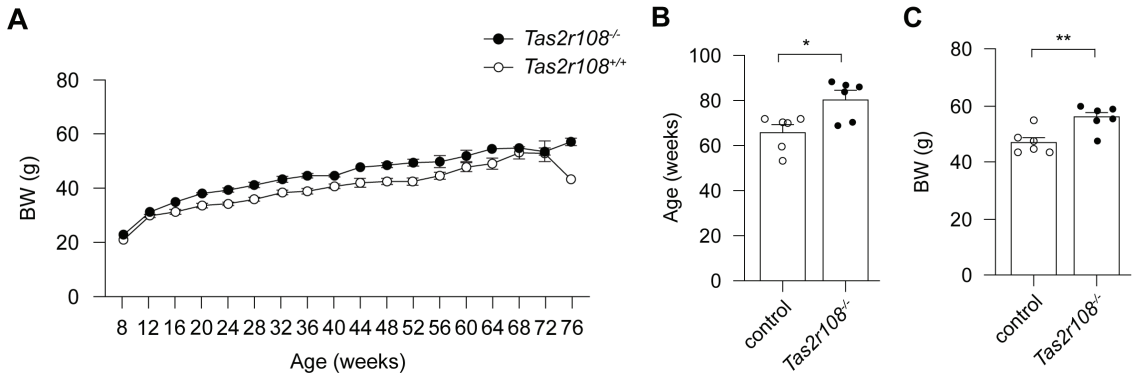

Fig. 5. Analysis of body weight (BW) and and lifespan in *Tas2r108*$^{-/-}$ mice. A. Longitudinal changes represent BW from 8 to 76 weeks of age in *Tas2r108*$^{-/-}$ and control mice. Data are presented as mean ± SEM (unpaired t-test). B. Comparison shows BW between *Tas2r108*$^{-/-}$ and control mice at 60 weeks of age. Data are presented as mean ± SEM (*$p < 0.01$, unpaired *t*-test). C. Survival analysis represents the recording of longevity in *Tas2r108*$^{-/-}$ and control mice. Data are presented as mean ± SEM (**$p < 0.001$, unpaired *t*-test).

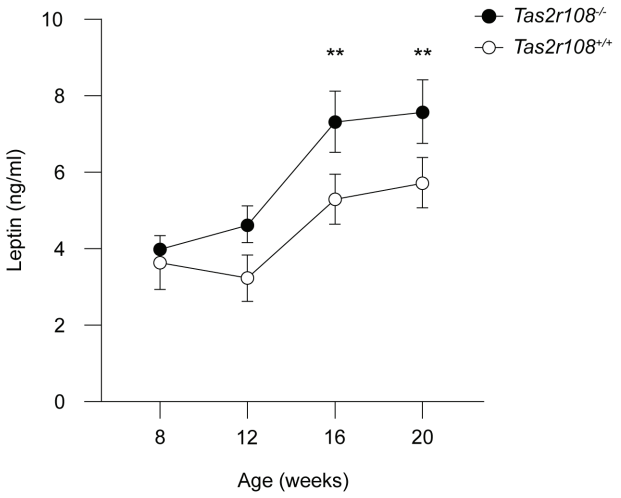

Fig. 6. Longitudinal analysis of plasma leptin levels in *Tas2r108*$^{-/-}$ and wild-type mice from 8 to 20 weeks of age. Changes in plasma leptin concentration are monitored in *Tas2r108*$^{-/-}$ and wild-type mice. Data are presented as mean ± SEM (**$p < 0.001$, unpaired t-test, n=3).

compared to the *Tas2r108*$^{+/+}$ group (Fig. 5B). Regarding BW, *Tas2r108*$^{-/-}$ mice exhibited greater weight gain between 16 and 60 weeks of age (Figs. 5A and C). Notably, both groups showed a characteristic rapid weight loss during the terminal phase of life. No adverse effects on embryonic development or reproductive capacity were observed in the *Tas2r108*$^{-/-}$ mice (data not shown).

Changes in plasma leptin levels during the lifespan

To assess the metabolic changes associated with the observed BW differences, we measured plasma leptin levels at 8, 12, 16, 20, and 24 weeks. Plasma leptin levels in *Tas2r108*$^{-/-}$ mice were significantly higher than those in *Tas2r108*$^{+/+}$ mice at the 12, 16, and 20-week marks (Fig. 6). This increase in leptin levels correlated with the period of significant weight gain observed in the *Tas2r108*$^{-/-}$ group. In contrast, no significant differences were found in blood pressure, blood glucose, or total food intake between the two groups (data not shown), suggesting that *Tas2r108* may specifically modulate systemic metabolic homeostasis and longevity through the leptin signaling pathway.

Discussion

In conclusion, our study provides a comprehensive functional characterization of *Tas2r108*, identifying it as a high-affinity receptor for CHX and DEN that serves as a critical systemic metabolic regulator. While Tas2r105 was previously identified as a CHX receptor[18], our in vitro data demonstrate that *Tas2r108* exhibits a significantly lower activation threshold, responding to concentrations as low as 5 μM. The significantly higher potency for CHX compared to DEN ($p < 0.001$) and the observed response to 50 μM DEN—a concentration far lower than the mil-

limolar ranges reported in HEK-293T systems[19,20]—suggest that *Tas2r108* functions as a specialized, high-sensitivity sensor. Interestingly, the lack of response at 500 μM CHX suggests a "bell-shaped" dose-response curve or a tight homeostatic signaling window, indicating that *Tas2r108*-mediated signaling may be subject to strict desensitization or regulatory feedback to prevent over-activation[21].

The in vivo physiological relevance of this high sensitivity was confirmed by the *Tas2r108*$^{-/-}$ mouse model. The most profound behavioral divergence between wild-type and KO mice occurred at the lowest tested concentration (5 μM CHX), where *Tas2r108*$^{-/-}$ mice failed to show typical avoidance behavior ($p < 0.001$). This identifies *Tas2r108* as the primary mediator for low-intensity bitter signals, whereas the maintenance of avoidance at higher concentrations suggests that other T2Rs provide redundant protection against toxic bitterants at high doses. Given its overwhelming expression in exocrine glands and its evolutionary conservation[22], *Tas2r108* likely exerts a systemic regulatory influence, possibly acting as a metabolic gatekeeper that modulates the expression of other type 2 taste receptors within the chromosome 6 cluster[23].

The most striking discovery of this study is the uncoupling of adiposity and mortality in *Tas2r108*$^{-/-}$ mice. Despite a 10.4% increase in body weight starting after maturity (16 weeks), these mice lived approximately 14 weeks (20%) longer than their wild-type counterparts. This phenomenon strongly supports the 'Obesity Paradox', wherein moderate weight gain in later life serves as a protective energy reservoir against aging-related frailty[24,25].

Crucially, our temporal analysis revealed that plasma leptin levels began to rise at 12 weeks, preceding the significant divergence in body weight. This temporal sequence suggests that *Tas2r108* deficiency does not simply cause obesity; rather, it directly alters the metabolic set-point or leptin secretion pathways. The elevation of leptin without a corresponding reduction in food intake indicates a state of adaptive leptin resistance or a fundamental shift in how the hypothalamus integrates metabolic signals[14,25]. The fact that this healthy obesity occurred without changes in blood pressure or glucose levels suggests that *Tas2r108*$^{-/-}$ mice maintain metabolic health despite increased adiposity. Collectively, these findings identify *Tas2r108* as a novel target for aging research, demonstrating that its modulation can decouple the negative effects of weight gain from the benefits of extended longevity.

Conflicts of Interest: None

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CASE REPORT

대한치과의사협회지 2026; 64(7): 254-258
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Differential diagnosis of an oral amalgam tattoo mimicking oral mucosal melanoma: A case report and literature review

악성 흑색종으로 오인된 구강 내 아말감 문신 병변의 감별 진단: 증례보고 및 문헌고찰

Donghyeon Kim[1], Donggi Ahn[2,*], Hyounmin Kim[3,*]

[1]Department of Oral and Maxillofacial Surgery, Yonsei University College of Dentistry, Seoul, Korea
[2]Department of Oral Pathology, Yonsei University Dental Hospital, Seoul, Korea
[3]Department of Oral and Maxillofacial Surgery, Gangnam Severance Hospital, Yonsei University Health System, Seoul, Korea

ABSTRACT

Amalgam tattoo, a commonly encountered exogenous oral pigmentation, is benign but can occasionally pose diagnostic challenges due to its clinical resemblance to oral mucosal melanoma. This report presents a case of a 55-year-old female patient with a 10-mm pigmented lesion on the right mandibular gingiva. The lesion exhibited asymmetry, border irregularity, and color variegation, characteristic features of oral mucosal melanoma. Notably, the right mandible had no teeth restored with amalgam or other foreign materials, and radiography revealed no metal materials. Intraoperatively, the lesion not only abutted the bone surface but also showed pigmentation extending beyond the periosteum. However, histopathological analysis revealed dense black particles resistant to melanin bleaching, surrounded by CD68- and LCA-positive lymphohistiocytic cells, confirming the diagnosis of amalgam tattoo. In this report, we review the literature on amalgam tattoos presenting with features resembling oral mucosal melanoma, including the present case, and emphasize their distinguishing characteristics. ***(J Korean Dent Assoc 2026; 64(7): 254-258)***

Key words : Melanoma; Pigmentation; Dental Amalgam; Mouth Mucosa

서론

구강 점막 병소의 색은 감별 진단에서 중요한 임상적 단서가 된다. 정상 구강 점막은 일반적으로 혈관 구조와 상피의 투명도에 따라 연분홍색에서 산호색을 띠나, 상피의 증식이나 과각화는 기저부의 혈관을 가려 백색 병소로 나타나게 한다[1]. 점막이 갈색이나 청색, 흑색으로 변색되는 것은 전신 질환 관련 색소침착, 흡연 관련 색소침착, 아말감 문신(amalgam tattoo), 흑모설(black hairy tongue) 등을 의미한다[2].

그 중 아말감 문신은 구강 점막에서 발생하는 국소 외인성 색소침착 중 가장 흔한 형태이다. 대개 치과 처치 중 아말감 입자가 우발적으로 점막하 조직에 유입되어 발생하므로, 방사선 검사가 해당 병소를 감별 진단하는 데 유용할 수 있으나, 입자가 매우 작거나 광범위하게 퍼져 있는 경우에는 관찰되지 않는다. 방사선학적 증거가 없고, 주변 치아에 수복물 또한 관찰되지 않는 경우 악성 흑색종과의 감별이 반드시 필요하다[3].

본 증례보고에서는 임상적으로 구강 점막에 발생한 악성 흑색종과 유사했던 아말감 문신 사례를 소개하고자 한다. 이는 기존에 보고된 4개의 증례에 이은 추가적인 사례로, 임상적, 방

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*Corresponding author: Prof. Donggi Ahn
Department of Oral Pathology, Yonsei University Dental Hospital, Yonsei University Health System 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-3036, E-mail: 01051705071@yuhs.ac
Prof. Hyounmin Kim
Department of Oral and Maxillofacial surgery, Gangnam Severance Hospital 20, Eonju-ro 63-gil, Gangnam-gu, Seoul 06229, Korea
Tel: +82-2-2019-4560, E-mail: netizen93@yuhs.ac

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사선학적, 조직병리학적 특징을 기술하고 아말감 문신이 악성 흑색종과 유사하게 나타날 가능성을 다시금 강조한다. 또한 기존 보고된 4개 증례에 대한 문헌 고찰을 통해 악성 흑색종과 유사한 양상을 보이는 아말감 문신의 임상병리학적 특징을 논의하고자 한다.

증례

본 연구는 저자 소속 기관의 기관생명윤리위원회(institutional review board, IRB)의 승인을 받았다(승인번호: 3-2026-0154).

55세 여성 환자가 하악 우측 치은의 흑색 병소가 구강 악성 종양 가능성이 의심되어 생검을 위해 타치과의원에서 연세대학교 치과대학병원 구강악안면외과로 의뢰되었다. 환자의 진술에 따르면, 해당 병소의 크기 변화나 관련 불편감은 없었다고 한다. 과거력으로는 유두갑상선암(papillary thyroid carcinoma)으로 인한 수술 경험이 있었다.

병소는 하악 우측 제2소구치의 협측 치은 및 인접 점막에 위치하였으며, 직경은 약 10 mm였다. 병소는 비대칭적이고 불규칙한 경계를 보였으며, 다양한 색조가 섞인 불균질한 색소침착을 나타냈다(Fig. 1). 하악 우측 제1 대구치의 금 인레이 수복 외에는 특기할 사항이 없었으며, 병소 인접 부위에 아말감 수복 병력은 확인되지 않았다. 파노라마 방사선 사진 및 하악골 컴퓨터 단층 촬영 결과, 금속 입자를 시사하는 방사선 불투과성 소견은 관찰되지 않아 구강내 악성 흑색종(oral mucosal melanoma)이 임상적으로 의심되어 절제 생검을 시행하였다. 수술 중 하부 골 표면까지 침착되어 있는 검은색 색소가 관찰되었으며, 골막을 포함하여 병소를 전절제(en bloc excision)하였다(Fig. 2).

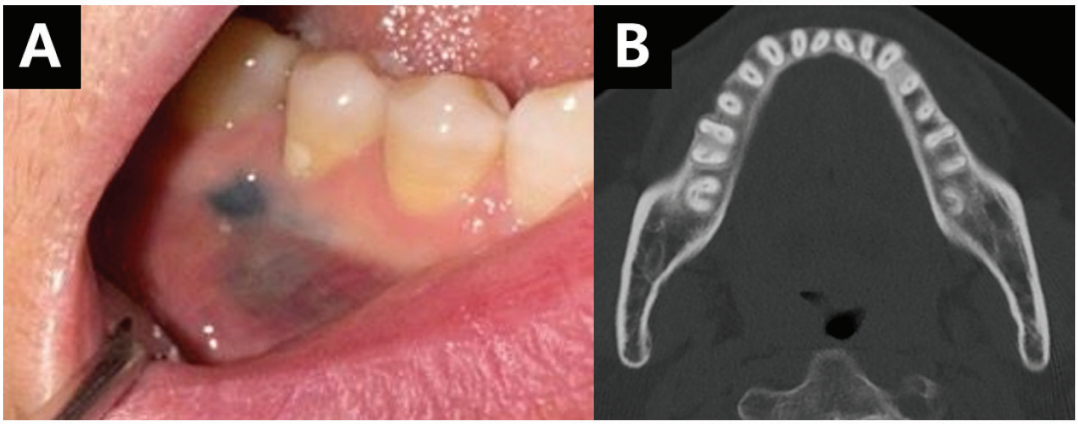

Fig. 1. Clinical and radiographical findings. A. The lesion is located on the buccal gingiva and mucosa adjacent to the right mandibular second premolar. It measured approximately 10 mm in diameter, exhibited heterogeneous pigmentation and irregular borders without symmetry. B. Computed tomographic image of the mandible reveals no evidence of metallic pigmentation. Additionally, no osteolytic lesion was identified in the buccal alveolar bone adjacent to the right mandibular second premolar.

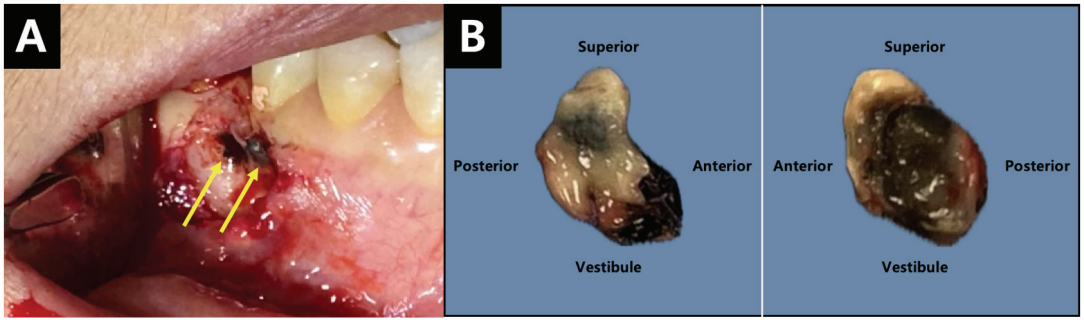

Fig. 2. After performing an excisional biopsy. A. Following excisional biopsy of the lesion, underlying bone staining is observed, while the periosteal junction remained. B. Gross view of the excised specimen. The left and right image shows the external mucosal and basal surface facing the underlying bone, respectively.

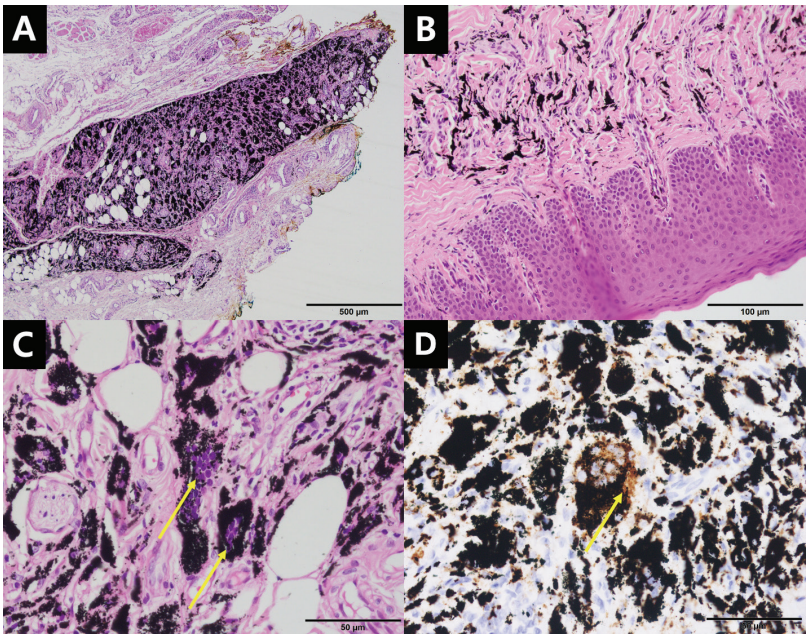

Fig. 3. Histopathologic and immunohistochemical features of the lesion. The lesion is sharply demarcated from adjacent mucosa and lacked melanocytic atypia. Dense, dark pigment deposits and intra-lesional macrophages are identified. The pigment is resistant to melanin bleaching, and CD68 positivity confirmed histiocytic infiltration. A. The lesion demonstrates a well-defined border sharply demarcated from adjacent normal mucosa, and the pigment remained resistant to melanin bleaching (H&E stain, x40). B. No atypical melanocytes are observed. A large, densely pigmented solid fragment is visible within the lesion, suggesting exogenous material (H&E stain, x200). C. Numerous macrophage-like cells are present in the pigmented region (yellow arrows) (H&E stain, x400, 2 ㎛ thin section). D. Strong cytoplasmic CD68 positivity is observed in histiocytes within the lesion (yellow arrow) (CD68 immunohistochemical staining using DAB chromogen, x400).

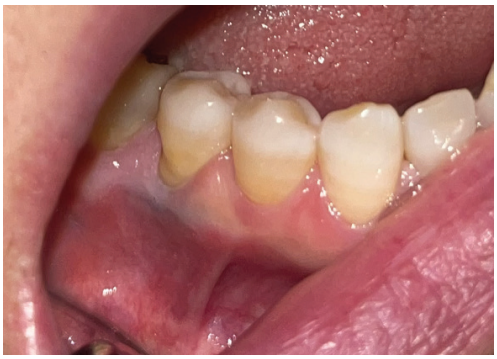

Fig. 4. Postoperative follow-up at 6 weeks. The surgical site demonstrates complete mucosal healing with residual pigmentation weakly.

절제된 조직의 조직병리학적 검사 결과, 주변 결합조직과 뚜렷하게 구별되는 흑색 병소가 관찰되었으며, 해당 색소는 멜라닌 탈색(melanin bleaching) 후에도 변화가 없어 비멜라닌성 기원임을 시사하였다(Fig. 3A). 점막하 조직 내에서 어두운 색의 고형 입자들이 관찰된 반면, 구강 점막이나 하부 결합조직에서 비정형 멜라닌세포(atypical melanocytes)는 발견되지 않았다(Fig. 3B). 2 ㎛ 두께의 절편을 고배율로 관찰한 결과, 색소 침착 부위 주변으로 다수의 림프조직구 유사 세포(lympho-histiocyte-like cells)가 둘러싸고 있는 것이 확인되었다(Fig. 3C). 면역조직화학검사 결과, S-100, HMB-45 및 Melan-A는 음성이었으며, leukocyte common antigen(LCA)와 CD68은 염증 세포에서 양성으로 나타나 조직구성 세포임을 시사하였다(Fig. 3D). 이러한 조직병리학적 및 면역조직화학적 소견은 아말감 문신에 합당하였으며, 이를 기반으로 최종 진단이 이루어졌다.

환자는 수술 6주 후 추적 관찰을 위해 내원하였으며, 기능적 또는 심미적 불편감을 호소하지 않았다. 임상 검사 결과 수술 부위의 점막은 완전히 치유되었으며 점막상 잔류 색소침착 및 재발 소견은 없었다. 다만, 하부 변색된 골 조직이 상부 점막을 통해 비쳐 보여 미세하게 변색된 부분만이 남아 있다(Fig. 4).

고찰

구강내 악성 흑색종은 모든 구강 악성 종양의 약 0.2-8%를 차지하며, 공격적인 성장과 높은 전이 가능성으로 인해 예후가 좋지 않다[5,6]. 임상적으로 구강내 악성 흑색종은 주로 경구개와 치조제에서 발생하며, 경계가 불규칙하고 짙은 갈색에서 청흑색을 띠는 무증상의 비특이적 색소침착 병소로 나타난다[4]. 조직병리학적으로 상피와 결합조직 내의 비정형 멜라닌세포 증

식 및 pagetoid spread가 특징적이며, 병소가 진행된 경우, 컴퓨터 단층 촬영(CT)이나 자기공명영상(MRI)을 통해 피질골 침윤, 연조직 확장 및 상악동 침범 등의 인접 골 파괴 양상이 확인된다[4,5]. 그러나 초기 병소의 경우, 임상 및 방사선학적 소견으로는 악성 흑색종과 양성 색소침착 병소를 감별하기 어렵다.

구강내 악성 흑색종과 임상적으로 유사해 보이는 질환으로는 구강 모반, 멜라닌세포성 가시세포종(melanoacanthoma), 생리적 색소침착, 흡연자 멜라닌 착색증 등이 있다. 이러한 감별 진단 대상 중, 본 증례와 같은 아말감 문신(amalgam tattoo) 또한 드물게 구강내 악성 흑색종과 유사한 양상을 보일 수 있다. 임상적으로 구강내 악성 흑색종을 아말감 문신이 모방한 증례는 현재까지 총 4증례만이 보고되었으며, 이는 이 현상의 희소성과 임상적 중요성을 강조한다[7-10].

기존 보고 사례들을 종합하기 위해 PubMed와 Google Scholar에서 영문 문헌 고찰을 시행하였다. 검색 Query로 ("amalgam tattoo" [Title]) AND (gingival OR diffuse OR extensive OR melanoma OR malignancy OR mimic)를 사용하였다. 총 35개의 증례 보고 중 전문 확인이 불가능하거나 임상 정보가 불충분한 경우를 제외하고 최종적으로 25개의 증례를 분석 대상으로 선정하였다. 이 중 임상 및 조직학적 도해를 모두 제공하는 증례 보고는 12개였으며, 그 중 악성을 시사하는 'ABCDE' 기준을 충족하는 증례는 4개였다[4](Table 1).

본 증례를 포함하여 총 5개 증례의 평균 연령은 59.2세(범위 49-73세)였으며, 발생 부위는 치은(3례), 혀(1례), 구강저(1례) 순이었다. 혀와 구강저에서 발생한 증례들은 아말감 수복물과 직접 접촉하지 않는 부위에서도 병소가 발생할 수 있음을 시사하였으며, 이는 노출이나 감작의 대안적인 경로가 존재함을 시사한다. 5개 증례 모두 비대칭성(asymmetry, 5례 중 5례), 경계 불규칙성(border irregularity, 5례 중 4례), 다양한 색조(color, 5례 중 5례), 6 mm 이상의 직경(diameter, 5례 중 4례) 등 악성 기준의 상당 부분을 충족하였다. 본 증례 또한, 확인할 수 없었던 변화 양상(evolution)을 제외한 다른 기준들을 모두 충족하였다. 또한 검토한 증례 중 2례는 본 증례와 마찬가지로 방사선 검사에서 금속 입자를 시사하는 특징적인 불투과성 소견이 관찰되지 않았다. 모든 증례에서 조직병리학적으로 망상섬유(reticulin fiber)의 착색 뿐만 아니라 어두운 고형 입자들(dark solid fragments)이 주로 확인되었다. 병리학적 감별 진단의 핵심은 비정형 멜라닌세포 증식이 없음을 확인하는 것이며, 이는 본 증례에서도 동일하게 관찰되었다. 이러한 소견은 면역조직화학(IHC) 검사를 통해 확증될 수 있다. 본 증례에서 보여주듯 비멜라닌성 병소는 HMB-45, Melan-A, S-100과 같은 멜라닌세포 표지자에 음성 반응을 보이며, 대신 아말감과 같은 이물질에 반응하는 조직구(histiocytes) 등의 염증 세포가 전형적으로 관찰된다.

이러한 증례들은 아말감 문신이 악성을 시사하는 임상적 소견을 보일 수 있으며, 조직생검 없이는 진단에 상당한 어려움이 있음을 시사한다. 기존 보고들과 대조적으로, 본 증례는 점막하부의 경조직(골) 표면에서도 검은색 색소침착이 관찰되었

Table 1. Reported cases of amalgam tattoo mimicking oral malignant melanoma

Author (year)	Age	Site	Clinical features	Radiographic findings	Histopathological findings
Amano et al.[7] (2011)	63	Floor of mouth	Dark pigmented lesion, suspicious for melanoma	No metallic radiopacity	H&E: fine granules/black fragments with chronic inflammation; Fontana-Masson and iron stain negative
Kamal et al.[10] (2019)	56	Palatal mucosa	Diffuse, dark pigmentation	No abnormalities on panoramic X-ray	H&E: brownish-black pigment along the collagenous fiber
Vera-Kellet and Del Barrio-Díaz.[8] (2016)	49	Ventral tongue	Asymmetrical gray-brown macule with central regression	Not reported	H&E: brown-black pigment deposits with foreign-body reaction; S-100 negative
Sasaki et al.[9] (2023)	73	Buccal gingiva	Grayish-blue gingival pigmentation	Not reported	H&E: black granules in the connective tissue; IHC: HMB-45 negative
Present case (2025)	55	Buccal gingiva	10 mm lesion with irregular border and heterogeneous pigmentation	No radiopaque foci on panoramic/CT	H&E: sharply demarcated pigment, bleaching-resistant; IHC: S-100/HMB-45/Melan-A negative, CD68 positive

CT: computed tomography

다는 점에서 매우 이례적이다. 조직학적으로 관찰된 검은색 고형 입자의 현저한 축적은 이들 병소가 구강내 악성 흑색종과 유사하게 강렬한 흑색 색소침착을 보이는 이유를 설명해 준다.

본 증례에서 확인된 치과적 과거력은 하악 우측 제1대구치의 금 인레이 수복 외에는 특기할 사항이 없었으며, 병소 인접 부위에 아말감 수복의 병력은 확인되지 않았다. 그럼에도 본 병변은 멜라닌 탈색에 저항성을 보이는 외인성 흑색 색소 침착, 비정형 멜라닌 세포의 부재, CD68 양성 조직구의 축적 등 아말감 문신에 합당한 조직병리학적 특징을 보였으며, 임상적으로는 구강내 악성 흑색종과 밀접하게 유사한 양상을 나타냈다. 따라서 본 증례는 정확한 물질 조성의 직접적 확인이라는 한계에도 불구하고, 임상병리학적 관점에서 아말감 문신 범주의 외인성 금속 색소침착 병변으로 해석될 수 있다.

본 증례는 임상적으로 악성 흑색종을 강력히 시사했던 드문 아말감 문신 사례이다. 수술 중 골 표면의 색소침착이 확인되었으나 최종 진단은 조직학적 검사를 통해 확정되었다. 이 사례는 아말감 문신이 임상 및 방사선학적으로 악성 색소 병소를 밀접하게 모방할 수 있음을 보여주며, 정확한 진단을 위한 조직학적 평가의 필수성을 강조한다. 본 증례 보고는 악성 흑색종을 모방하는 아말감 문신에 관한 문헌 고찰을 시도한 첫 사례로서, 비전형적인 임상 양상을 보이는 구강 색소 병소에서는 방사선학적 증거나 수복 병력이 없더라도 악성 가능성을 배제하기 위한 적극적인 조직학적 평가가 필수적임을 강조한다.

Conflicts of Interest: None

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CASE REPORT

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Challenges in distinguishing chondrosarcoma from synovial chondromatosis of the temporomandibular joint

Jong-Seong Chae[1], Dae Ho Leem[1], Jeong-Kui Ku[1,2*]

[1]Department of Oral and Maxillofacial Surgery, School of Dentistry, Jeonbuk National University, Jeonju, Korea
[2]Department of Oral and Maxillofacial Surgery, Section of Dentistry, Seoul National University Bundang Hospital, Seongnam, Korea

ABSTRACT

Synovial chondromatosis is a rare benign disorder that can closely mimic chondrosarcoma, particularly in the temporomandibular joint (TMJ), where both conditions are uncommon. We report a diagnostically challenging case of an 81-year-old female presenting with preauricular pain, swelling, and limited mouth opening. Radiologic evaluation, including computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) revealed multiple calcified loose bodies, condylar erosion, and a poorly defined mass, initially suggesting synovial chondromatosis. Surgical intervention was performed under the assumption of a benign lesion. However, histopathologic examination demonstrated high-grade (grade III) chondrosarcoma with marked cellular atypia and increased mitotic activity. This case highlights the limitations of relying solely on clinical and radiologic findings for diagnosis. Accurate differentiation between synovial chondromatosis and chondrosarcoma requires comprehensive evaluation, including histopathologic confirmation. Clinicians should maintain a high index of suspicion when atypical or aggressive imaging features are present in TMJ lesions. ***(J Korean Dent Assoc 2026; 64(7): 259-264)***

Key words : Chondromatosis, Synovial; Chondrosarcoma; Temporomandibular Joint; Diagnosis, Differential

Introduction

Synovial chondromatosis is an uncommon benign disorder characterized by the metaplastic formation of multiple cartilaginous nodules within the synovial lining of joints. While large joints such as the knee, hip, and shoulder are commonly affected, involvement of temporomandibular joint (TMJ) is exceedingly uncommon and can pose significant diagnostic challenges due to symptom overlap with other joint pathologies[1]. Clinical presentations typically include preauricular swelling, pain, joint noise, and progressive limitation of jaw movement. However, these symptoms often overlap with those of other TMJ disorders, including osteoarthritis. Thus, accurate diagnosis requires a multimodal approach, incorporating imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT), and histopathological evaluation[2].

Chondrosarcoma is a malignant cartilaginous tumor that often progresses insidiously. Although craniofacial chondrosarcoma is rare, the TMJ represents an even more infrequent location, often leading to misdiagnosis. Histologically, chondrosarcoma is graded based on cellularity, atypia, and mitotic activity, with higher grades portending worse prognosis and increased metastatic

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*Corresponding author: Prof. Jeong-Kui Ku
Department of Oral and Maxillofacial Surgery, Section of Dentistry, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Korea
Tel: +82-31-787-2780, E-mail: kujk@snubh.org

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potential[3,4]. Synovial chondromatosis and chondrosarcoma may share overlapping features, including joint space expansion, condylar erosion, and intra-articular calcifications, complicating the diagnostic process. A retrospective cohort study found that approximately 6.4% of synovial chondromatosis cases demonstrated malignant transformation, prompting calls for caution in presumed benign presentations[5].

Given the significant differences in prognosis and treatment, distinguishing between primary benign synovial chondromatosis and malignant chondrosarcoma is critically important. In fact, both diseases can present with similar clinical manifestations such as pain, swelling, and restricted joint movement, which can make differentiation quite difficult. In this case report, we diagnosed a patient with synovial chondromatosis in the TMJ based on clinical symptoms, as well as radiological examinations including cone-beam computed tomography (CBCT) (Alphard VEGA, Asahi Roentgen, Kyoto, Japan), MRI (Ingenia 1.5-T, Philips Healthcare, Best, Netherlands) and PET-CT (Biograph Vision 600, Siemens Healthineers, Erlangen, Germany). However, surgical excision and histopathological analysis resulted in a diagnosis of chondrosarcoma grade III (high-grade). This report aims to show cases presenting challenges in distinguishing between synovial chondromatosis and chondrosarcoma.

Case Report

This study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB No. CUH 2025-05-063). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study and the use of anonymized patient data.

An 81-year-old female presented with a four-day history of progressive left preauricular pain and swelling, accompanied by decreased mandibular mobility. Physical examination revealed a comfortable mouth opening of 15 mm and a maximum mouth opening of 25 mm, with marked leftward deviation and tenderness over the TMJ. Panoramic radiographs showed irregularity of the left condylar articular surface and multiple radiopaque calcifications surrounded by radiolucent rims near the condylar head.

CBCT revealed multiple punctate and nodular calcified loose bodies distributed within the joint space, predominantly surrounding the condylar head. These findings were accompanied by irregular cortical erosion and os-

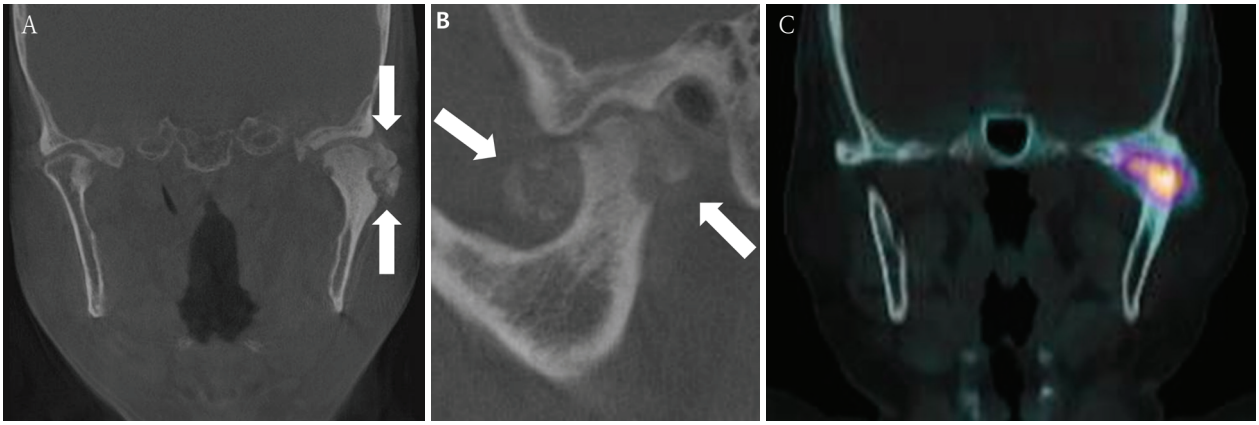

Fig. 1. Radiographic findings of the left temporomandibular joint. A. Coronal cone-beam computed tomography (CBCT) image shows multiple calcified loose bodies (arrows) around the left condylar head. B. Sagittal CBCT image demonstrates bony erosion and sclerotic changes of the left condyle, along with multiple calcified loose bodies (arrows). C. Bone single-photon emission computed tomography/computed tomography reveals increased radiotracer uptake in the left condyle, suggesting active bone metabolism.

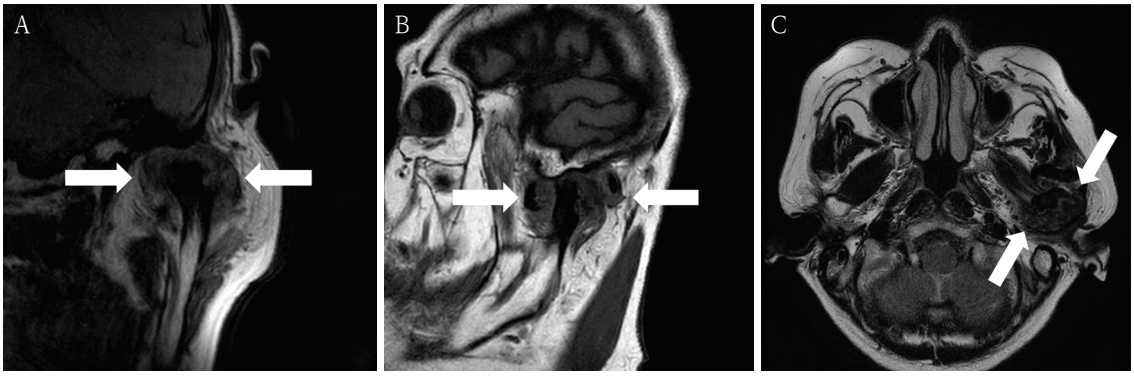

Fig. 2. Magnetic resonance imaging findings of the left temporomandibular joint. A. Coronal view demonstrates a heterogeneous mass lesion (arrows) involving the left temporomandibular joint with poorly defined margins. B. Sagittal view shows the lesion (arrows) causing cortical destruction of the condylar head and irregular contour deformity. C. Axial view illustrates the extent of the lesion (arrows) around the temporomandibular joint with indistinct borders, suggesting an infiltrative growth pattern.

teolytic destruction involving both the condylar head and neck. The cortical margins appeared indistinct with focal areas of cortical discontinuity, suggesting aggressive bone involvement. In addition, mild expansion of the joint space with adjacent subchondral sclerosis was noted. The extent of cortical disruption and bone destruction was considered atypical for a purely benign process such as synovial chondromatosis, raising suspicion for a possible malignant lesion (Fig. 1).

MRI demonstrated a heterogeneous lesion involving the left TMJ with poorly defined and indistinct margins. The lesion involved the condylar head and was associated with cortical destruction and deformity. The internal architecture appeared irregular, without clear demarcation from surrounding structures, suggesting a possibly infiltrative growth pattern. These imaging features, particularly the ill-defined margins and osseous destruction, raised suspicion for a malignant tumor rather than a benign synovial condition (Fig. 2).

Despite several imaging features suggestive of a malignant tumor, including poorly defined margins and cortical destruction, the initial clinical impression favored synovial chondromatosis. This was primarily based on the presence of multiple calcified loose bodies within the joint space, a characteristic finding of synovial chondromatosis, along with associated sclerotic changes. In addition, the patient's clinical presentation, including preauricular pain, swelling, and limited mouth opening, was consistent with a benign TMJ disorder. Based on this preliminary diagnosis, surgical intervention was planned under the assumption of a benign condition, with the aim of improving mandibular function and relieving symptoms. A preauricular approach was used to access the TMJ under general anesthesia. Intraoperatively, multiple creamy-white and brownish tissue fragments were identified within the joint space (Fig. 3). These materials appeared irregular in shape and were loosely distributed around the condylar head, initially suggesting cartilaginous loose bodies. Curettage was performed around the condylar head, including the surrounding joint space, followed by condyloplasty to improve joint contour. The articular disc, which was found to be medially displaced and folded, was repositioned. Postoperatively, the maximum mouth opening improved to 40 mm with satisfactory mandibular movement.

Histopathological examination revealed grade III chondrosarcoma, characterized by high cellularity, nuclear pleomorphism, abundant mitoses, and disrupted lobular architecture. The histopathologic findings are consistent with grade III chondrosarcoma, with a Ki-67 proliferation index of approximately 10%. The final diagnosis was high-grade chondrosarcoma of the TMJ (Fig.

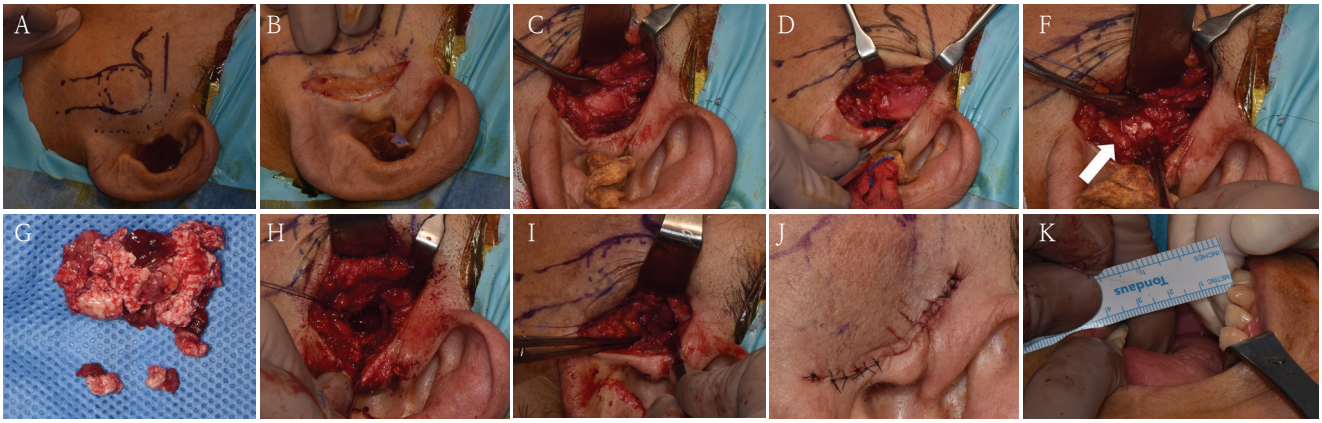

Fig. 3. Intraoperative findings and surgical procedure of the left temporomandibular joint. A-D. Surgical exposure of the temporomandibular joint through a preauricular approach. E. Intra-articular view shows multiple creamy-white and brownish tissue fragments (arrows) within the joint space. F. Removed intra-articular tissue fragments, appearing as creamy-white and brownish masses. G. Intra-articular view after removal of the tissue, shows a cleared joint space around the condylar head. H. Condyloplasty with repositioning of the articular disc. I. Closure of the surgical site. J. Postoperative maximum mouth opening demonstrating improvement to approximately 40 mm.

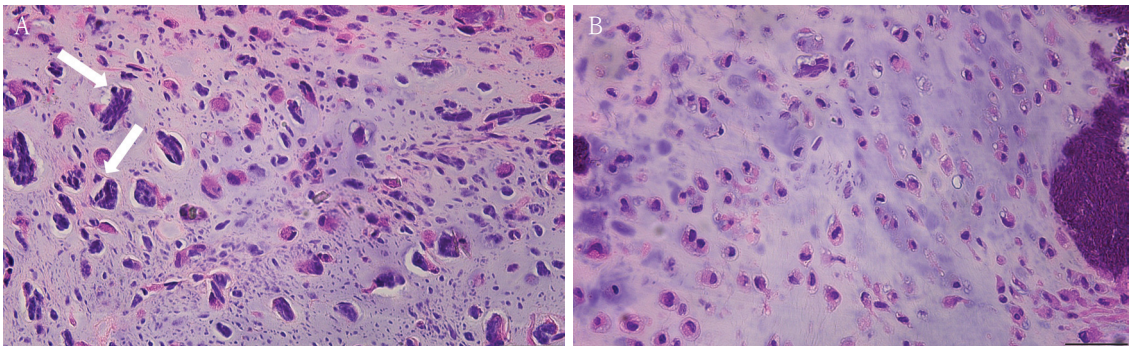

Fig. 4. Histopathological findings of the temporomandibular joint lesion (H&E stain). A. High-power photomicrograph demonstrates hypercellularity, prominent nuclear pleomorphism, and multinucleated cells. The white arrows indicate cells with severe nuclear atypia and increased mitotic activity (original magnification, x400). B. Low-power photomicrograph showing the disrupted lobular architecture. These overall histopathological features are consistent with grade III chondrosarcoma (original magnification, x200).

4). Given the high-grade diagnosis, additional surgical resection and adjuvant radiotherapy were recommended. However, the patient declined further treatment, citing improved function and age-related considerations. At the 12-month telephone follow-up, the patient remained asymptomatic and functionally stable, with no clinical evidence of disease progression.

Discussion

This case highlights the inherent diagnostic difficulty in distinguishing synovial chondromatosis from chondrosarcoma of the TMJ, especially given the rarity of both entities in this anatomic location. The patient's initial presentation, including preauricular pain, limited mandibular range of motion (comfortable mouth opening: 15 mm, maximum mouth opening: 25 mm), and imaging findings of condylar sclerosis, bony erosion, and calcified loose bodies, were all suggestive of synovial chondromatosis. However, the MRI findings of a poorly marginated mass and osseous destruction warranted further oncologic consideration.

Recent studies have proposed imaging-based criteria to improve diagnostic precision[6]. Among several evaluated radiologic markers, infiltration of the lateral ptery-

goid muscle tendon demonstrated the highest diagnostic value, followed by lesion size (typically > 4 cm), internal enhancement, and sclerosis of adjacent bone structures. If at least one of these four features is present, clinicians should include chondrosarcoma in the differential diagnosis. In fact, chondrosarcoma lesions tend to be larger in volume, with average dimensions around 3.9 cm × 1.7 cm, and frequently exceed 4 cm in maximum diameter[7,8].

Nevertheless, the overlapping clinical and radiologic features of synovial chondromatosis and chondrosarcoma often render preoperative differentiation elusive. Both entities can manifest with pain, trismus, condylar irregularity, and calcified intra-articular bodies. As such, diagnosis cannot rely solely on imaging[9]. In our case, radiologic findings such as multiple calcified loose bodies and sclerotic changes closely mimicked synovial chondromatosis, leading to an initial misdiagnosis. Notably, the final diagnosis of high-grade chondrosarcoma was established only after histopathologic examination, despite relatively benign-appearing imaging findings. This highlights the limitation of imaging alone and emphasizes the importance of histopathologic confirmation in ambiguous TMJ lesions.

However, histologic examination also has its limitations. The grading of chondrosarcoma is inherently subjective and often plagued by interobserver variability, especially in borderline or low-grade lesions[10]. Additionally, when chondrosarcoma arises in unconventional locations such as the TMJ, it may mimic the benign histologic architecture of synovial chondromatosis, further complicating diagnosis[11]. Although advanced imaging modalities such as MRI and PET-CT provide valuable insights into tumor biology and invasiveness, they remain insufficient for definitive diagnosis. Accordingly, a multidisciplinary approach that integrates clinical, radiological, and histopathological data is imperative. In select cases, intraoperative frozen section biopsy may serve as a pragmatic adjunct to guide real-time surgical decision-making, particularly in elderly patients or those presenting with high-risk imaging features such as cortical destruction or ill-defined margins.

Furthermore, this case underscores the ethical and therapeutic challenges posed by treatment refusal in geriatric oncology. Despite the histological confirmation of high-grade chondrosarcoma, the patient's decision to decline adjuvant therapy—coupled with her satisfactory functional status and lack of clinical recurrence at one year—raises the possibility that conservative surgery may be considered in exceptional cases with patient-centered goals of care. Nonetheless, long-term surveillance remains essential given the risk of local recurrence and distant metastasis associated with high-grade lesions[11].

In conclusion, accurately distinguishing synovial chondromatosis from chondrosarcoma of the TMJ is essential, given their markedly different biological behaviors and treatment strategies. This case highlights the limitations of relying solely on clinical and radiologic findings and underscores the importance of thorough histopathologic evaluation. Clinicians should maintain a high index of suspicion for malignancy in TMJ lesions presenting with atypical or aggressive features, even when initial impressions suggest a benign condition.

Conflicts of Interest: None

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