Universitat Internacional de Catalunya

Cone-beam computerized tomography (CBCT) evaluation of the upper airway in the context of orthognathic surgery

Raquel Guijarro Martínez

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PhD Thesis
Department of Oral and Maxillofacial Surgery
Universitat Internacional de Catalunya

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Prof. Dr. Federico Hernández Alfaro
Prof. Dr. Gwen R. J. Swennen

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PhD student: **Raquel Guijarro Martínez**

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Evaluación mediante tomografía computarizada de haz cónico (CBCT) de la vía aérea superior en el contexto de la cirugía ortognática

Tesis Doctoral Europea

Departamento de Cirugía Oral y Maxilofacial

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Prof. Dr. Gwen R. J. Swennen

A Manuel

A mis padres

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Index

Preliminary remarks

The present PhD investigation is a compendium of three related publications.

For the purpose of uniformity and consistency, an effort has been made to merge abbreviations, figures, tables and bibliographical references. As a result,

1. Abbreviations have been standardized throughout the whole text. A comprehensive list that summarizes all of them is provided.
2. Figures and tables have been renumbered. Those belonging to the individual publications have two numbers separated by a decimal point. The first number refers to the particular paper to which they belong (1 for paper one, 2 for paper two, 3 for paper three) and the second number to the consecutive order in which they appear.
3. Bibliographical references of all three papers have been unified in order to provide a single reference list at the end of this project. Each publication's individual reference list can be separately consulted in journal PDF format in appendix 1.

List of abbreviations

AAOMS: American Association of Oral and Maxillofacial Surgeons

ANOVA: Analysis of variance

ANS: Anterior nasal spine

BMI: Body mass index

BSSO: Bilateral sagittal split osteotomy

CBCT: Cone-beam computed tomography

CI: Confidence interval

CPAP: Continuous positive airway pressure

CT: Computed tomography

C2ia: Most inferior-anterior point of the body of C2

C2ip: Most inferior-posterior point of the body of C2

C2od: Tangent point at the most superior-posterior point of the odontoid process of C2

C2sp: Superior-posterior extremity of the odontoid process of C2

C3ai: Most anterior-inferior point of the body of C3

C4ai: Most anterior-inferior point of the body of C4

DICOM: Digital Imaging and Communications in Medicine

IAOMS: International Association of Oral and Maxillofacial Surgeons

ICC: Intraclass correlation coefficient

F: Repeated measures ANOVA

FH: Frankfort horizontal

FOV: Field of view

Fri: Friedman’s test

kV: Kilovolt

kVp: Peak kilovoltage

mA: Milliampere

Min: Minimum

Max: Maximum

MRI: Magnetic resonance imaging

N: Sample size

NHP: Natural head position

OBS 1: Observer 1

OBS 2: Observer 2

OSA: Obstructive sleep apnea

PNS: Posterior nasal spine

RPE: Rapid palatal expansion

SARPE: Surgically assisted rapid palatal expansion

SD: Standard deviation

SDB: Sleep-disordered breathing

SN: *Sella-nasion* line

SR: Systematic review

2D: Two-dimensional

3D: Three-dimensional

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1. Summary

1.1. INTRODUCCIÓN

El interés de la comunidad dental y maxilofacial por la morfología y las dimensiones de la vía aérea superior ha ido en aumento durante las últimas décadas [1]. Esta creciente atención deriva de dos hechos principales. En primer lugar, de la relación patogénica entre la configuración del tracto respiratorio superior y el desarrollo del macizo facial. En este sentido, se ha comprobado una asociación estadísticamente significativa entre las anomalías respiratorias altas durante la edad pediátrica y el desarrollo de un patrón dolicofacial con hiperdivergencia, compresión maxilar, apiñamiento anterior e inserción baja de la lengua [2, 3]. En segundo lugar, el firme interés de la comunidad científica por las características de la vía aérea superior se relaciona estrechamente con la correlación observada entre las anomalías cualitativas y cuantitativas de ésta y la instauración de problemas de apnea obstructiva del sueño. De hecho, de forma genérica, los trastornos respiratorios durante el sueño (que categóricamente reciben en inglés el acrónimo de sleep-disordered breathing, SDB) constituyen en la actualidad un problema de salud pública por constituir un factor de riesgo para el desarrollo de hipertensión arterial y enfermedad cardiovascular [4-7], somnolencia nocturna [5, 8], déficits neuropsicológicos [9-11] y accidentes [12].

En la actualidad se dispone de numerosas técnicas para estudiar la vía aérea superior. Desde los primeros estudios con tele-radiografía lateral, procedentes sobre todo del campo de la Ortodoncia, se han desarrollado sofisticados sistemas de evaluación tanto cuantitativa como cualitativa, cada uno con ventajas e inconvenientes particulares. Sin embargo, la introducción durante la década de los 90 de la tomografía computarizada de haz cónico (CBCT) ha supuesto la incorporación de un arma muy potente tanto para el diagnóstico como para la planificación terapéutica y el seguimiento de la patología dental y maxilofacial en general y de la configuración de la vía aérea superior en particular. Efectivamente, mientras que la tomografía computarizada clásica y la resonancia magnética son superiores a la CBCT en cuanto a discriminación de estructuras blandas, la CBCT tiene ventajas importantes en cuanto a menores costes, facilidad de acceso y tiempos de adquisición más cortos [1, 13, 14]. Además, en comparación a la tomografía computarizada, la CBCT implica dosis de radiación significativamente menores para el paciente. Por otra parte, a pesar de la citada inferioridad en cuanto a discriminación de tejidos blandos frente a la tomografía computarizada y resonancia magnética, la CBCT consigue una excelente discriminación entre tejidos blandos y aire [14, 15], característica fundamental para estudios del tracto respiratorio. Diversos estudios han evaluado su exactitud y su fiabilidad para esta indicación concreta y han asegurado, en efecto, su validez en este contexto [16-26]. Asimismo, el procesamiento posterior de los archivos DICOM (Digital Imaging and Communications in

Medicine) por softwares específicos permite un análisis cualitativo y cuantitativo de la vía aérea superior sin precedentes [1, 27].

Aunque en sus orígenes la cirugía ortognática se concebía como la cirugía correctora de las deformidades dentofaciales, en la actualidad está claro que la esfera de acción de esta cirugía va mucho más allá de la corrección dental y esquelética aisladas. Así, el alcance - y con ello los objetivos - de esta cirugía han sido redefinidos y en la actualidad se erigen sobre tres pilares fundamentales: 1) Oclusión, 2) Hueso y 3) Tejidos blandos. De hecho, en la vanguardia de la ortodoncia y cirugía maxilofacial se concibe el tercer pilar, los tejidos blandos, como un factor tan importante en la planificación terapéutica y en la evaluación de resultados como los otros dos. En efecto, aunque las osteotomías faciales puedan conseguir una normooclusión y normoposición esquelética, lo que el paciente realmente percibe y lo que determina su satisfacción con el tratamiento son los cambios en los tejidos blandos faciales [28]. Estas modificaciones resultan del cambio relativo de posición de las inserciones musculares y ligamentosas y de los nuevos juegos de tensión generados a partir de la nueva posición ósea. Pero estos cambios no se limitan a las estructuras blandas suprayacentes al hueso, o lo que podríamos llamar la “máscara externa”, sino que afectan también a las partes blandas que se insertan por la cara interna, constituyendo, por su parte, una “máscara interna”. Esta “máscara interna” de tejidos blandos cuya configuración se altera al modificar la posición ósea estaría representada sobre todo por la musculatura suprahioidea, el paladar blando, la lengua y los tejidos blandos perifaríngeos. Por tanto, la cirugía ortognática tiene el potencial de modificar tanto la apariencia facial como las características morfológicas y dimensionales de la vía aérea superior [29].

Por su parte, el potencial inductivo de SDB de los retrocesos mandibulares aislados (es decir, sin procedimiento compensatorio de la reducción de la vía aérea asociado) está ampliamente documentado en la literatura [30-36]. Los estudios han demostrado una disminución de volumen de la vía aérea superior sobre todo a nivel oro e hipofaríngeo [30, 31, 33, 37-40] y un desplazamiento posteroinferior de la lengua y del hioides [39, 41-43]. Por su parte, la evidencia de mejoría de los SDB tras procedimientos de avance maxilomandibular también está sólidamente establecida [44-50]. En este caso, las dimensiones de la vía aérea superior aumentan gracias al avance de las inserciones de la musculatura suprahioidea y velofaríngea [44, 47, 49, 51]. Además, si al avance esquelético se le asocia un componente de rotación antihoraria del complejo maxilomandibular, el avance relativo de los tubérculos geni es cuantitativamente mayor que el de los dientes, maximizando así el avance del hioides, la base de la lengua y los tejidos blandos asociados [46, 52]. En el momento de plantear esta tesis doctoral, todos los estudios disponibles sobre los cambios producidos en el tracto respiratorio superior tras cirugía ortognática habían sido realizados con tele-radiografía lateral [30-33, 37, 38, 41-43] o tomografía computarizada clásica [36, 39, 44, 51], pero la CBCT no había sido utilizada aún para este fin concreto.

1.2. RESUMEN DE OBJETIVOS Y PLAN DE TRABAJO

En este contexto de renovado interés de la comunidad científica dento-maxilofacial por el estudio de la vía aérea superior y de creciente supremacía de la CBCT como técnica de imagen para el diagnóstico y la planificación en la cirugía ortognática, el presente proyecto de investigación se articuló en base a los siguientes objetivos:

1. En primer lugar, y como punto de partida del proyecto, realizar una revisión sistemática de la literatura acerca del uso de la CBCT para la indicación concreta de estudiar la vía aérea superior. Esta consulta bibliográfica representaría una evaluación exhaustiva de los estudios realizados hasta el momento, intentando con ello definir los parámetros técnicos recomendables para evaluar la vía aérea superior, conocer los software de procesamiento DICOM empleados por otros autores y analizar su rigor en función de la presencia o no de estudios previos de validación, comparar la capacidad de la CBCT para evaluar el tracto respiratorio superior con otras técnicas de imagen de reconocida utilidad en este contexto, y con todo ello, concluir acerca de la eficacia y fiabilidad de la CBCT para esta indicación concreta.
2. Asumiendo que el análisis de la literatura disponible permitiese concluir que la CBCT es, en efecto, válida para la indicación estudiada, el siguiente paso sería realizar un estudio piloto sobre los cambios producidos en la vía aérea faríngea en una muestra de pacientes sometidos a cirugía ortognática. En este caso, los objetivos serían no sólo el investigar los cambios cualitativos y cuantitativos en sí, sino desarrollar un protocolo propio para el estudio de la vía aérea superior a partir de nuestra experiencia piloto. Con la intención de contemplar cambios en todas las regiones de la vía aérea faríngea (tanto en la naso como en la oro e hipofaringe) así como de comparar la repercusión individual de las distintas osteotomías maxilofaciales, se decidió constituir la muestra con tres tipos de pacientes: 1) Pacientes sometidos a cirugía bimaxilar, 2) Pacientes sometidos a cirugía maxilar aislada, y 3) Pacientes sometidos a cirugía mandibular aislada. Se obtuvo el necesario permiso del Comité Ético de Investigación Clínica para revisar, de forma retrospectiva, los datos clínicos de los pacientes incluidos. Puesto que en nuestra práctica diaria se procura evitar

realizar procedimientos de retroceso mandibular aislado por su potencial efecto deletéreo en la vía aérea superior, se decidió por conveniencia estudiar procesos de avance, tanto mono como bimaxilar.

3. Una de las principales conclusiones extraídas a partir de la revisión sistemática realizada en primer lugar fue la llamativa falta de consenso entre autores respecto a los límites anatómicos de cada subregión de la vía aérea superior (naso, oro e hipofaringe). En contra de lo que cabría esperar dado el uso relativamente frecuente de estos términos, los límites exactos de estas áreas no se encuentran específicamente definidos en la literatura anatómica en general y en la maxilofacial en la particular. Como consecuencia, los estudios publicados hasta el momento utilizan límites muy discordantes y en muchas ocasiones ni siquiera los definen en su apartado de material y métodos. Así pues, la tercera publicación se encaminó a definir unos límites anatómicos lógicos para cada subregión de la vía aérea superior y a traducir estas referencias anatómicas a límites radiológicos prácticos en estudios de CBCT. Teniendo en cuenta las enseñanzas adquiridas a partir de nuestra experiencia piloto, se procuró establecer y validar un protocolo de evaluación de la vía aérea faríngea que considerara todos las posibles fuentes de error que existen en el estudio de esta particular región anatómica. Finalmente, se decidió constituir la muestra de estudio a partir de pacientes sanos representativos de una población normal, de forma que los resultados cuantitativos preliminares del análisis de la vía aérea superior pudieran servir a su vez como valores de referencia.

Como se deduce de estos objetivos, el presente proyecto de investigación supone una unidad de conocimiento integrada por una parte de trabajo bibliográfico y una parte de trabajo clínico. Las tres publicaciones que la componen pretenden ser trabajos de valor científico independiente y a la vez constituir tres ramas de un mismo tronco conceptual y metodológico. La investigación fue realizada durante los años 2010-13 en dos centros de reconocido prestigio nacional e internacional en cirugía maxilofacial:

- El Instituto Maxilofacial del Centro Médico Teknon (Barcelona), centro de referencia en el tratamiento quirúrgico de las deformidades dento-maxilofaciales. La doctoranda colabora activamente con este centro tanto en trabajo clínico como de investigación desde el año 2010.
- El Servicio de Cirugía Maxilofacial del Hospital St. Jan de Brujas (Bélgica), uno de los principales centros de formación de residentes en cirugía maxilofacial a nivel internacional y unidad pionera en la aplicación de nuevas tecnologías – entre ellas, la CBCT - al diagnóstico de la patología maxilofacial. Desde 2010, la doctoranda

colabora con este centro en materia de investigación y ha realizado diversas estancias clínicas. [*]

1.3. RESUMEN DE METODOLOGÍA, RESULTADOS Y CONCLUSIONES DE LAS TRES PUBLICACIONES

1.3.1. Artículo primero:

El primer trabajo se publicó en el *International Journal of Oral and Maxillofacial Surgery* [†]. Esta revista es la publicación oficial de la IAOMS (International Association of Oral and Maxillofacial Surgeons). Tras su primera revisión fue propuesto como "artículo de revisión invitada" en la categoría de apnea obstructiva del sueño, mención que gratamente aceptamos.

Tras la selección de dos series de palabras clave adecuadas – la primera sobre terminología relacionada con CBCT y la segunda sobre terminología relacionada con la vía aérea superior - la búsqueda sistemática se realizó en la base de datos PubMed (National Library of Medicine, NCBI). Tras un resultado inicial de 382 referencias, la aplicación de estrictos criterios de selección permitió la selección de 46 publicaciones. Éstas fueron analizadas minuciosamente y clasificadas según su temática en cinco grupos: 1) Exactitud y fiabilidad de la CBCT para la evaluación de la vía aérea superior; 2) Exactitud y fiabilidad de los visores DICOM para la evaluación de la vía aérea superior; 3) Artículos de sinopsis; 4) Aplicaciones técnicas; y 5) Aplicaciones clínicas. Asimismo, se estudiaron a fondo los parámetros técnicos de los distintos dispositivos de CBCT utilizados, las condiciones de escaneado del paciente, el software empleado y los límites anatómicos empleados en cada estudio.

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[*] En cumplimiento con el requisito de realizar parte de la investigación en un centro extranjero para optar a la mención europea del grado de doctor, la doctoranda realizó varias estancias en el Servicio de Cirugía Maxilofacial del Hospital St. Jan de Brujas (Bélgica) durante las fechas siguientes:

- 20-09-10 al 04-11-10.
- 01-08-11 al 02-09-11.
- 06-11-11 al 15-12-11.
- 05-08-12 al 31-08-12.

[†] Referencia completa:

Guijarro-Martínez R, Swennen GR. Cone-beam computerized tomography imaging and analysis of the upper airway: a SR of the literature. Int J Oral Maxillofac Surg 2011; 40(11): 1227-37.

doi: 10.1016/j.ijom.2011.06.017.

Las principales conclusiones extraídas a partir de este trabajo fueron las siguientes:

- Según la literatura científica disponible, la CBCT permite estudiar la vía aérea superior de manera exacta y fiable tanto en dos como en tres dimensiones.
- Sin embargo, existen todavía problemas pendientes de resolución. Estas dificultades son inherentes de la medición del tracto respiratorio superior e incluyen la influencia de la posición lingual y morfología mandibular, el impacto de la fase respiratoria, la falta de límites anatómicos claros para las distintas subregiones de la vía aérea faríngea y la falta de consenso entre autores respecto a los parámetros descriptivos mínimos para estudios de la vía aérea superior, softwares de medición, condiciones de escaneado y región anatómica estudiada.
- Los estudios de la vía aérea superior requieren necesariamente un sistema de evaluación tridimensional además de bidimensional (es decir, la descripción de la vía aérea superior exige tanto parámetros volumétricos como áreas).

1.3.2. Artículo segundo:

A partir de la revisión sistemática, nuestro primer trabajo clínico y segunda publicación del compendio que constituye esta tesis doctoral se publicó en el *Journal of Oral and Maxillofacial Surgery,* publicación oficial de la AAOMS (American Association of Oral and Maxillofacial Surgeons) [‡].

Con el objetivo de evaluar con CBCT los cambios volumétricos producidos en la vía aérea superior tras cirugía ortognática de avance, se realizó un análisis retrospectivo de 30 pacientes divididos en tres categorías en función del procedimiento quirúrgico: 1) Avance bimaxilar; 2) Avance maxilar aislado; y 3) Avance mandibular aislado. Todos los casos de rotación del complejo maxilomandibular, modificación de la dimensión transversal o mentoplastia asociada se excluyeron con el fin de analizar exclusivamente el efecto del avance puro en el plano sagital. Los cambios se evaluaron a corto plazo, es decir, tras una media de 133.5 días postoperatorios.

Los principales resultados de este estudio pueden resumirse en los siguientes

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[‡] Referencia completa:

Hernández-Alfaro F, Guijarro-Martínez R, Mareque-Bueno J. Effect of mono and bimaxillary advancement on pharyngeal airway volume: Cone-beam computerized tomography evaluation. J Oral Maxillofac Surg 2011; 69(11): e395-400.

doi: 10.1016/j.joms.2011.02.138.

puntos:

- La cirugía ortognática de avance (tanto mono como bimaxilar) produjo de forma sistemática un incremento de volumen en la vía aérea superior. Además del incremento volumétrico cuantitativamente objetivado, cabe destacar que cuatro pacientes con SDB comunicaron una mejoría subjetiva de su respiración. Uno de estos pacientes, que había sido diagnosticado de apnea obstructiva del sueño y era usuario de un dispositivo nocturno de presión positiva continua en la vía aérea (continuous positive airway pressure, CPAP), dejó de precisarlo dada la mejoría tan significativa de su índice de apneas-hipopneas.
- En la muestra estudiada, el porcentaje de variación de volumen fue mayor en el grupo de avance mandibular aislado (78.3%), seguido del grupo bimaxilar (68.4%). El grupo de avance maxilar aislado fue el que menor incremento volumétrico mostró (37.7%). Estos resultados fueron estadísticamente significativos para un nivel α de 0.05.

Con todo ello, se concluyó que la cirugía ortognática de avance es una cirugía con capacidad de corregir una maloclusión, restablecer la armonía facial y mejorar la sintomatología de SDB gracias a su capacidad de incrementar significativamente el volumen de las vías respiratorias altas. El hecho de que en nuestro estudio el porcentaje de incremento fuera mayor en el grupo de avance mandibular aislado y no en el grupo bimaxilar, como quizá cabría esperar de antemano, hace hincapié en el papel fundamental que juega el avance de las inserciones de la musculatura suprahioidea y tejidos blandos perifaríngeos en las dimensiones de la VAS.

1.3.3. Artículo tercero:

Finalmente, el tercer artículo perteneciente a esta línea argumental fue aceptado para su publicación en el *International Journal of Oral and Maxillofacial Surgery* [§].

Como se ha mencionado, uno de los hallazgos principales de la revisión sistemática realizada en primer lugar fue la comprobación de la gran variabilidad de límites anatómicos

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[§] Referencia completa:

Guijarro-Martínez R, Swennen GR. Three-dimensional CBCT definition of the anatomical subregions of the upper airway: A validation study. Int J Oral Maxillofac Surg 2013; 42(9): 1140-9.

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empleados por los distintos grupos de estudio para evaluar la vía aérea superior. Como consecuencia, la comparación de resultados se convierte en una tarea prácticamente imposible. Incluso trabajos que aseguran haber analizado una misma subregión de la vía aérea faríngea describen no obstante límites anatómicos distintos en su metodología. En el peor de los casos, los límites utilizados ni siquiera se especifican. En este contexto, nos planteamos definir unos límites anatómicos tridimensionales adecuados para describir las subregiones de la vía aérea superior (naso, oro e hipofaringe). Asimismo, con un fin práctico, procuramos traducir estos límites anatómicos a referencias cefalométricas estables en estudios de CBCT y elaborar un protocolo de validación de las mismas.

Para ello, se analizaron los estudios de CBCT de 40 sujetos sanos armónicos esquelética y dentalmente, con edades comprendidas entre 25 y 35 años. Tras seguir un protocolo específico de posicionamiento de la cabeza durante el escáner y de reorientación virtual de la imagen en los tres planos del espacio, se evaluó el área mínima transversal y el volumen de cada una de las tres subregiones de la vía aérea superior de acuerdo a los límites propuestos. Cada uno de los dos investigadores implicados evaluó por duplicado cada estudio con el fin de estudiar la reproducibilidad intra e interobservador.

Los principales resultados fueron los siguientes:

- La inclinación craneocervical de los pacientes, reflejo de la eficacia del protocolo de posicionamiento de la cabeza durante el escáner, mostró una excelente reproducibilidad, con un coeficiente de correlación intraclase (intraclass correlation coefficient, ICC) de 0.992.
- El ángulo de la base craneal, reflejo de la homogeneidad de los pacientes, considerados representantes de una población “normal”, mostró también una reproducibilidad excelente (ICC de 0.983).
- Tanto la reproducibilidad intraobservador como la interobservador fueron excelentes para volúmenes (ICC entre 0.986 y 0.998) y moderadas para áreas (ICC entre 0.837 y 0.876).
- El análisis de dimorfismo sexual reveló en los hombres un volumen orofaríngeo e hipofaríngeo mayor. Asimismo, el área mínima transversal orofaríngea fue mayor en los hombres que en las mujeres.

A partir de estos resultados pudo concluirse que la categorización de la vía aérea superior de acuerdo a los límites anatómicos propuestos en este estudio es técnicamente factible y estadísticamente fiable. Por ello, es de suponer que la adopción de estos límites por la comunidad científica supondría la estandarización del análisis del tracto respiratorio superior y posibilitaría la comparación imparcial entre distintos estudios. Frente a la excelente reproducibilidad de las mediciones tridimensionales, la moderada reproducibilidad de las mediciones bidimensionales puede explicarse por el hecho de que los volúmenes son cifras de varios miles de voxels (milímetros cúbicos), mientras que las áreas se miden en pixels (decenas de milímetros cuadrados). Por ello, pequeñas variaciones en la orientación de la cabeza del paciente dan lugar a modificaciones muy importantes en los valores de área y por ello tienen una influencia mucho mayor en la reproducibilidad bidimensional. Así, puede concluirse que debe prestarse especial atención a la técnica de posicionamiento de la cabeza durante el escáner y subsiguiente reorientación virtual de la misma con el fin de optimizar las cifras de reproducibilidad bidimensional de este protocolo [53].

2. Introduction

2.1. RELEVANCE OF UPPER AIRWAY ANALYSIS IN THE CONTEXT OF ORTHOGNATHIC SURGERY

Upper airway analysis has become one of the main centers of attention in the fields of Orthognathic Surgery and Orthodontics. This is due to the well-acknowledged relationship between a narrow upper airway and SDB, and to the association between airway configuration and specific craniofacial phenotypes. In particular, SDB is currently a critical public health issue as a potential source of morbidity, especially hypertension and cardiovascular disease [4], daytime sleepiness [5, 8] and accidents [12]. Although some risk factors for SDB potentially modifiable through adequate habit acquisition and health education (such as smoking and obesity), most risk factors are nevertheless intrinsic and hence genetically determined (such as male sex, middle age or upper airway morphology). However, in the case of upper airway morphology, it has been proven that significant changes can be introduced through orthodontic regulation of craniofacial growth and, especially, surgical repositioning of the facial bones.

Indeed, Orthognathic Surgery has solidly established itself as a powerful instrument to improve – and worsen – the anatomical configuration of the pharyngeal airway space. This is due to the direct or indirect attachment of the tongue, soft palate, hyoid bone and related musculature to the maxilla and mandible. Depending on the direction and magnitude of bone repositioning, the dimensions of the oral cavity and upper airway are increased or decreased [40, 48, 54]. Isolated mandibular setback is presently a documented risk factor for SDB [30-33] due to postoperative narrowing of the retrolingual and hypopharyngeal airways [30, 31, 33, 37-40] and posteroinferior displacement of the hyoid bone and tongue [39, 41, 42]. On the contrary, favorable improvement of SDB symptoms can be achieved with maxillomandibular advancement [44-50]. In this case, a volumetric increase in pharyngeal airway space is achieved as a result of the advancement of the skeletal attachment of the suprahyoid and velopharyngeal muscles and tendons [44, 47, 49, 51]. Moreover, when counterclockwise rotation of the maxillomandibular complex is performed, the genial tubercles move forward more than the teeth, thereby maximizing the advancement of the hyoid bone, base of the tongue and related soft tissues [46, 52].

2.2. THE SOFT TISSUE MASK

For many years, the lateral cephalogram was the standard imaging technique for the diagnosis and treatment planning of a dentomaxillofacial deformity. In an era where

Orthognathic Surgery was basically aimed at the correction of malocclusion, lateral cephalometry seemed a satisfactory method to plan the ideal position of the misplaced hard tissues. Little or no attention was paid to soft tissue improvement. At any rate, the inherent technical limitations of two-dimensional (2D) cephalometry hindered adequate facial soft tissue and upper airway analysis. Gradually, surgeons and orthodontists realized that a normal occlusion and normal bone position were often not enough to produce facial harmony and optimal function. What is more, it was found that many orthodontic treatments and surgical osteotomies gave way to esthetical decay and or SDB problems, despite having achieved a perfect occlusion and skeletal relationship. The perception that this additional dimension – soft tissue (face and airway) – had to be incorporated into the ordinary treatment scheme, led to the investigation of ways to integrate facial soft tissue parameters and adequate airway imaging techniques to the fields of Orthodontics and Orthognathic Surgery.

Conventionally, the term "facial soft tissue" refers to the soft tissue layer on the outer surface of the facial bones. For illustrative purposes, this outer facial coating may be considered an "external mask" so as to differentiate it from the soft tissue layer related to the inner surface of the maxillofacial bones, or "internal mask". The best way to assess the external mask continues to be clinical assessment. Nevertheless, the advent of virtual treatment planning software programs calls for a method to technically register and accurately incorporate the characteristics of the external mask to a virtually augmented skull model. The CBCT image of the facial skeleton augmented with a digital dental model is currently the most accurate fusion model to display the facial skeleton and the dentition, but it does not represent skin texture adequately [55]. In fact, an objective method to evaluate and predict the external facial soft tissue changes caused by Orthognathic Surgery does not yet exist [55-57].

On the other hand, substantial investigation in the field of airway imaging, that is, "internal mask" analysis, has led to a significant improvement in the understanding and management of the upper airway in the context of dentomaxillofacial deformity. As aforementioned, lateral cephalometry provides a limited method to evaluate the airway; three-dimensional (3D) analysis is impossible, and hard tissue structures often overlap [39]. However, a significant correlation between the posterior airway space measured on cephalographs and airway volume calculated from conventional computed tomography (CT) studies has been demonstrated [48]. Therefore, though incomplete, results are still valid. The possibility to analyze the airway in three dimensions has been introduced by more modern imaging techniques such as CT [58], magnetic resonance imaging (MRI) [59], cine-MRI [60], endoscopy [61], and optical coherence tomography [62]. Nevertheless, CBCT technology has emerged as a potential alternative to obtain a thorough two-dimensional (2D) and 3D evaluation of the upper airway at relatively modest costs, with greater accessibility and shorter scanning times.

2.3. CONVENIENCE OF CBCT FOR UPPER AIRWAY ANALYSIS

Immediately after the introduction of CBCT in the 1990's, it was recognized that CBCT provided a paradigm shift in imaging of the cranio-maxillofacial complex. Utilizing relatively low ionizing radiation, it offered the possibility of multiplanar imaging plus the attainment of excellent 3D representation of hard tissues. Up to then, in-office imaging tools consisted of periapical, bitewing or panoramic radiographs, and lateral or frontal cephalographs. The ability to generate images in different planes was only offered by CT, MRI, ultrasonography, and other medical imaging techniques of limited access and much higher costs.

The competence of CBCT for hard tissue imaging was evident from the beginning. Eventually, its possibilities for soft tissue analysis became apparent too. Indeed, although CBCT is inferior to multidetector CT and MRI in soft tissue discrimination, the boundaries between soft tissues and empty spaces are defined with high spatial resolution [14, 15]. Several studies tested its accuracy and reliability and confirmed its potential for the evaluation of the upper airway [16-18, 20-26, 63]. Other major advantages of CBCT include the fact that the patient is exposed to substantially lower radiation in comparison to multidetector CT [22-27, 64-66], easy handling, and DICOM compatibility. Post-processing of these DICOM files by third-party software allows visualization and quantification of the airway in an unprecedented way. Finally, the fact that the patient can be scanned vertically in a natural seated position is also a key feature for baseline airway analysis. As a result, CBCT has become a key in-office imaging technique in oral and maxillofacial diagnosis and treatment planning in general, and in Orthognathic Surgery in particular.

At the time this PhD project was designed, soft tissue changes – of both the external and internals masks - after Orthognathic Surgery had been studied with lateral cephalometry [30-33, 37, 38, 41-43] and CT [36, 39, 44, 51]. However, to our knowledge, no previous reports with CBCT evaluation existed. In this context of increasing interest about the airway and growing dominance of CBCT-in the field of Oral and Maxillofacial Surgery, this PhD thesis was born.

3. Aims

The aims of this investigation can be classified as follows:

3.1. GENERAL AIM

To use CBCT to evaluate upper airway changes after orthognathic surgery.

3.2. SPECIFIC AIMS

1. To investigate the clinical applications of upper airway analysis with CBCT.
2. To evaluate the accuracy and reliability of current methodologies for upper airway analysis with CBCT.
3. To use CBCT to study the effect of mono- and bimaxillary advancement on the dimensions of the upper airway.
4. To provide logical anatomical limits for the different subregions of the upper airway. Subsequently, to translate these anatomical limits into cephalometric landmarks that can be used reliably in CBCT analysis.
5. To validate a specific CBCT protocol for the predefined subregions of the upper airway.

4. Paper one

Cone-beam Computerized Tomography (CBCT) Imaging and Analysis of the Upper Airway: a Systematic Review of the Literature

4.1. ARTICLE DESCRIPTION

Title:

Cone-beam Computerized Tomography (CBCT) Imaging and Analysis of the Upper Airway: a SR of the Literature

Authors:

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[doi: 10.1016/j.ijom.2011.06.017]

4.2. ABSTRACT

A systematic review (SR) of the literature concerning upper airway imaging and analysis using CBCT was performed. A PubMed search (National Library of Medicine, NCBI; revised January 9th, 2011) yielded a total of 382 papers published between 1968 and 2010. The 382 full papers were screened in detail. A total of 46 articles were considered clinically or technically relevant and were included in this SR. These were classified as articles on accuracy and reliability of CBCT imaging of the upper airway (n=4), accuracy and reliability of DICOM viewers (n=2), synopsis (n=10), technical (n=7) and clinical applications (n=27). When one paper was considered related to two or more categories, it was assigned to each relevant group. Results indicate that 3D analysis of the upper airway using CBCT can be achieved in an accurate and reliable manner. Important obstacles, however, still need to be addressed, including the impact of respiration phase, influence of tongue position and mandible morphology, longitudinal and cross-sectional 3D CBCT upper airway evaluation, and 3D CBCT definition of the anatomical boundaries of the upper airway.

4.3. MAIN TEXT

Introduction

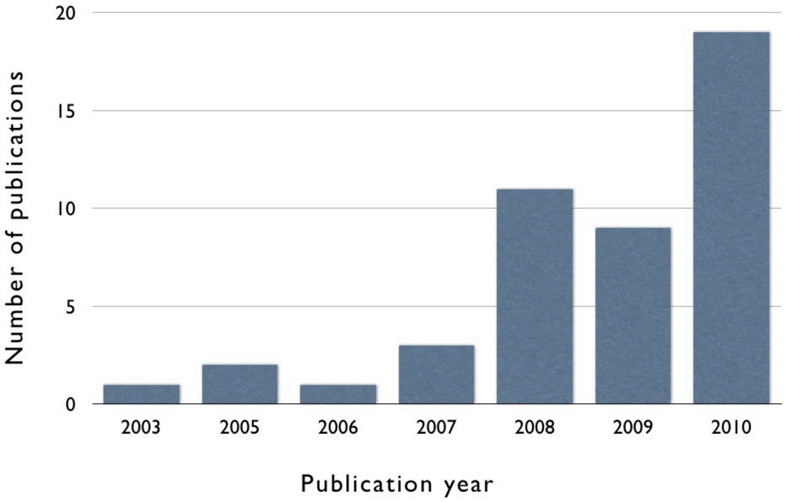
Since its development in the 1990's, CBCT has become a well-accepted tool for oral and maxillofacial diagnosis and treatment planning, mainly due to its advantages in lower effective radiation dose, lower costs, easy access and shorter acquisition times in comparison to conventional multidetector CT (also called multislice CT) [14, 25]. The interest on upper airway shape and dimensions has increased steadily during the past decades due mainly to the relationship between upper airway configuration and obstructive sleep apnea (OSA) as well as craniofacial morphology. According to the medical literature, airway evaluation can be performed with MRI [59, 67-69], cine-MRI [60, 70], multidetector CT [58, 71-81], endoscopy [61] and optical coherence tomography [62]. Although CBCT is inferior to multidetector CT in discriminating between different soft-tissue structures, it has meanwhile shown to be capable to define the boundaries between soft tissues and empty spaces with high spatial resolution [14, 15]. Several studies have tested its accuracy and reliability and have confirmed its potential for the evaluation of the upper airway [16-18, 20-26, 63]. Moreover, post-processing of DICOM (Digital Imaging and Communications in Medicine) images by third-party software allows visualization and quantification of the airway in an unprecedented way. As a result, better understanding of the upper airway anatomy and physiology is to be expected [82].

The number of publications related to upper airway analysis with CBCT is increasing exponentially, especially during the last five years (Fig. 1.1). Although some articles [25, 27, 64, 65, 83] already provide a synopsis on CBCT imaging of the OMF region and refer to the possibility of upper airway evaluation, a SR on CBCT imaging and analysis of the upper airway has not been published yet.

Hence, the purpose of this article was to conduct a SR of the literature on CBCT imaging and analysis of the upper airway in order to: (1) determine current and potential clinical indications of upper airway analysis with CBCT; (2) report technical parameters and (3) verify the accuracy and reliability of CBCT for upper airway analysis according to the available studies.

Figure 1.1

Distribution of published articles on CBCT imaging and analysis of the upper airway yielded by the PubMed search (National Library of medicine, NCBI; updated 9th January 2011) and thoroughly analyzed in this SR



Material and Methods

A SR of the literature concerning upper airway imaging and analysis with CBCT was performed. A PubMed database (National Library of Medicine, NCBI) search was performed and updated on January 9th, 2011. A total of 12 primary keywords related to CBCT terminology were used in combination to 24 secondary keywords in order to restrict the search to CBCT evaluation of the upper respiratory tract relevant to the oral and maxillofacial region (Table 1.1). All possible combinations between one primary keyword and each secondary keyword were explored. The upper respiratory tract was considered to comprise the respiratory structures above the trachea from the nostrils to the larynx.

The initial search yielded a total sample of 382 references. The full papers of all these references were analyzed thoroughly and subsequent categorization produced the following clusters (Table 1.2): (1) A total of 155 references had no relevant relationship to CBCT or airway (upper / lower) analysis; (2) 66 papers concerned the use of CBCT technology in the head and neck region for other purposes (e.g., dental implant imaging and planning, cephalometric analysis, temporomandibular joint evaluation, or radiotherapy treatment planning for head and neck cancer); (3) upper airway evaluation with methods other than

CBCT was described in 47 papers, and (4) 68 articles concerned the evaluation of the lower airway. These four groups were excluded from further evaluation.

The remaining 46 articles were found clinically or technically relevant to the subject of study and were included in this SR. According to their emphasis, these relevant papers were categorized as follows (Table 1.3): (1) accuracy and reliability of CBCT imaging of the upper airway; (2) accuracy and reliability of DICOM viewers; (3) synopsis; (4) technical aspects, and (5) clinical applications. The latter category was further subdivided according to the focus on upper airway evaluation of normal subjects, the relationship between the oropharyngeal airway and dentomaxillofacial morphology or OSA, and evaluation of sinus anatomy and pathology. When one paper was considered related to two or more categories, it was assigned to each relevant group. This explains why the total sum of articles in each group is larger than the total number of papers included in the SR, and why the sum of the separate percentages does not equal 100%.

Table 1.1

Primary and secondary keywords used for the systematic research

Primary keywords	***Secondary keywords***
1. Cone-beam 2. Conebeam 3. CBCT 4. CB-CT 5. Digital volume tomography 6. DVT 7. Compact computed tomography 8. Compact CT 9. Volumetric computed tomography 10. Volumetric CT 11. Ortho cubic 12. Flat panel	1. Air space 2. Airspace 3. Airway 4. Upper airway 5. Airflow 6. Pharynx 7. Pharyngeal 8. Oropharynx 9. Oropharyngeal 10. Nasopharynx 11. Nasopharyngeal 12. Hypopharynx 13. Hypopharyngeal 14. Larynx 15. Laryngeal 16. Nose 17. Nasal 18. Sinus 19. Sinusal 20. Obstructive sleep apnea syndrome 21. Obstructive sleep apnea 22. Sleep apnea 23. OSA 24. OSAS

Table 1.2

Articles yielded by the PubMed search (National Library of Medicine, NCBI) updated on January 9th, 2011 using the primary and secondary keywords listed in table 1.1

Condition	***Article types***	***Number of papers (n)***
Excluded from the SR	1. No relevance to CBCT or airway analysis	155
	2. CBCT of the head and neck region for other purposes	66
	3. Upper airway evaluation with other methods	47
	4. Lower airway evaluation	68
Included in the SR	CBCT imaging and evaluation of the upper airway Table 1.3	46

Table 1.3

Classification of relevant papers that were analyzed in detail for this study

Category	***Number of papers (n)***	***References***	***Percentage***
1. Accuracy and reliability of CBCT imaging of the upper airway	4	14, 17, 18, 84	8.7%
2. Accuracy and reliability of DICOM viewers	2	13, 16	4.3%
3. Synopsis	10	25, 64, 65, 83, 85-90	21.7%
4. Technical aspects	7	15, 91-96	15.2%
5. Clinical applications	27		58.7%
• Upper airway evaluation in normal subjects	1	21	2.2%
• Relationship between upper airway and dentomaxillofacial morphology	7	63, 82, 97-101	15.2%
• Relationship between upper airway and obstructive sleep apnea	5	20, 26, 102-104	10.9%
• Evaluation of sinus anatomy and pathology	14	15, 22-24, 66, 86, 88, 96, 98, 105-109	30.4%

Results

This SR comprised a total of 46 papers. The complete classification of the articles included in each category is displayed in table 1.3. An additional classification according to the specific anatomical region assessed is shown in table 1.4.

1. Accuracy and reliability of CBCT imaging of the upper airway

Two studies compared anatomic information of the nasopharyngeal airway between lateral cephalometric headfilms and CBCT [18, 84]. The authors concluded CBCT is an effective method to accurately analyze the airway, although they found high variability in the airway volume of patients with relatively similar airways on the lateral headfilm. Another paper [17] evaluated the reliability of CBCT measurements of the oropharyngeal airway as compared to those obtained by multidetector CT and found the measurement of air spaces with CBCT reasonably accurate. Finally, the correlations between linear measurements, cross-sectional areas and volumes of the nasopharyngeal and oropharyngeal airways on CBCT datasets were evaluated in one paper [14]. The authors emphasized an adequate assessment of the airway requires the combination of linear measurements, area and volume.

2. Accuracy and reliability of DICOM viewers

One single study [13] compared the accuracy and reliability of three commercially available DICOM viewers (Dolphin3D®, InVivoDental®, OnDemand3D®) for measuring nasopharyngeal and oropharyngeal volumes. The three third-party softwares showed high correlation of results but poor accuracy, suggesting systematic errors. Another paper [16] analyzed the accuracy and precision of one particular DICOM viewer (3dMD Vultus®) using an airway phantom in different orientations as a test standard. The software proved to be an accurate, reliable and fast method to evaluate the airway. Moreover, the authors predicted that incorporation of upper airway imaging using CBCT will facilitate the screening and evaluation of anatomically-related obstructed sleep disordered breathing.

3. Synopsis

The systematic search yielded five papers that dealt with CBCT evaluation of the head and neck for maxillofacial and otorhinolaryngological purposes which included, but did not focus on, upper airway evaluation [25, 64, 83, 87, 89]. One study [65] did focus on airway assessment and offered a general overview of CBCT applications to improve airway management from an anesthesiological perspective. Two papers [86, 88] offered a general overview about imaging of the paranasal sinuses. An editorial discussing the standards on which the definition of the field of view (FOV) should be based in cranio-maxillofacial studies [85] and a paper discussing the legal implications of CBCT imaging [90] were also assigned to this group.

4. Technical aspects

This group comprised two basic type of papers: (1) papers describing a methodology for detection and 3D reconstruction of the airway using CBCT data [94, 95] and (2) studies dealing with practical features that have relevant clinical implications in methodology and interpretation of results [15, 91-93, 96]. One of these studies [92] analyzed the response of oropharyngeal structures to gravity by comparing postural changes between sitting upright (assessed with CBCT) and lying down in a supine position (assessed with multidetector CT). The gravitational effect in response to postural changes caused relevant changes in the position of oropharyngeal structures. Another study [93] evaluated soft tissue image quality of a mobile C-arm with an integrated flat panel detector in comparison to multidetector CT and MRI. The conclusion was that integration of a flat panel detector improves soft tissue visualization. The possibilities and challenges of image superimposition of 3D CBCT models were addressed by another paper [91]. The authors emphasized the possibilities of 3D model superimposition and surface distance calculations to identify treatment outcomes and stability after treatment. The dose and image quality performance between a dedicated CBCT and multidetector CT scanner were compared in another study [96] for a sinus scanning protocol in a phantom model. CBCT proved comparable high-contrast resolution but inferior low-contrast resolution relative to multidetector CT. Finally, a study [15] comparing the quality of paranasal sinus CBCT imaging with different acquisition times was also assigned to this subgroup. The authors concluded image quality is directly related to scan time and accordingly radiation dose.

5. Clinical applications

5.1. Upper airway evaluation in normal subjects

The oropharynx and hypopharynx of ten healthy adults with normal class I occlusion were evaluated in one study [21]. The authors performed a 3D volumetric analysis of the airway and defined the area of maximum cross-sectional constriction, which was most frequently found in the oropharyngeal region.

5.2. Relationship between upper airway and dentomaxillofacial morphology

A total of three papers [63, 99, 100] emphasized the effects of respiratory function on craniofacial growth and morphology. One of them [63] compared the 3D volume of four predefined subregions of the upper airway in healthy children with a retrognathic mandible and those with normal craniofacial growth. As expected, retrognathic patients were found to have a decreased total airway volume. Another paper [100] focused on the oropharyngeal airway differences between children with class I malocclusion and children with class III malocclusion. In this case, class III malocclusion was associated to a larger and flatter oropharyngeal airway. Finally, one study [99] assessed nasopharyngeal and oropharyngeal airway volume and shape in non-growing patients (adolescents and adults) with different facial patterns. The authors found that airway shape and volume vary among different anteroposterior jaw relationships, whereas only airway shape differs with various vertical relationships.

On the other hand, the effects of surgical-orthodontic treatment of dentofacial anomalies on the upper airway were the subject of four papers [82, 97, 98, 101]. Three of them [97, 98, 101] analyzed the effects of rapid palatal expansion (RPE). One study [101] evaluated the effects of RPE on the volume of the oropharynx and found no evidence of oropharyngeal airway volume increase. The other two [97, 98] evaluated the dimensional changes of the nasal cavity and maxilla after RPE. Interestingly, one [98] of the latter studies found a statistically significant decrease in maxillary sinus width. Finally, the effects of extraction vs. non-extraction orthodontic treatments on oropharyngeal airway volume were analyzed by one research group [82]. The extraction of four premolars with retraction of the incisors was not found to alter the volume of the oropharynx.

5.3. Relationship between upper airway and obstructive sleep apnea (OSA)

The SR yielded a total of five papers [20, 26, 102-104] focusing on the OSA-airway relationship. One of them [26] was a synopsis article on diagnostic imaging of OSA, including CBCT as well as other techniques. Another study [104] used CBCT to investigate the correlation between retroglossal airway dimensions and body mass index, comparing OSA and non-OSA patients. Of all the studied parameters, only the ratio "airway cross-section area / square area" showed statistically significant differences between both groups. Other studies compared the cross-sectional configuration of the oropharynx in OSA and non-OSA patients [20] and developed a prediction model for OSA based on CBCT features and sleep questionnaires [102]. Both studies [20, 102] found a statistically significant smaller minimum cross-sectional area in OSA patients. Conversely, another study [103] found significant group differences regarding total airway volume and anteroposterior diameter of the smallest cross-sectional area. There were no significant differences with respect to the smallest cross-sectional area or its lateral dimension.

5.4. Evaluation of sinus anatomy and pathology

The group to which most papers were assigned (n=14) was the one concerning CBCT assessment of sinus anatomy and pathology. Two papers [86, 88] were synopses about imaging of the paranasal sinuses in general. The authors affirmed CBCT introduces a new era in the use of imaging for evaluation of maxillofacial and otorhinolaryngologic pathology [86, 88]. However, whereas intraoperative CBCT seem to increase accuracy and safety, in-office use raises important issues related to patient and clinician convenience [86].

One research group evaluated the efficiency of CBCT as a diagnostic modality for the anterior skull base in general [24] and the olfactory cleft and olfactory fossa in particular [22, 23]. The authors concluded that CBCT evaluation of these areas is accurate and extremely helpful for preoperative assessment [22-24]. Moreover, three other studies described CBCT intraoperative imaging based on a mobile C-arm to guide surgery of the frontal recess [66], sinuses in general and skull base [106, 109].

Clinical aspects such as the relationship between maxillary sinusitis and the prevalence of concha bullosa and nasal septal deviation were evaluated in one paper [108], but no statistically significant association was detected. The effects of RPE on the maxilla were studied by one research group, [98] who reported a statistically significant increase in nasal width and a decrease in maxillary sinus width. CBCT was also used to investigate the prevalence of sphenoid sinus hypoplasia and agenesis in the Turkish population [107] and the formation of the maxillary sinus in Japanese fetuses [105].

Finally, one study [15] compared the image quality and diagnostic accuracy of CBCT scanning with three different data acquisition times on paranasal sinus imaging in general and found that image quality was directly related to scan time and, consequently, radiation dose. Similarly, the comparison of dose and image quality performance between a dedicated CBCT and multidetector CT scanner in the context of a sinus scanning protocol [96] found CBCT had similar high-contrast resolution but inferior low-contrast resolution relative to multidetector CT with a matched radiation dose. Hence, the authors proposed that while CBCT may be comparable to multidetector CT for the assessment of bony anatomy or gross sinus pathology, current CBCT image quality is probably inadequate for the diagnosis and follow-up of certain neurosurgical conditions.

The settings of different CBCT devices for visualization and/or analysis of the upper airway as reported by the articles included in this SR are displayed in table 1.5. Tables 1.6 and 1.7 summarize the conditions in CBCT evaluation of the upper airway and the software used for viewing, measuring and analyzing, respectively. Finally, the anatomical limits of the upper airway in the sagittal plane as defined by each paper are illustrated in table 1.8.

Table 1.4

Classification of CBCT studies of the upper airway according to the specific anatomical region assessed

Anatomical region	***Number of papers (n)***	***References***	***Percentage (%)***
Nasal airway	5	15, 24, 63, 97, 98	10.9%
Sinuses	Sphenoid: 1	107	2.2%
	Ethmoid: 3	22, 23, 66	6.5%
	Maxillary: 3	98, 105, 108	6.5%
	Sphenoid, ethmoid and maxillary: 1	106	2.2%
	Sphenoid, ethmoid, maxillary and frontal and osteomeatal unit: 4	15, 24, 86, 88, 109	8.7%
Nasopharynx	2	18, 84	4.3%
Intraoral space	1	100	2.2%
Oropharynx	8	17, 20, 65, 82, 101-104	17.4%
Nasopharynx and oropharynx	4	13, 14, 63, 99	8.7%
Oropharynx and hypopharynx	2	21, 92	4.3%
Larynx	2	65, 93	4.3%

Table 1.5

Reported settings of different CBCT devices for the visualization and/or analysis of the upper airway

Type of image detector	**Image intensifier**				
Scanner	**NewTom 3G QR srl**	**NewTom QR-DVT 9000**	**NewTom 3G QA srl**	**PSR 9000N**	**Master 3D**
Manufacturer	Quantitative Radiology, Verona, Italy	Quantitative Radiology, Verona, Italy	Quantitative Radiology, Verona, Italy	Asahi Roentgen Industry, Kyoto, Japan	Vatech, Seoul, Korea
References	14, 91, 102, 104	18, 20, 84, 103, 104, 107	101	105	63
Tube voltage		110 kV, 14 mA [107]		60 kV, 4 mA [105]	
Grayscale depth	4096 [104]	256 [103, 104]			
Scan time (seconds)	12 [14]	75-77 [20, 103]	36[101]		
Rotation		360° [103]			
Field of view (cm)		13 [107]			12 in [63]
Slice thickness (mm)		0.8-1 [18] 1 [20] 0.2 axial, 2 coronal, 2 sagittal [107]			
Slice number	360 [104]	360 [20]			
Voxel size	0.36 mm [14]	0.3 mm [18] 0.28 mm [84]		0.1 mm [105]	0.3 mm [63]
Scanned volume dimensions		150x150 mm [20, 103]			
Pixel set					
Bits per pixel	12 [104]	8 [20, 103]			
Data output	DICOM [14, 102]	DICOM [18, 84]			
Patient positioning	Supine	Supine [18, 20, 84, 103]	Supine [101]		Sitting upright [63]

DICOM: Digital imaging and communications in Medicine

* The following settings were not reported: exposure control, exposure time, radiation source, exposure time per image, projections per rotation, detector type, amplification, cone beam angle, scanned volume height, scanned volume diameter, proprietary software, total filtration, front panel attenuation.

Table 1.5

(continued)

Type of image detector	**Image intensifier**			**Flat panel**	
Scanner	**Accu-I-Tomo F17**	**i-CAT**	**CB Mercuray**	**MiniCAT**	**Paxscan 4030 CB**
Manufacturer	Morita, Kyoto, Japan	Imaging Sciences International, Hatfield, Pennsylvania	Hitachi Medical Systems, Tokyo, Japan	Xoran Technologies, Ann Arbor, Michigan	Varian, Palo Alto, California
References	22-24	16, 91, 97, 99, 108	13, 17, 21, 65, 82, 91, 92, 100	15, 96	66, 93
Tube voltage	80 kV, 8 mA [22-24]		120 kV, 2 mA [13, 82] 100 kV, 10 mA [17] 120 kV, 15 mA [92, 100] 120 kV, 10 mA [21]	125 kVp, 67.9 mAs [96]	100 kV, 2.3 mA [93]
Grayscale depth			4096 [13, 17, 21, 82]		
Scan time (seconds)	18 [22-24]	40 [16] 20-38 [99] 10 and 20 [97]	9.6 [13, 92, 100] 10[21]	10 [15] 20 [15] 40 [15]	≤60 [66]
Rotation		360°			
Field of view (cm)	10 [22-24]	13[16]	12 [13, 82] 15 [17, 92] 19 [17]		20x20x15 cm^3 [66, 93]
Slice thickness (mm)	0.08 [22-24]		0.377 [13] 0.3 [17] 0.37 [21]		
Slice number	580 [22-24]		512 [13, 82]		200-500 [66]
Voxel size		0.25 mm [16] 0.3 mm [99, 108]	0.3x0.3x0.3 mm [17, 92] 0.377 mm [82, 100] 0.6 mm[21]		0.5 mm [93]
Scanned volume dimensions					40 x 30 cm^2 [93]
Pixel set			1024x1024 [13, 82]		
Bits per pixel			12 [13]		
Data output		DICOM [16]	DICOM [13, 100]		
Patient positioning	Sitting upright [22-24]	Sitting upright [99]	Sitting upright [13, 17, 92, 100]		

Table 1.6

Reported conditions in CBCT evaluation of the upper airway

Head posture control	Yes	Frankfort plane perpendicular to the floor [20, 101, 102] Frankfort plane parallel to the floor [92, 97] Natural head position [63, 82] Craniocervical inclinations were examined to ensure they were between 90 and 110º [100] Head fixed in the operative position at the center of the C-arm using a brace [66] After image acquisition, head was oriented so that it was straight with no cant [21] After image acquisition, head was oriented according to a line 6º down from the sella-nasion as the horizontal axis [99]
	No	
	Not specified	13, 14, 18, 22-24, 84, 98, 103, 108
	Not relevant	16, 17, 86, 88, 93, 96, 105, 106, 109
Mandibular position control	Yes	In occlusion [14, 92] In maximum intercuspation [63, 82 101]
	No	18
	Not specified	13, 20, 21, 65, 84, 97, 99, 100, 102, 103
	Not relevant	16, 17, 22-24, 66, 86, 88, 93, 96, 98, 105-109
Tongue position control	Yes	The patient was asked not to swallow during the exposure [21, 63, 92]
	No	18
	Not specified	13, 14, 20, 21, 65, 82, 84, 97, 99-103
	Not relevant	16, 17, 22-24, 66, 86, 88, 93, 96, 98, 105-109
Breathing stage control	Yes	Modified Muller test [65]
	No	21, 99
	Not specified	13, 14, 17, 18, 21, 63, 82, 84, 97-101, 103
	Not relevant	16, 17, 22-24, 66, 86, 88, 93, 96, 98, 105-109
Threshold definition	Individually determined for each CBCT on the basis of a profile line and the correspondent vertical intersecting lines	14
	User-initialized 3D surface evolution	99
	Manual segmentation	20, 92
	Automatic segmentation	101, 103
	Not specified	13, 16, 18, 21-24, 63, 66, 82, 84, 86, 88, 93, 96-98, 100, 105-109

Table 1.7

Reported software used for viewing, measuring and analyzing the data from CBCT scanning of the upper airway

Software	***References***
Mimics (version 12.13, Materialise Interactive Medical Image Control System, Leuven, Belgium)	14
3D Doctor (Able Software Corporation, Lexington, Massachusetts)	18, 84
Dolphin 3D (Dolphin Imaging & Management Solutions, Chatsworth, California)	13, 82, 97
InVivoDental (version 4.0.70, Anatomage, San Jose, California)	13, 63
OnDemand3D (version 1.0.1.8407, CyberMed, Seoul, Korea)	13
OrthoSegment (Department of Orthodontics, School of Medicine, Case Western University)	13
VGStudio MAX1.2.1 (Nihon Visual Science, Tokyo, Japan)	17 92
3dMDVultus (3dMD, Atlanta, Georgia)	16
InsightSNAP (version 1.4.0, Cognitica, Philadelphia, Pennsylvania)	99
INTAGE Volume Editor (KGT, Tokyo, Japan)	100
CBworks (Cybermed Inc., Seoul, Korea)	21, 65
OsiriX Medical Imaging Software (Pixmeo, Geneva, Switzerland)	65 108
vWorks (Cybermed, Seoul, Korea)	102, 104
Amira (Mercury Computer Systems/3D Viz group, San Diego, California)	20, 103
ASAHI vision software (Asahi Roentgen Industry, Kyoto, Japan)	105
Micro AVS (KGT, Tokyo, Japan)	105
Idixel (Morita, Kyoto, Japan)	22-24
Syngo (Siemens Medical Solutions)	93
DICOM viewer not specified or not used	66, 86, 88, 96, 98, 107

Table 1.8

Anatomical limits of the upper airway (in the sagittal plane) as reported in the literature included in the SR (PUBMED, National Library of Medicine, NCBI; search revised January 9th, 2011)

Nasal airway	Anterior limit: ANS (frontal plane perpendicular to the FH plane passing through ANS [63]
	Posterior limit: PNS (frontal plane perpendicular to the FH plane passing through PNS [63]
Oral airway	Anterior limit: Incisive canal and midline of the upper incisors [82]
	Posterior limit: not reported
Nasopharynx	Superior limit: *Last slice before fusion of the nasal septum with the posterior wall of the pharynx [13] *Intersection of the line PNS-So (midpoint of the sella-basion line) and the posterior wall of the pharynx [14] *Soft tissue contour of the posterior pharyngeal wall extending from the superior aspect of the pterygomaxillary fissure [18] *Plane perpendicular to the plane through PNS at the height of the pterygomaxillary fissure [84] *Highest point of the nasopharynx, coinciding with the posterior choanae [99] *Posterior nasal plane (frontal plane perpendicular to the FH plane passing through PNS [63]
	Inferior limit: *Palatal plane (ANS-PNS) extended to the posterior wall of the pharynx [13, 18, 82, 84, 100, 101] *Plane including the PNS and the lower medial border of the 1st cervical vertebra [99] *Plane including the PNS and basion [92] *Plane parallel to the FH plane passing through PNS [20, 63, 102]
Oropharynx	Superior limit: ~ inferior limit of the nasopharynx.
	Inferior limit: *Plane parallel to the palatal plane that passes through the most anteroinferior point of the 2nd cervical vertebra [13, 103] *Plane parallel to the FH plane that passes through the most anteroinferior point of the 2nd cervical vertebra [20, 102] *Horizontal line through the superior point of the epiglottis [14, 92, 101] *Horizontal line through the base of the epiglottis [100] *Plane tangent to the most caudal medial projection of the 3rd cervical vertebra perpendicular to the sagittal plane [99] *Plane extending from the most anteroinferior point on the body of the 3rd cervical vertebra to the base of the epiglottis [82] *Plane parallel to the FH plane passing through the superior margin of the epiglottis [63]
Hypopharynx / laryngopharynx	Superior limit: ~ inferior limit of the oropharynx
	Inferior limit: Plane connecting the entrance to the esophagus to the body of the hyoid bone and left and right greater horns of the hyoid [92]

FH: Frankfort horizontal; ANS: anterior nasal spine; PNS: posterior nasal spine.

Discussion

The interest in dedicated CBCT scanners for the oral and maxillofacial region has increased exponentially since their introduction in the late 1990's [110, 111]. As a result, new possibilities and applications of CBCT have arisen in the fields of Oral and Maxillofacial Surgery, Dentistry and Otorhinolaryngology. Upper airway analysis in particular has become increasingly relevant mainly due to the relationship between morphological airway characteristics and craniofacial growth, dentomaxillofacial pathology and OSA. Due to its easy access, low cost and decreased radiation compared to multidetector CT and especially its capability to accurately define the boundaries between soft tissue and empty spaces (air), CBCT has become an unprecedented diagnostic method to analyze the airway three-dimensionally [14, 15]. As a result, the number of publications related to upper airway evaluation with CBCT has increased significantly during the last few years (Fig. 1.1). Although a SR of the literature on CBCT imaging of OMF region in general has already been performed [27], to our knowledge this is the first SR on CBCT evaluation of the upper airway.

Objective airway evaluation is possible by several techniques including multidetector CT and MRI. There is still a lack in basic clinical research to quantify and analyze the upper airway with multidetector CT and MRI protocols in the clinical routine [95]. CBCT technology has emerged as a potential alternative to obtain a thorough 2D and 3D evaluation of the upper airway at relatively modest costs, with easy access and short scanning time compared to conventional CT. Other major benefits of CBCT include the potential for vertical scanning in a natural seated position, easy handling, DICOM compatibility and high resolution [27]. Moreover, compared to standard multidetector CT, CBCT exposes the patient to substantially lower radiation [22-27, 64-66]. Although MRI is still superior in soft tissue rendering [93], its use is limited by its cost and restricted accessibility [14].

After meticulous scrutiny, this SR included a total of 46 relevant papers on CBCT imaging and analysis of the upper airway. As previously noted, [27] there was great inconsistency and discrepancy in how authors reported the settings of the CBCT devices used in their studies (Table 5). The reported conditions of CBCT image acquisition and threshold definition were also very irregular and often unreported (Table 6). De Vos et al. [27] recommended a minimum set of parameters for dedicated oral and maxillofacial scanners. Systematic report of these factors would reduce the reader's confusion and enable unbiased comparisons between different studies.

In particular, patient positioning during data acquisition is of major importance. While the patient is scanned in a supine position in some devices, other CBCT apparatus scan the patient in a vertical seated position (Table 5). The upright position is closer to the natural head position (NHP) and recommendable for baseline assessment of upper airway morphology and dimensions. Moreover, it allows excellent visualization of the pharyngeal recess, the “fossa of Rosenmüller”, a frequent location of nasopharyngeal carcinoma [64, 92]. Conversely, the supine position offers an incomplete representation of the upper airway but is very adequate for OSA research. Sutthiprapaporn et al. [92] studied the response of oropharyngeal structures to gravity by comparing the position of key anatomical landmarks in patients sitting upright (using CBCT) versus supine position (using multidetector CT). The authors found the soft palate, epiglottis and entrance of the esophagus moved caudally with a change from supine to sitting upright, and posteriorly when the position changed from upright to supine. Interestingly, the hyoid bone moved caudally but not posteriorly in response to the same postural changes. As anticipated, they found the cross-sectional area in the upright position was larger than in the supine position. These findings imply that morphological changes in the upper airway and related soft tissues should be expected as a result of gravity and posture. Other studies confirmed the size of the pharyngeal airway changes with different head positions [112-114]. In fact, a strong correlation between the posterior airway space and head posture defined by the craniocervical angulation at the uppermost part of the cervical spine has been reported [113]. This study found that a change of 10 degrees in craniocervical angulation could produce a 4 mm change in posterior airway space. Another important issue is manipulation of head posture by stabilizing the patient’s head during CBCT scanning (e.g. with a strap around the forehead or a chin platform) in order to optimize resolution by minimizing patient movement. The first generation iCAT devices enabling vertical scanning of the patient required the technician to position the patient with a strap around the forehead and a chin support. A prominent chin was prone to cause extension of the head, while less prominent chins the opposite [99]. The new generation iCATs advocate only the strap around the forehead but no longer the chin platform for airway studies. Other CBCT apparatus furnishers propose to avoid a forehead strap and to orientate the patient towards NHP with the aid of a mirror or a laser beam. The variability of NHP between individuals and also at different time points for the same subject, however, is still controversial and direct reproducibility continues to be questionable [115, 116]. Comparisons of qualitative and quantitative studies of the upper airway should systematically involve an evaluation of how head posture was controlled since it may affect the results.

As far as software is concerned, numerous software packages are dedicated to manage and analyze DICOM records. Many of them have incorporated tools to segment and measure the airway. In their study to compare the accuracy and reliability of three different DICOM viewers, El et al. [13] found calculation of upper airway volume with three commercially available viewers (Dolphin3D®, InVivoDental® and OnDemand3D®) to be reliable. Results showed a high correlation but nevertheless poor accuracy, suggesting systematic errors.

Table 7 lists the 18 different software packages that were reported for viewing and analyzing CBCT data of the upper airway according to this SR. Unfortunately, validation studies with a clear study design were only performed in 4 (22%) of the latter software packages. Consequently, the results of some studies are scientifically questionable and comparisons among papers become prone to analysis bias. Indeed, decent studies assessing the accuracy and reliability of current and new software packages have to be conducted before these applications can be implemented for airway analysis.

One important software-related issue is thresholding. The 3D image of a CBCT scan is the result of surface or volume rendering of the DICOM data. In volume rendering each gray value of the volume image is assigned a color and opacity, while in surface rendering a threshold filter, defined by the user, is applied [117]. Manual segmentation based on surface rendering seems to be more accurate but is significantly more time-consuming and not practical for clinical purposes [13, 18]. The automation of image-analysis procedures has the advantage of being less prone to observer error [91]. Most studies in this SR did not specify the threshold definition in their methodology. Lenza et al. [14] reported the use of a single threshold value to segment the airway in each patient's CBCT scan. This approach may generate errors especially in volume analysis, but it is certainly more reproducible than the use of a dynamic threshold.

Although the advent of CBCT allows clinicians to steer away from the limitations of conventional cephalometrics, other obstacles arise and need to be solved: (1) influence of respiration phase; (2) influence of tongue position and mandibular morphology; (3) longitudinal and cross-sectional upper airway evaluation and (4) 3D CBCT definition of the anatomical boundaries of the upper airway. Regarding the first two issues, changes in airway dimensions and shape depending on the breathing stage have been acknowledged [58, 59, 118]. However, there are no normative data currently available [82]. Newer scanners have reduced acquisition times to about 10 seconds, so respiratory phase control is practicable. This enables, for example, the performance of a Muller test during data acquisition. With this manoeuvre and modified variants, volumetric measurements can be performed under different negative inhalation pressures, thereby measuring the plasticity of the airway and its tendency to collapse [65]. This SR revealed most studies did not control respiratory phase during data acquisition and/or did not refer to it in the materials and methods section (Table 6). Similarly, the position of the mandible and tongue, which have been shown to influence the shape and size of the oropharyngeal airway [101], were not specified by most papers included in this SR either (Table 1.6). As far as longitudinal and cross-sectional upper airway evaluation is concerned, there is still a need to allow comparison of CBCT to conventional cephalograms [91]. In order to compare CBCT images with 2D data, virtual cephalograms and multiplanar slices can be reconstructed out of the CBCT data by mathematical algorithms [14, 117]. Linear accuracy of CBCT virtually-reconstructed lateral cephalograms has meanwhile been validated [119, 120]. Subsequent superimposition of 2D and 3D data becomes feasible theoretically for evaluation of treatment outcome and growth assessment. The patient's head could be virtually oriented to a position that permits image superimposition. However, in the context of upper airway analysis, intra- and inter-individual comparisons are very dependent on the patient's head posture during CBCT data acquisition. Unfortunately, virtual head orientation cannot obviate this problem and only includes analysis bias. Therefore, in CBCT upper airway assessment it is crucial to consider and report patient positioning properly to avoid erroneous conclusions [82, 91, 92]. Another important obstacle to comparison among studies is the 3D definition of the different anatomical regions of the upper airway. This SR showed that anatomical definitions of the airway from the nasal and oral cavities to the larynx were extremely variable (Table 8). As a result, the boundaries of a particular region of interest should be carefully defined in the materials and methods section in order to allow accurate interpretation of quantitative analyses of the airway and permit comparison between papers.

As far as the indications for CBCT imaging and analysis of the upper airway are concerned, this SR revealed 4 major groups: (1) craniofacial growth and morphology; (2) effect of combined orthodontic-surgical treatment on airway; (3) OSA and (4) sinus pathology. The relationship between respiratory function and craniofacial growth and morphology has been studied for decades. There is a vast amount of literature this topic, although most studies are 2D. Multidetector CT evaluation of the upper airway offers high-quality images, but due to its high radiation dose it is restricted to patients with severe craniofacial deformities or undergoing orthognathic surgery [63]. The fact that radiation is significantly reduced with CBCT has widened the range of indications of upper airway analysis. Besides, CBCT is able to provide accurate measurements of cross-sectional areas and volumes [16-18, 20-26, 63]. This SR included three papers emphasizing the effects of respiratory function on craniofacial growth and morphology based on CBCT studies [63, 99, 101]. According to these, it seems 3D airway measurements do not exhibit sexual dimorphism [63, 99, 101]. Conversely, volumetric measurements of the airway are significantly correlated to anteroposterior and vertical cephalometric variables [63, 100]. Indeed, recent studies have shown airway volume and shape vary significantly among patients with different anteroposterior jaw relationships [63, 99, 100]. Some authors report healthy preadolescent children with retropositioned mandibles have decreased total pharyngeal airway volumes [63], while others find class III malocclusion in this age group is associated to a larger oropharyngeal airway and intraoral space [100]. When comparing various vertical jaw relationships, however, it is airway shape but not volume that differs [99] .

Changes in airway volume and shape after surgical-orthodontic treatment of dentofacial anomalies have also been assessed with CBCT [82, 97, 98, 101]. Craniofacial abnormalities have been linked to the pathogenesis of OSA due to their repercussion on the dimensions of the upper airway. In particular, there is a concern that maxillary constriction leads to inferior repositioning of the tongue, which can result in oropharyngeal airway narrowing. Studies have shown growing patients with maxillary constriction have a smaller retropalatal airway volume than age- and sex-matched controls [101]. An increase in nasal width and maxillary basal bone width has been shown after RPE [97, 101]. However, there is no evidence to support RPE increases the oropharyngeal volume [101]. Similarly, no statistically significant oropharyngeal airway volume changes have been found between cases treated with premolar extractions versus non-extraction treatments, despite anticipated changes in the angulation and position of the incisors and subsequent tongue repositioning [82].

Significant anatomical differences between OSA patients and normal subjects have been reported regarding mandible size and position, posterior airway space morphology and dimensions, tongue size and position, and soft palate morphology [20, 26, 102-104]. In children and young adults, adenotonsillar hypertrophy has been emphasized as a major risk factor of OSA [26, 63, 102]. Similarly, the turbinates can protrude significantly into the nasopharyngeal airway space and cause severe airway restrictions too [18]. Craniofacial skeletal abnormalities are another acknowledged risk factor for OSA in children and non-obese adults [20, 63, 99-102, 104]. Since its introduction, CBCT has significantly contributed to improve the understanding of the pathophysiology of OSA and aid in treatment planning of surgical and non-surgical interventions. Compared to conventional 2D cephalometry, a 3D evaluation of the airway as provided by CBCT can better assess the cross-sectional and volumetric dimensions of the airway [18, 20, 26, 63, 82, 99-103]. Moreover, a major disadvantage of cephalometric measurements is the fact that the patient is scanned in an upright posture (which is not a natural sleeping position), while OSA events typically occur when the patient is asleep supine. Therefore, the Newtom device, which is currently the only commercially available CBCT that images the patient in supine position, is ideal for OSA studies [102]. In these, the most common measurements to compare the static morphology of the upper airway between OSA patients and healthy controls are the minimum surface area of the oropharynx and the anteroposterior and lateral dimensions of this area [20, 102, 104]. Research has shown the minimum cross-sectional area of the upper airway is significantly smaller in OSA patients [20, 102-104] and has been described at the dorsum of the tongue to the posterior pharyngeal wall on the bisected occlusal plane [14, 21, 26, 92] or at the most posteroinferior point of the soft palate to the line perpendicular to Frankfort horizontal passing through porion [14, 20, 26, 92]. In addition, the morphology of the upper airway in OSA patients is more spherical or elliptical than in non-OSA subjects [20, 102]. No statistically significant differences between the airways of male and female OSA patients have been found [104].

Finally, focusing on the radiological display of the paranasal sinuses, CBCT has become a useful alternative to traditional multidetector CT due to its high resolution, ease of use, low radiation, in-office clinical availability and comparatively low costs [15, 22-25]. It seems the quality of CBCT imaging of the sinuses is directly related to the scan time and radiation dose [15]. With correct patient positioning, a selected volume of 10 x 10 cm is sufficient to display the nasal cavity, lateral nasal wall, paranasal sinuses and adjacent vital structures [24]. Various studies have tested the efficiency of CBCT as a diagnostic modality of the anterior skull base [22-24]. In this context, CBCT has proved to be a valuable tool to assess the olfactory area. Preoperative, bilateral evaluation of the latter region is mandatory in order to avoid complications during sinus surgery [22-24, 66]. Intraoperative CBCT guidance during paranasal sinus surgery is also a possibility nowadays. It is especially desirable in areas that are close to vital anatomical structures, distorted anatomy, revision sinus surgery, extensive sino-nasal polyposi and increased risk of intraoperative bleeding [66, 106].

In conclusion, the results of this SR confirm CBCT is an accurate and reliable tool for upper airway evaluation [16-18, 20-26, 63]. This includes the assessment of the paranasal sinuses [22-25, 64, 66, 107]. Lateral headfilms offer limited information about the airway, with the inherent errors of a 2D representation of a 3D structure and the lack of information about cross-sectional area and volume [14, 18, 20, 24, 63, 84, 99-102]. The advent of CBCT has provided the opportunity to precisely assess the cross-sectional area and volumetric depiction of the upper airway with an accessible, rapid, non-invasive, low-radiation scan. Important obstacles, however, still need to be addressed, including: (1) influence of tongue position and mandible morphology; (2) impact of respiration phase; (3) longitudinal and cross-sectional 3D CBCT upper airway evaluation and (4) 3D CBCT definition of the anatomical boundaries of the upper airway. Moreover, authors should make an effort to overcome the inconsistency in reported CBCT settings and conditions, DICOM software and assessed regions in order to facilitate the integration of information and permit unbiased comparison among studies.

5. Paper two

Effect of Mono- and Bimaxillary Advancement on Pharyngeal Airway Volume: Cone-beam Computed Tomography Evaluation

5.1. ARTICLE DESCRIPTION

Title:

Effect of Mono and Bimaxillary Advancement on Pharyngeal Airway Volume: Cone-beam Computerized Tomography Evaluation

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5.2. ABSTRACT

Purpose:

To evaluate pharyngeal airway volume changes after forward movements of the maxilla, mandible or both using CBCT.

Patients and methods:

A retrospective evaluation of 30 patients who underwent maxillomandibular advancement, maxillary advancement or mandibular advancement was performed. Three groups comprising 10 subjects each were established as follows: Group 1: Bimaxillary surgery (Le Fort I maxillary osteotomy and mandibular bilateral sagittal split osteotomy (BSSO) with maxillomandibular advancement); Group 2: Maxillary advancement (Le Fort I maxillary osteotomy); and Group 3: Mandibular advancement (BSSO). Pre and postoperative CBCT scans were taken in each case. Changes in pharyngeal airway volume were compared.

Results:

A statistically significant increase in pharyngeal airway volume occurred systematically. The average percentage increase was 69.8% in group 1 and 78.3% in group 3. Group 2 exhibited a lower magnitude increase (37.7%).

Conclusions:

CBCT provides a new means for airway evaluation using a non-invasive, rapid, low-radiation, cost-effective scan. It seems the influence of mandibular advancement on pharyngeal airway volume is greater than the effect of the forward movement of the maxilla.

5.3. MAIN TEXT

Introduction

Orthognathic surgery aims to restore proper dental occlusion and facial harmony through the modification of the position, shape and size of the facial bones. Bone movement implies secondary positional and tensional changes in the attached soft tissues. These new soft tissue relationships introduce significant changes in facial appearance and, in addition, in the pharyngeal airway space dimensions, especially when there is a significant anteroposterior component [40].

In truth, the tongue, soft palate, hyoid bone and related musculature are directly or indirectly attached to the maxilla and mandible; therefore, the dimensions of the oral cavity and pharyngeal airway change depending on the direction and magnitude of the skeletal movements [40, 48, 54]. Several authors have reported induction of sleep-related breathing disorders following isolated mandibular setback procedures [30-33]. Research has shown postoperative narrowing of the retrolingual and hypopharyngeal airway [30, 31, 33, 37-40] and posteroinferior displacement of the hyoid bone and tongue [39, 41, 42]. This is an issue receiving growing attention during the last two decades due to the potentially serious adverse systemic consequences of OSA.

On the other hand, favorable improvement of OSA can be achieved with maxillomandibular advancement [44-50]. An increase in pharyngeal airway space is achieved as a result of the advancement of the skeletal attachment of the suprahyoid and velopharyngeal muscles and tendons [44, 47, 49, 51]. Moreover, when counterclockwise rotation of the maxillomandibular complex is performed in patients with high occlusal plane morphology, the genial tubercles move forward more than the teeth, thereby maximizing the advancement of the hyoid bone, base of the tongue and related soft tissues [46, 52].

In the medical field, airway evaluation is possible by several techniques including MRI [59], cine-MRI [60], CT [58], endoscopy [61], and optical coherence tomography [62]. However, the advent of CBCT has provided the chance to evaluate the airway using a non-invasive, rapid, low-radiation scan. In their study to measure the human airway with CBCT, Tso et al. demonstrated this appliance achieves highly correlative linear, cross-sectional area and volumetric measurements besides morphometric analysis of the airway. They found the narrowest region in a subject who is awake, sitting upright and breathing quietly is located chiefly in the oropharynx [21]. Although several authors have studied pharyngeal airway and soft tissue changes after orthognathic surgery procedures using lateral cephalometry [30-33, 37, 38, 41-43] and CT [36, 39, 44, 51], there are no previous reports with CBCT evaluation. To our knowledge, this is the first study in the literature to assess the effects of orthognathic surgery, in particular mono and bimaxillary advancements, on the pharyngeal airway space using CBCT.

Patients and methods

A retrospective analysis of 30 patients who underwent orthognathic surgery during 2009 at the Institute of Maxillofacial Surgery and Implantology of the Teknon Medical Center (Barcelona, Spain) was performed. The Helsinki Declaration guidelines were followed. Being a retrospective analysis, the study was exempt from institutional review board approval. However, approval from the Ethics Committee on Clinical Investigation was nevertheless obtained to review patients' clinical files. Patients were randomly selected from the Institute's database according to the orthognathic procedure performed. Three groups comprising 10 subjects each were established as follows: Group 1: Bimaxillary surgery (Le Fort I maxillary osteotomy and mandibular bilateral sagittal split osteotomy (BSSO) with maxillomandibular advancement); Group 2: Maxillary advancement (Le Fort I maxillary osteotomy); and Group 3: Mandibular advancement (BSSO). Procedures involving changes in the transverse dimensions (segmented Le Fort I osteotomy, surgically assisted rapid palatal expansion, mandibular midline expansion) or isolated or combined genioplasty, were excluded for evaluation with the aim to analyze "pure" sagittal advancements without changes in hard palate inclination. Written informed consent was obtained in all cases. All procedures were performed by the same surgeon with the use of rigid fixation and postoperative box elastics for 2-6 weeks. Patients received routine preoperative and postoperative orthodontic treatments.

Every patient had pre and postoperative CBCT scans taken with the IS i-CAT version 17-19 (Imaging Sciences International, Hatfield, Pennsylvania). A 7-second scan was taken with the patient breathing quietly, sitting upright, with the clinical Frankfort horizontal plane parallel to the floor, the tongue in relaxed position, and the mandible in centric relation with a wax bite in place. The radiologic parameters used were 120 kV and 5 mA. Axial slice distance for each scan was 0.300 mm^3. The facial mode with the 23-cm FOV was used. Primary images were stored as 576 DICOM data files.

Each CBCT was processed using the SimPlant Pro Crystal software (Materialise, Leuven, Belgium). Special attention was paid to the correspondence of the hard palate and cervical vertebrae between the pre and postoperative scans in order to minimize the influence of head and cervical posture on airway evaluation. It was established that if this correspondence was not achieved despite having followed our head posture protocol, the patient would be excluded from evaluation.

In order to digitally excise the airway, a distinctive high-contrast border was defined using threshold segmentation. In the resulting set of masks (highlighted areas representing the region of interest within each slice), areas occupied by air corresponded to a range of CT units below the ranges for the denser soft tissue and bone. Threshold limits were modified to an appropriate range that adequately captured all spaces filled by air within the volume of each particular CBCT scan. Therefore, other areas besides the pharyngeal airway space were defined, including the oral cavity, maxillary sinuses, nasal cavity and trabecular matrix within dense bones. These undesired structures, together with any artifacts or background scatter, were eliminated by hand from each slice by using the tools “Edit Mask in Single Slice” and “Edit Mask in Multiple Slices”. Similarly, the air space above the palatine plane and below the plane tangent to the superior border of the body of the fourth cervical vertebra was eliminated from evaluation (Fig. 2.1).

Volume of the segmented region was calculated from the “Masks List Window”. A 3D display of the excised area was attained. In this way, a pair of values (pre and postoperative pharyngeal airway volume) and the corresponding pair of airway reconstructions was obtained for each patient (Fig. 2.2).

Data analysis was carried out using SPSS for Windows (v 15.0.1, SPSS Inc., Chicago, IL). Descriptive statistics was used for quantitative analysis. Each patient’s percentage variation in volume was calculated as follows: [Postoperative volume · 100 / Preoperative volume] – 100. Student’s t test for paired samples was used to compare pre and postoperative pharyngeal airway space volumes. The α level was set at 0.05.

Figure 2.1

Digital excision of the pharyngeal airway space in patient 3 (bimaxillary surgery):

Preoperative (left) and postoperative (right) CBCT scans

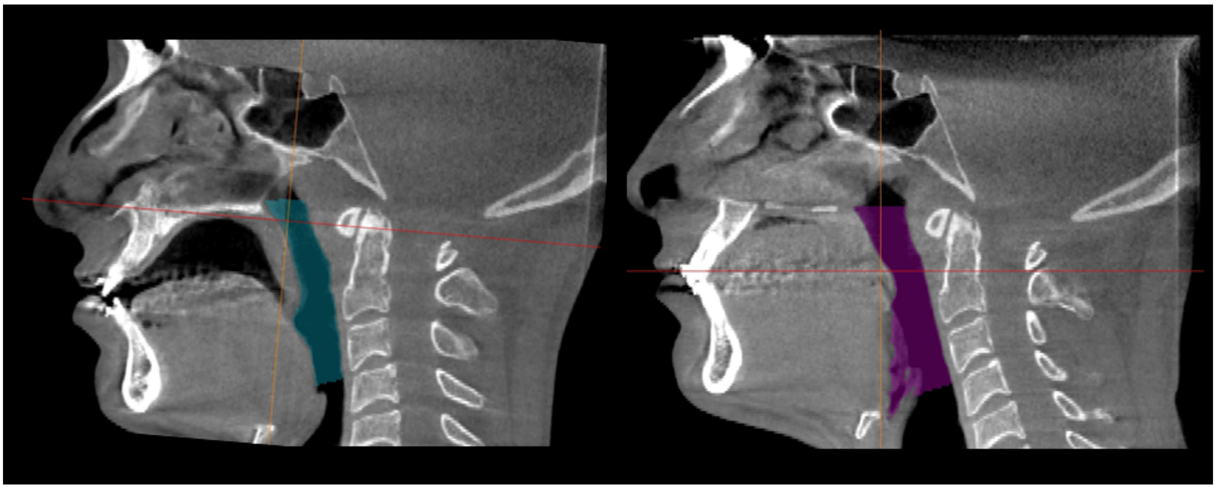
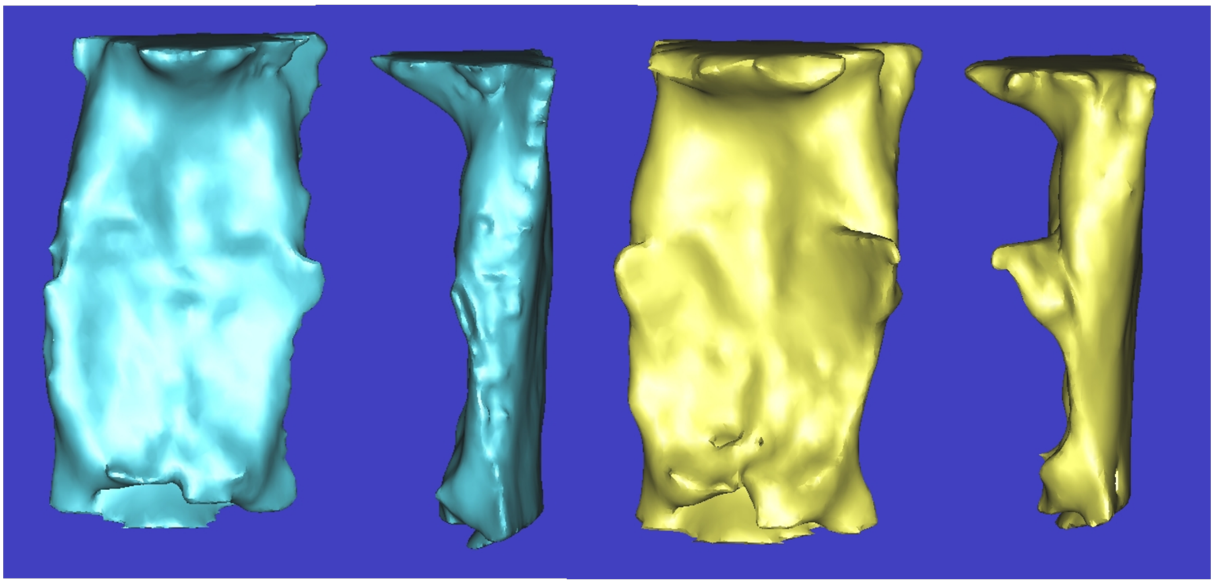


Figure 2.2

3D pharyngeal airway space of patient 3 (bimaxillary surgery):

Preoperative (left) and postoperative (right) volumes



Results

The studied sample comprised 22 women and 8 men with a median age at the time of surgery of 32.2 years. Preoperative scans were taken on the day before surgery. The average period of time elapsed between the pre and postoperative scans was 146.3 days for group 1, 132.9 days for group 2 and 121.4 days for group 3 (average for all 3 groups: 133.5 days).

Table 2.1 and figure 2.3 display the pre and postoperative volumetric measurements and percentage variation of airway volume in each group. The average variation was positive in all 3 groups, that is, an average increase in airway volume occurred systematically. The average increase was 68.4% in group 1 and 78.3% in group 3. Group 2 exhibited a lower magnitude increase (37.7%). For an α level of 0.05, these positive variations were found to be statistically significant ($t_{o=}$ 8,07, 29 degrees of freedom).

Figure 2.3

Pre and postoperative volumetric measurements and percentage variation of airway volume in the studied sample

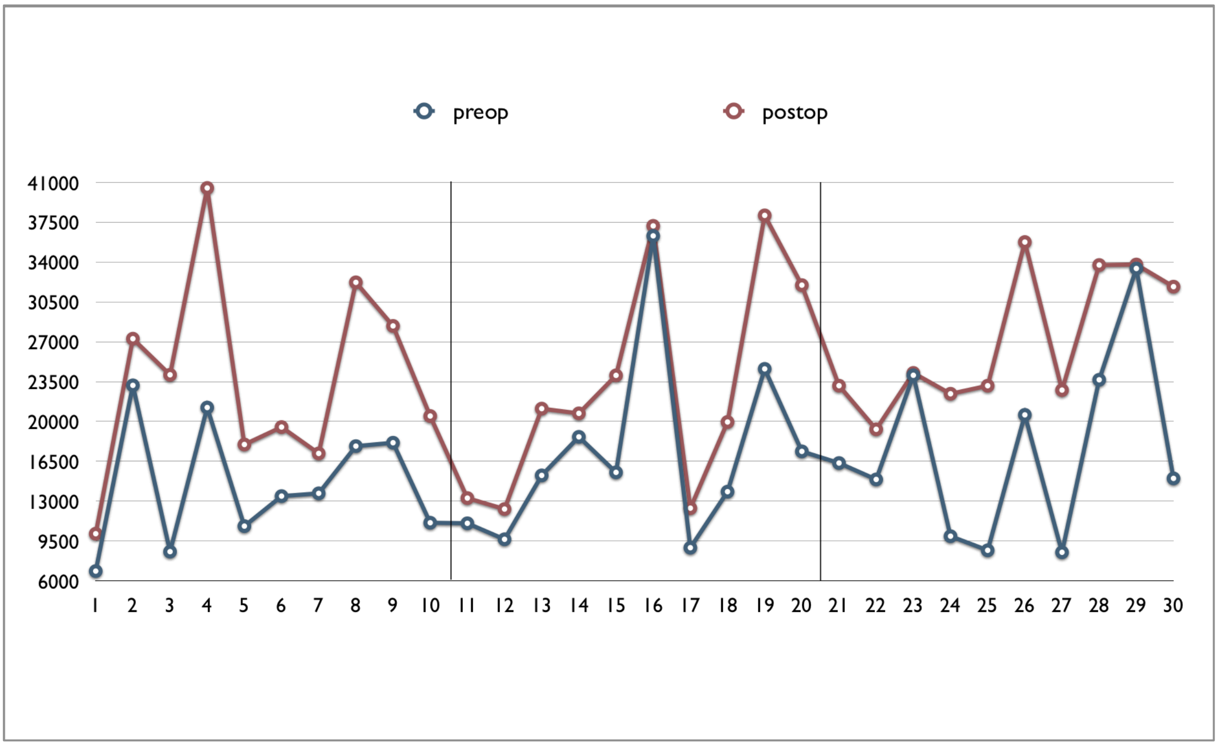


Table 2.1

Pre and postoperative measurements and percentage variation of airway volume:

Group 1: Bimaxillary advancement. Patients 1-10.

Group 2: Maxillary advancement. Patients 11-20.

Group 3: Mandibular advancement. Patients 21-30.

Patient	***Preoperative volume (mm^3)***	***Postoperative volume (mm^3)***	***Percentage variation (%)***
1	6851.61	10136.67	**47.9**
2	23173.56	27270.36	**17.7**
3	9077.91	24296.35	**167.6**
4	21225.29	40517.03	**90.9**
5	10803.17	17975.48	**66.4**
6	13439.98	19508.32	**45.2**
7	13683.65	17190.77	**26.6**
8	17832.68	32224.76	**80.7**
9	18131.64	28395.94	**56.6**
10	11100.53	20478.20	**84.5**
11	11051.06	13265.68	**20.0**
12	9644.50	12301.71	**27.6**
13	15260.35	21125.43	**38.4**
14	18647.53	20711.63	**11.1**
15	15526.51	24050.31	**54.9**
16	36309.92	37187.14	**2.4**
17	8905.06	12381.79	**39.0**
18	13831.24	19953.76	**44.3**
19	24620.72	38109.47	**54.8**
20	17371.64	31979.38	**84.0**
21	16345.32	23145.30	**41.6**
22	14904.35	19313.97	**29.6**
23	24058.36	24264.57	**0.9**
24	9918.28	22432.04	**146.3**
25	8677.63	23141.80	**166.7**
26	20580.04	35766.55	**73.8**
27	8504.14	22756.92	**167.6**
28	23662.25	33746.96	**42.6**
29	33442.49	33792.43	**1.0**
30	14996.70	31847.19	**112.4**

Discussion

To our knowledge, the present study is the first to evaluate changes in the pharyngeal airway after orthognathic surgery using CBCT technology. Cephalometric radiography has been used commonly to evaluate postoperative pharyngeal airway and soft tissue changes [30-33, 37, 38, 41-43]. This method was chosen on the basis that it is an essential imaging tool for orthodontic treatment planning and follow-up [39]. Although airway changes are only assessed two-dimensionally, a significant correlation between the pharyngeal airway space measured on the cephalographs and the volume of the airway calculated from CT studies was demonstrated [48]. Therefore, results are still relevant. However, it is difficult to evaluate the airway three-dimensionally with conventional cephalometric radiography, and hard tissue structures often overlap [39]. On the other hand, CT, especially with 3D reconstruction, permits excellent visualization of the pharyngeal airway without hard tissue superimposition and can create various types of images repeatedly [36, 39, 44, 50, 51].

Recently, CBCT has proven to be a practical technique for quantitative assessment of the pharyngeal airway space with important advantages over other current scanning systems: It is a non-invasive, low-radiation, fast scanning (< 60 seconds) technique which is more cost-effective than other systems such as spiral CT or MRI [21, 121]. The system is highly accurate in its measurements, images are not distorted and the relative range of CT units for different tissues provides a method to rapidly segment the airway [21].

However, CBCT does have some inherent deficiencies, in particular its static evaluation of the airway. Airway imaging studies have shown that airway dimensions change at different levels with breathing [58, 59], especially in the lateral dimension [122]. One weakness of our study is that the patient is scanned while breathing normally, suggesting that both inspiration and expiration contribute to the final airway volume that is calculated. It is essential that the patient does not to swallow, cough, speak or do any motor response other than breathe quietly during the scanning process [21]. Accordingly, besides standardizing a repeatable head posture protocol in our study, the patient was carefully instructed to breathe normally during the 7-second scan and avoid any other motor reaction.

Muto et al. reported a strong correlation (r=0.807) between the pharyngeal airway space and head posture defined as the craniocervical angulation at the uppermost part of the cervical spine: A change of 10° in craniocervical angulation produced a 4 mm change in the pharyngeal airway space [113]. Taking into account these findings, head posture correspondence between each patient's pre and postoperative CBCT scans was checked prior to airway volume measurement in our study. Using the SimPlant software, it was ensured that the hard palate plane and cervical vertebrae coincided at the superimposed sagittal midline in the pre and post scans. No significant discrepancy was found to exclude any subject from evaluation. A possible explanation to this is that particular care was taken to correctly position the patient for the scan (patient sitting upright, with the clinical Frankfort horizontal plane parallel to the floor, tongue in relaxed position, and mandible in centric relation with the help of a wax bite).

Our results support other authors' findings that maxillomandibular advancement can achieve an increase in the upper airway [44, 47, 49, 51]. A systematic increase in pharyngeal airway volume occurred in all cases. On average, bimaxillary and mandibular advancement achieved a percentage increase in airway volume of 69.8% and 78.3%, respectively. Maxillary advancement also increased the pharyngeal airway volume but to a lesser extent (37.7%). These results suggest the influence of mandibular advancement on the pharyngeal airway space is greater than the effect of the forward movement of the maxilla. In other words, the advancement of the skeletal attachment of the suprahyoid muscles and tendons could play a major role in the widening of the pharyngeal airway space. An ongoing study will try to determine if there is any correlation between the magnitude of skeletal forward movement and increase in pharyngeal airway volume.

The relationship between OSA and a narrow pharyngeal airway has been emphasized by numerous studies [30, 31, 33, 47]. Patients with OSA have a retropositioned mandible and maxilla, short mandibular body length and long anterior facial height when compared to age- and sex-matched controls [123, 124]. These craniofacial abnormalities can be minimized with maxillomandibular advancement, thereby improving OSA symptoms [44-50]. In this study, patients 1, 3, 10 and 25 reported subjective significant improvement of OSA symptoms postoperatively. Moreover, patient 10 stopped requiring CPAP nocturnal support after a bimaxillary advancement procedure. Therefore, forward movements of the mandible and/or maxilla in the context of orthognathic surgery procedures can be aimed at correcting malocclusion, restoring facial harmony, and improving OSA symptoms as a result of pharyngeal airway volume enlargement.

6. Paper three

Three-dimensional CBCT Definition of the Anatomical Subregions of the Upper Airway: a Validation Study

6.1. ARTICLE DESCRIPTION

Title:

Three-dimensional CBCT Definition of the Anatomical Subregions of the Upper Airway: A Validation Study

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6.2. ABSTRACT

The exact boundaries of the upper airway subregions remain undefined. Consequently, anatomical limits vary greatly among different research groups and impede unbiased comparisons. The aim of this study was to provide clinical three-dimensional anatomical limits for the upper airway subregions, translate them into accurate and reliable cephalometric landmarks in CBCT data, and validate the proposed measuring protocol. The upper airway of 40 normative individuals aged 23-35 years was evaluated with Dolphin Imaging® software. An appropriate grey-scale threshold value was pre-calculated. After adapting specific head positioning and virtual orientation protocols, the volume and minimum cross-sectional area of the nasopharynx, oropharynx and hypopharynx, as previously defined by the authors, were calculated. Intra- and inter-observer reliability was excellent for volumes and moderate for areas. Sexual dimorphism analysis revealed a significantly greater oropharyngeal volume, hypopharyngeal volume and minimum cross-sectional oropharyngeal area in males. In conclusion, the proposed subregion definition proved technical feasibility and statistical reliability, especially for 3D calculations. The reliability of 2D calculations may be increased with improved head positioning during CBCT scanning and subsequent virtual head orientation. Standardization of the proposed anatomical limits has the potential to homogenize upper airway subregion analysis and permit comparisons among future studies.

6.3. MAIN TEXT

Introduction

During the past decade, CBCT has become a widely acknowledged tool for oral and maxillofacial diagnosis and treatment planning. Besides its irrefutable advantages in lower effective radiation dose, lower costs, easy access and shorter acquisition times in comparison to conventional multidetector CT, its high spatial resolution between soft tissue and empty space provides an unprecedented method to analyze the airway three-dimensionally [1, 14, 125-127].

Recently, a SR of the scientific literature on CBCT imaging and analysis of the upper airway was performed [1]. It was found that 3D analysis of the upper airway using CBCT is accurate and reliable, though important obstacles still need to be addressed. These include the impact of respiration phase, influence of tongue position and mandible morphology, longitudinal and cross-sectional 3D CBCT upper airway evaluation, and 3D CBCT definition of the anatomical boundaries of the upper airway. Regarding the latter aspect, it was found that the anatomical definitions of the airway subregions from the nasal and oral cavities to the larynx were extremely variable among different authors. What is more, many studies included in the SR did not specify the anatomical boundaries of the particular region of interest in their methodology. As a result, comparison among studies, even between those claiming to analyze the same airway subregion, is often difficult and prone to error.

In this context, the objectives of this paper were the following: (1) To provide 3D anatomical limits for the different subregions of the upper (pharyngeal) airway; (2) To precisely translate these anatomical limits into cephalometric landmarks that can be used reliably in CBCT analysis; and (3) To validate a measuring protocol for the predefined subregions of the upper airway on a widespread third-party software.

Material and Methods

The study protocol was approved by the Local Ethics Review Board of the General Hospital St. Jan Bruges (Bruges, Belgium). CBCT scans from 40 healthy individuals (20 females and 20 males) were prospectively obtained. Inclusion criteria were the following: (1) Caucasian; (2) Age between 23 and 35; (3) Angle class I molar relationship; (4) Class I facial profile and no clinically obvious facial asymmetries; (5) Normal body mass index; (6) No prior surgery in the head and neck. Individuals in risk of sleep-disordered breathing according to the Epworth Sleepiness Scale [128], and with congenital or acquired craniofacial anomalies were excluded from evaluation.

Scans were performed using a standardized scanning protocol (i-CAT^{TM}, Imaging Sciences International, Inc., Hatfield, PA) between March and May 2011. The period of data acquisition was strictly limited to these dates in order to ensure the same calibration parameters. In addition, calibration of the CBCT apparatus was checked daily during the data acquisition period. Vertical scanning was performed in “extended field” modus (FOV 17 cm diameter, 22 cm height; scan time 2x20 sec; voxel size 0.4 mm) at 120 kV (according to DICOM field 0018,0060 kVp) and 48 mA (according to DICOM field 0018,1151 X-ray tube current). Special attention was paid to proper patient positioning for the scan: Patients were instructed to sit upright and position themselves in NHP [129, 130] with the help of a mirror and a laser beam. They were also taught to place the mandible in maximum intercuspation without the use of a wafer in order to avoid tongue displacement. They were asked to rest the tongue in a relaxed position, breathe lightly and avoid any other motor reaction.

The DICOM (Digital Imaging and Communications in Medicine) data were processed with a third-party software (Dolphin Imaging®, version 11.0, Chatsworth, CA). Prior to airway evaluation, all 40 CBCT databases were preliminarily assessed in order to determine the most appropriate threshold value for upper airway analysis in this study. The automatically fixed threshold value was manually increased for each dataset until the nasopharyngeal airway was adequately depicted. The average of all patients’ threshold values thus defined was 70 (range 48-81) and was established as the reference threshold for this study.

Subsequently, all CBCT datasets were evaluated separately by the two investigators of this study (RGM, GRJS) in order to determine the inter-observer error. In addition, each patient was reassessed separately by each investigator 4 weeks after the first evaluation with the aim to establish the intra-observer error. Separate spreadsheets were used for the first and second measurements in order to avoid analysis bias from the first results.

On multiple planar reconstruction images, the skull was reoriented to the Frankfort Horizontal (FH) using the following guidelines: (1) In the frontal view, the mid-sagittal plane was fixed through the centre of ANS (anterior nasal spine) and the axial plane was constructed through both *infraorbitale* skeletal landmarks. When a bifid ANS was encountered in the frontal view, the mid-sagittal plane was established at the midpoint between both bony prominences. (2) In the right sagittal view, the axial plane was placed through the right *porion* and right *infraorbitale* landmarks. For standardization, the left sagittal view was not processed in order to avoid orientation problems due to asymmetrically positioned *porions*. (3) In the transversal view (patient facing down or endocranial view), the mid-sagittal plane was constructed through *crista galli* and *basion*. In the opposite transversal view (patient facing up or exocranial view), it was ensured that no “yaw” (transversal rotation) of the mandible or the zygomatic arches was present. Fig. 3.1 illustrates the coronal, sagittal and axial reconstruction slices after head orientation in a male patient.

In the sagittal view, the cranial base angle and craniocervical inclination were additionally measured. The cranial base angle served for descriptive purposes of the analysed population sample; the craniocervical inclination was evaluated in order to test the homogeneity of head inclination during the scanner, and hence the effectiveness of our head positioning protocol. The cranial base angle was measured between the points *nasion, sella* and *basion,* as decribed by Enlow (Fig. 3.2). Following other authors’ recommendations [113, 131], the craniocervical inclination was measured as the angle between the line formed by connecting C2od (tangent point at the most superior-posterior point of the odontoid process of C2) and C2ip (the most inferior-posterior point of the body of C2) and the SN line *(sella-nasion)* (Fig. 3.3).

Figure 3.1

Coronal, sagittal and axial reconstruction slices after head orientation

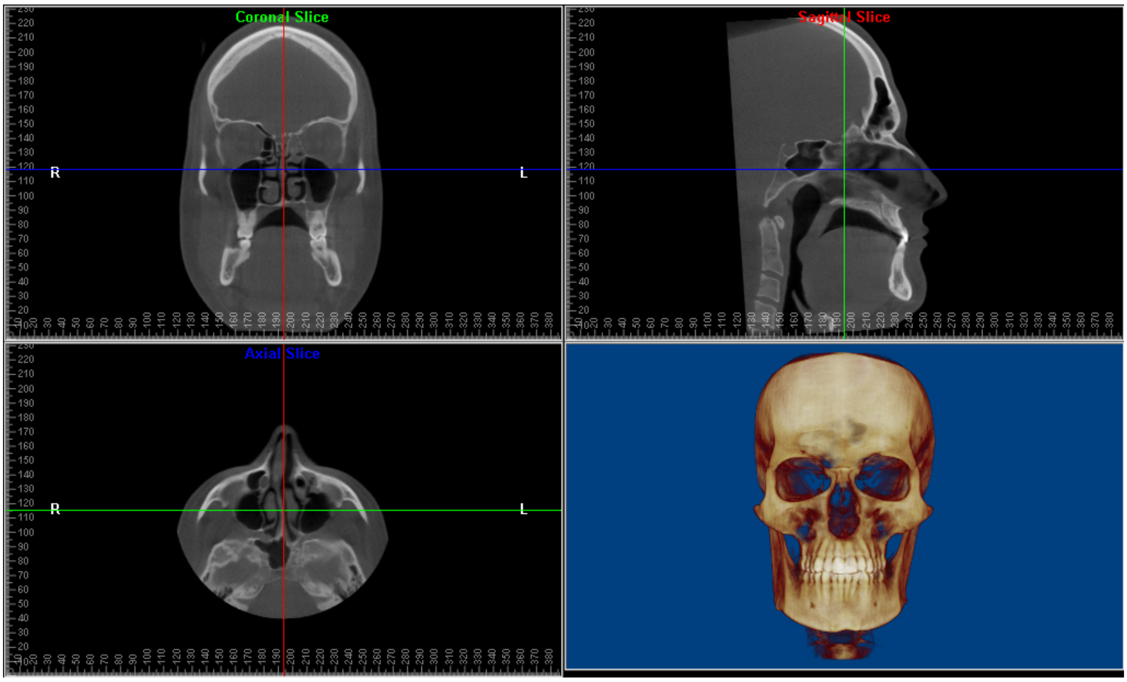


Figure 3.2

Cranial base angle

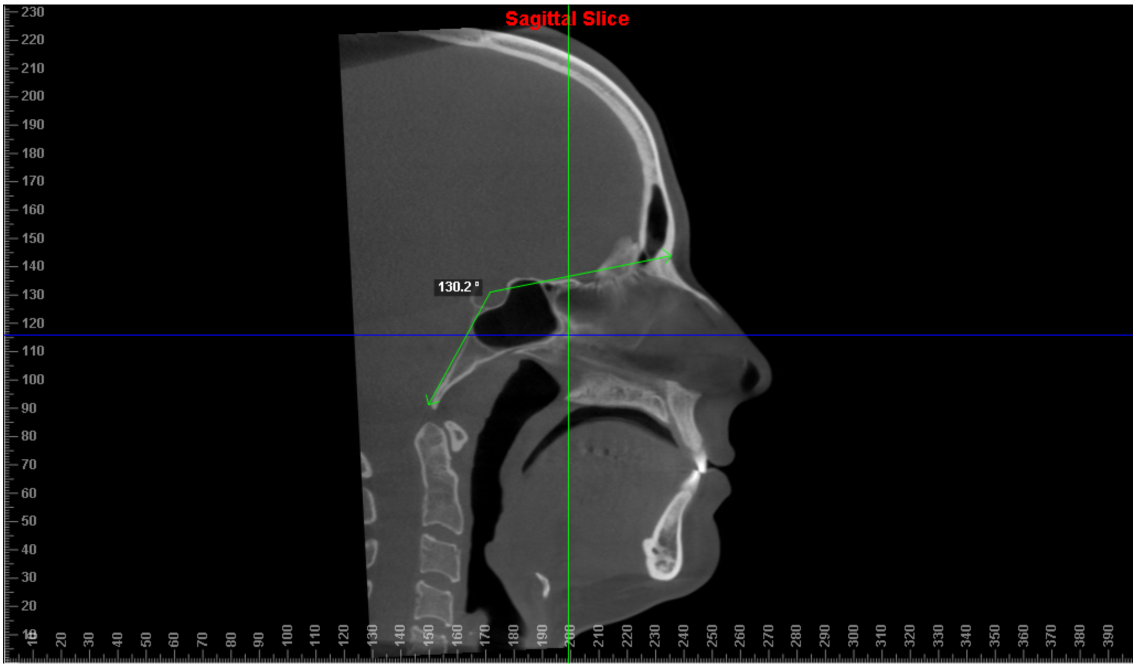
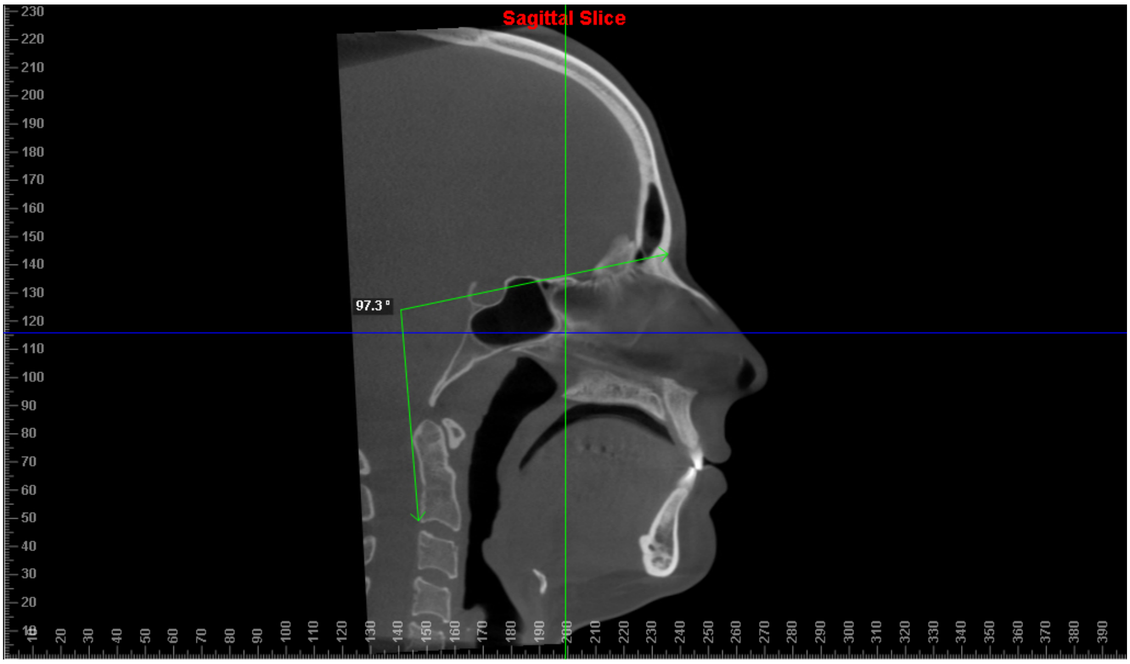


Figure 3.3

Craniocervical inclination



The process of airway segmentation was systematized as follows: A virtual marker for region-of-interest definition, referred to as “seed point” by the software, was placed in the airway region immediately anterior to C2ia (the most inferior-anterior point of the body of C2). The automatic threshold thus determined by the program was manually increased to the value of our predefined airway sensitivity (70). Subsequently, the limits of the nasopharynx, oropharynx and hypopharynx were outlined by the investigator. Within each separate region, the software calculated the total airway volume (mm^3) and minimum cross-sectional area (mm^2) automatically. The anatomical limits of each subregion were established by the authors according to clinical experience and previous work [1]. Ensuing technical boundaries were determined with the aim to define reproducible limits based on reliable anatomical cephalometric landmarks that are easily identifiable on CBCT studies. Table 3.1 details the anatomical and technical boundaries of each subregion of the upper airway. Figures 3.4 to 3.6 exemplify the independent evaluation of the nasopharynx, oropharynx and hypopharynx according to these limits. In the case of the hypopharynx, care was taken to add a second virtual “seed point” when the epiglottis was positioned half way across the air space of the airway in order to adequately include all the air within the predefined limits (Fig. 3.7).

Figure 3.4

Evaluation of the nasopharyngeal airway

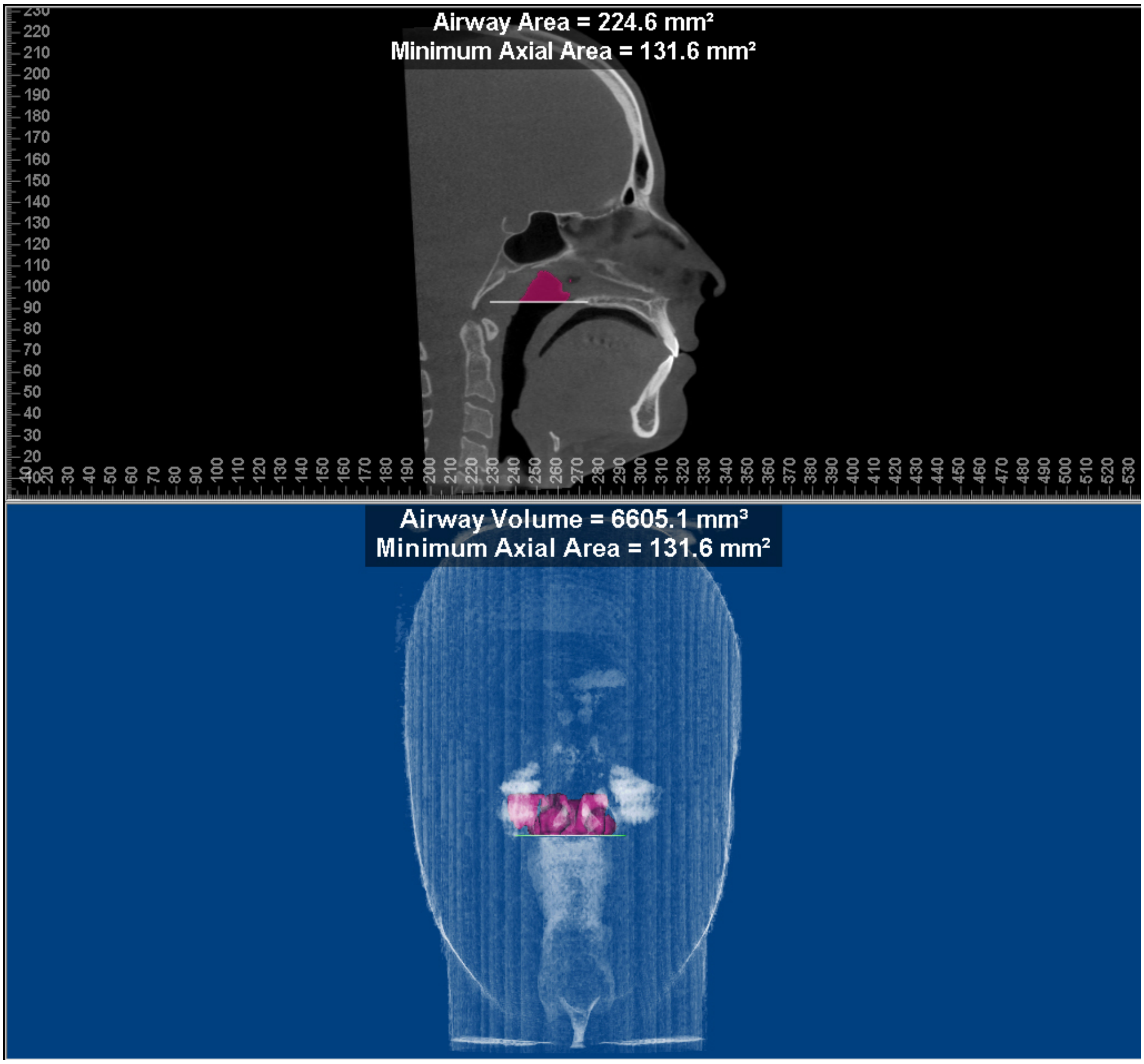


Figure 3.5

Evaluation of the oropharyngeal airway

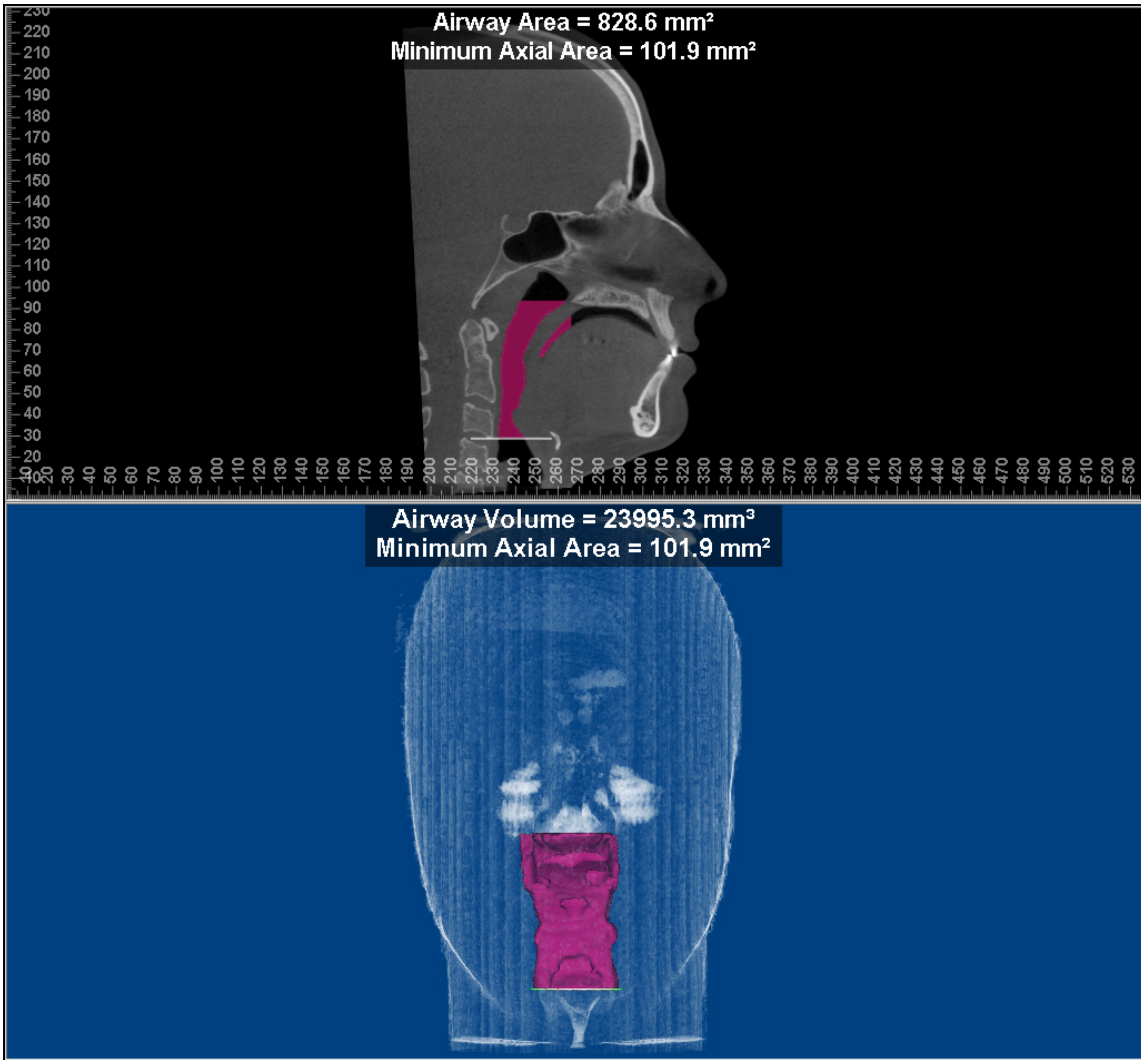


Figure 3.6

Evaluation of the hypopharyngeal airway

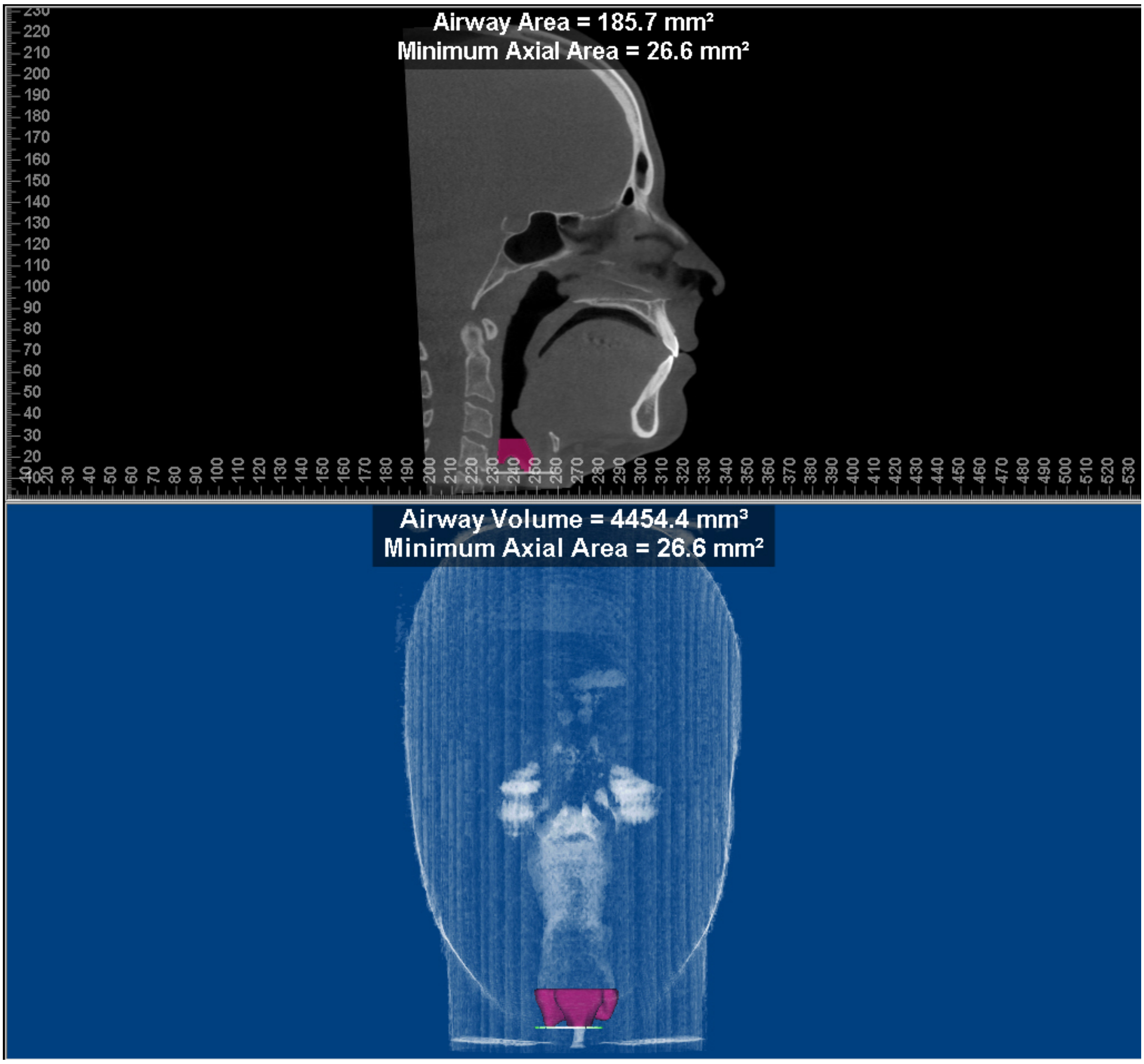


Figure 3.7

If the epiglottis was positioned halfway across the hypopharynx, thereby determining a secluded air space, a second virtual “seed point” was added in order to include this area / volume within the region of interest.

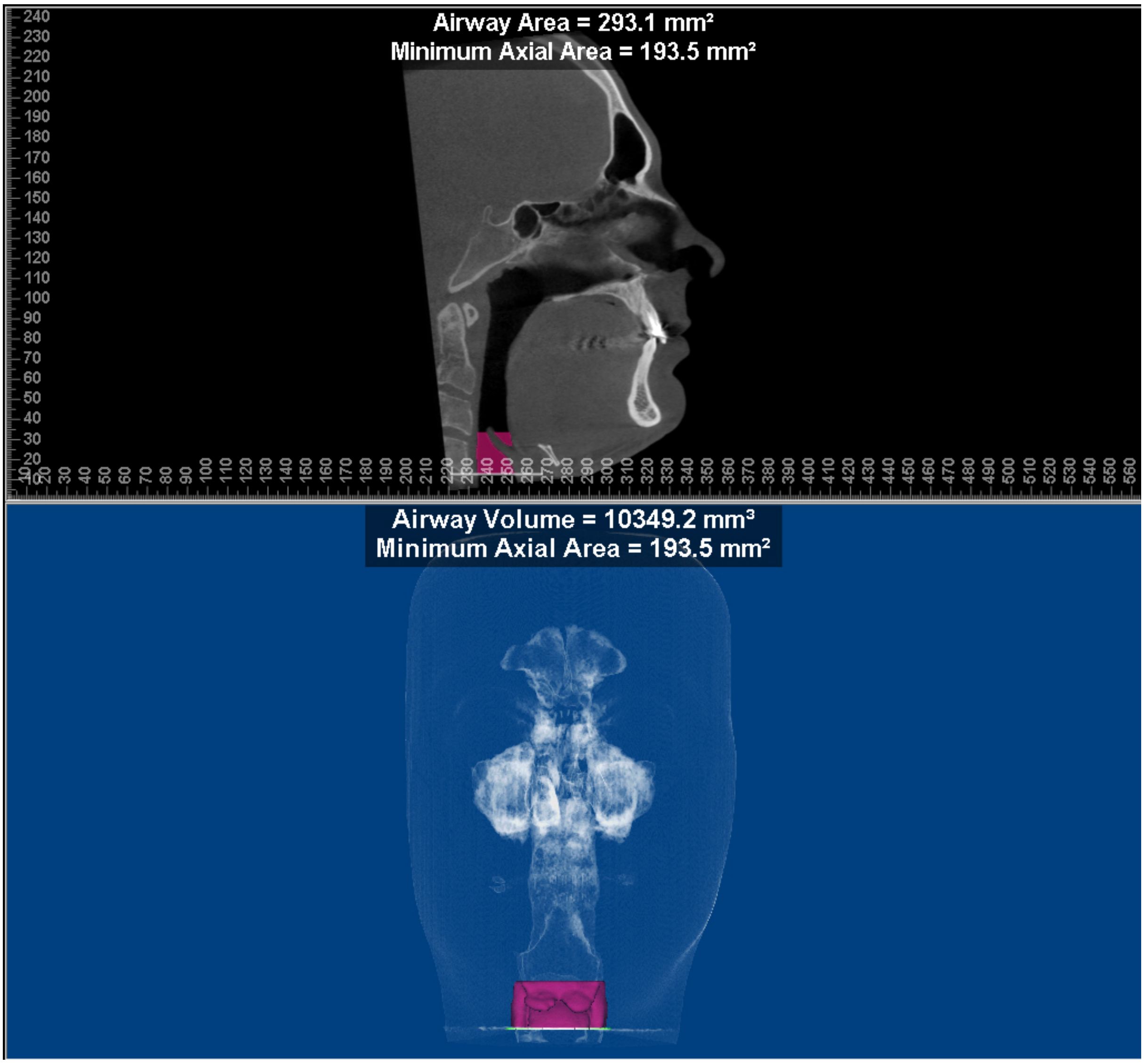


Table 3.1

Anatomical and technical limits of the upper airway

Region	Limits	Anatomical	Technical
NASOPHARYNX	**Anterior**	Frontal plane perpendicular to FH passing through PNS	=
	Posterior	Soft tissue contour of the pharyngeal wall	Frontal plane perpendicular to FH passing through C2sp
	Upper	Soft tissue contour of the pharyngeal wall	Transversal plane parallel to FH passing through the root of the clivus
	Lower	Plane parallel to FH passing through PNS and extended to the posterior wall of the pharynx	=
	Lateral	Soft tissue contour of the pharyngeal lateral walls	Sagittal plane perpendicular to FH passing through the lateral walls of the maxillary sinus
OROPHARYNX	**Anterior**	Frontal plane perpendicular to FH passing through PNS	=
	Posterior	Soft tissue contour of the pharyngeal wall	Frontal plane perpendicular to FH passing through C2sp
	Upper	Plane parallel to FH passing through PNS and extended to the posterior wall of the pharynx	=
	Lower	Plane parallel to FH plane passing through C3ai	=
	Lateral	Soft tissue contour of the pharyngeal lateral walls	Sagittal plane perpendicular to FH passing through the lateral walls of the maxillary sinus
HYPOPHARYNX	**Anterior**	Frontal plane perpendicular to FH passing through PNS	=
	Posterior	Soft tissue contour of the pharyngeal wall	Frontal plane perpendicular to FH passing through C2sp
	Upper	Plane parallel to FH plane passing through C3ai	=
	Lower	Plane parallel to FH connecting the base of the epiglottis to the entrance to the esophagus	Plane parallel to FH connecting the base of the epiglottis to C4ai
	Lateral	Soft tissue contour of the pharyngeal lateral walls	Sagittal plane perpendicular to FH passing through the lateral walls of the maxillary sinus

FH: Frankfort horizontal

PNS: Posterior nasal spine

ANS: Anterior nasal spine

C2sp: Superior-posterior extremity of the odontoid process of C2

C3ai: Most anterior-inferior point of the body of C3

C4ai: Most anterior-inferior point of the body of C4

Statistical analysis was performed with the Statistical Package for Social Sciences for Windows, version 19.0 (SPSS, Chicago, IL). Reproducibility was evaluated by calculating the inter- and intra-observer error with Dahlberg's formula [132]. Intraclass correlation coefficients (ICC) were obtained. Descriptive analysis was used to obtain preliminary normative data for the sample as a whole and also when stratified by gender. After corroborating the sample's normal distribution with Kolmogorov-Smirnov's test, Student's t test for independent samples was used to compare both sex groups. Repeated measures ANOVA was used to compare the three subregions of the upper airway. Friedman's test was used to stratify the analysis by gender. Statistical significance was fixed at $\alpha=0.05$.

Results

Of the initial 40 patients whose CBCTs were analysed, one male and one female were excluded because of inadequate localization of *crista galli* for skull orientation purposes, and 3 females were excluded for pathological radiological findings (hypertrophic adenoids in one case and inadequately ventilated sinuses in 2 other). Thus, the studied sample comprised n=35 subjects, of which 19 were males (54.3%) and 16 females (45.7%). Moreover, adequate hypopharyngeal analysis was impossible in 3 of these 19 males because the FOV did not include the most anterior-inferior point of the body of C4 (C4ai); in these 3 male patients, hence, only the nasopharynx and oropharynx were quantified.

Tables 3.2 and 3.3 summarize intra- and inter-observer reproducibility analysis, respectively. Whereas intra-observer error for volumetric calculations was below 4% for both investigators, it ranged between 11 and 20% for minimum cross-sectional area calculations. In terms of ICC, volumetric measurements ranged between 0.981 and 0.999 and thus were highly reproducible, but area measurements ranged between 0.780 and 0.937 and hence were moderately reproducible. The fact that all confidence intervals included 0, ruled out bias tendency when performing the second measurement for both investigators. Inter-observer error analysis revealed excellent reproducibility for cranial base angle and craniocervical inclination measurements (ICC 0.983 and 0.992, respectively), good reproducibility for volumetric calculations (ICC between 0.986 and 0.998) and again moderate reproducibility for cross-sectional area calculations (ICC between 0.837 and 0.876).

Table 3.2

Intra-observer error analysis

		Difference between first and second measurement		95% CI for the difference		Dahlberg's d	Relative error (%)	ICC
		Mean	SD	Inferior limit	Superior limit			
OBS 1	**Minimum cross-sectional area of the nasopharynx**	3.76	22.07	-3.56	11.08	15.61	19.74	0.848
	Nasopharyngeal volume	59.61	394.51	-71.23	190.44	278.16	3.73	0.981
	Minimum cross-sectional area of the oropharynx	-3.15	20.62	-9.98	3.69	14.54	15.92	0.780
	Oropharyngeal volume	5.94	459.72	-146.52	158.40	320.42	1.53	0.997
	Minimum cross-sectional area of the hypopharynx	-1.89	21.18	-8.91	5.14	14.82	14.60	0.904
	Hypopharyngeal volume	-31.95	220.01	-104.92	41.01	154.99	2.33	0.994
OBS 2	**Minimum cross-sectional area of the nasopharynx**	3.30	14.84	-1.62	8.22	10.60	12.11	0.937
	Nasopharyngeal volume	-33.67	259.65	-119.78	52.44	182.52	2.49	0.992
	Minimum cross-sectional area of the oropharynx	1.19	17.23	-4.53	6.90	12.04	13.45	0.825
	Oropharyngeal volume	42.29	308.55	-60.04	144.61	217.10	1.03	0.999
	Minimum cross-sectional area of the hypopharynx	2.32	17.46	-3.47	8.11	12.28	11.70	0.936
	Hypopharyngeal volume	-50.71	167.05	-106.12	4.69	121.82	1.84	0.996

OBS 1: Observer 1

OBS 2: Observer 2

SD: Standard deviation

CI: Confidence interval

ICC: Intraclass correlation coefficient

Means, SD and CI for volumes are expressed in mm^3. Means, SD and CI for areas are expressed in mm^2.

Table 3.3

Inter-observer error analysis

	Difference between OBS 1 and OBS 2		95% CI for the difference		Dahlberg's d	Relative error (%)	ICC
	Mean	SD	Inferior limit	Superior limit			
Cranial base angle	0.37	1.04	0.03	0.72	0.77	0.58	0.983
Craniocervical inclination	0.16	1.51	-0.34	0.66	1.06	1.11	0.992
Minimum cross-sectional area of the nasopharynx	-8.71	18.36	-14.80	-2.62	14.20	18.40	0.876
Nasopharyngeal volume	77.95	337.98	-34.14	190.04	241.92	3.26	0.986
Minimum cross-sectional area of the oropharynx	3.99	15.97	-1.31	9.29	11.48	12.36	0.837
Oropharyngeal volume	-30.91	435.79	-175.43	113.62	304.50	1.45	0.998
Minimum cross-sectional area of the hypopharynx	-0.99	27.18	-10.00	8.03	18.95	18.48	0.839
Hypopharyngeal volume	42.02	219.91	-30.91	114.95	156.11	2.34	0.994

OBS 1: Observer 1

OBS 2: Observer 2

SD: Standard deviation

CI: Confidence interval

ICC: Intraclass correlation coefficient

Means, SD and CI for volumes are expressed in mm^3. Means, SD and CI for areas are expressed in mm^2.

Table 3.4

Descriptive analysis

Measurement		N	Mean	SD	Typical error	95% CI for the mean		Min	Max	Median
						Inferior limit	Superior limit			
Cranial base angle	TOTAL	35	131.61	4.12	0.70	130.19	133.03	123.05	140.30	131.65
	Male	19	131.02	4.58	1.05	128.80	133.22	123.05	140.30	131.15
	Female	16	132.33	3.51	0.88	130.45	134.19	126.35	138.15	133.18
Craniocervical inclination	TOTAL	35	95.04	8.14	1.38	92.24	97.83	77.95	113.85	96.60
	Male	19	96.38	8.97	2.06	92.05	100.70	78.20	113.85	96.95
	Female	16	93.45	6.97	1.74	89.73	97.16	77.95	103.60	95.25
Minimum cross-sectional area of the nasopharynx	TOTAL	35	81.54	39.03	6.60	68.12	94.94	16.00	158.63	74.40
	Male	19	80.35	42.52	9.75	59.85	100.84	16.00	144.90	83.70
	Female	16	82.95	35.78	8.94	63.88	102.01	36.80	158.63	72.14
Nasopharyngeal volume	TOTAL	35	7385.84	2035.17	344.01	6686.73	8084.94	3842.85	11503.28	6859.18
	Male	19	7415.11	2101.63	482.15	6402.15	8428.05	4242.20	11503.28	6859.18
	Female	16	7351.09	2021.33	505.33	6273.99	8428.17	3842.85	10459.83	6981.99
Minimum cross-sectional area of the oropharynx	TOTAL	35	90.90	27.23	4.60	81.55	100.25	36.25	141.73	91.20
	Male	19	101.32	25.48	5.84	89.03	113.59	40.80	141.73	104.28
	Female	16	78.54	24.52	6.13	65.47	91.60	36.25	115.53	81.19
Oropharyngeal volume	TOTAL	35	20994.20	6104.37	1031.83	18897.27	23091.12	9297.43	39481.75	19306.43
	Male	19	23980.83	6241.83	1431.97	20972.35	26989.29	16008.13	39481.75	24510.53
	Female	16	17447.59	3604.90	901.23	15526.66	19368.50	9297.43	23991.90	17593.58
Minimum cross-sectional area of the hypopharynx	TOTAL	32	103.13	47.39	8.38	86.04	120.21	15.78	216.43	107.35
	Male	16	108.85	46.79	11.70	83.01	133.78	15.78	177.00	111.78
	Female	16	97.41	48.80	12.20	71.40	123.41	27.55	216.43	98.95
Hypopharyngeal volume	TOTAL	32	6654.92	2076.01	366.99	5906.44	7403.40	3341.73	10477.70	6366.20
	Male	16	8101.75	1799.95	449.99	7142.62	9060.87	3341.73	10477.70	7949.74
	Female	16	5208.09	1096.08	274.02	4624.03	5792.15	3706.75	7711.85	4995.26

N: Sample size

SD: Standard deviation

CI: Confidence interval

Min: Minimum

Max: Maximum

Angles and inclinations are measured in degrees. Volumes are expressed in mm^3 and areas in mm^2.

Table 3.4 shows the descriptive variables for the whole sample and for males and females independently. When analyzing sexual dimorphism with Student's t test for independent samples, males showed a significantly greater oropharyngeal volume (p=0.001) and hypopharyngeal volume (p<0.001) (Fig. 3.8). In addition, the minimum cross-sectional area for the oropharynx was significantly greater in males than in females (p=0.011) (Fig. 3.9).

Figure 3.8

Sexual dimorphism analysis for minimum cross-sectional areas: Student's t test for independent samples

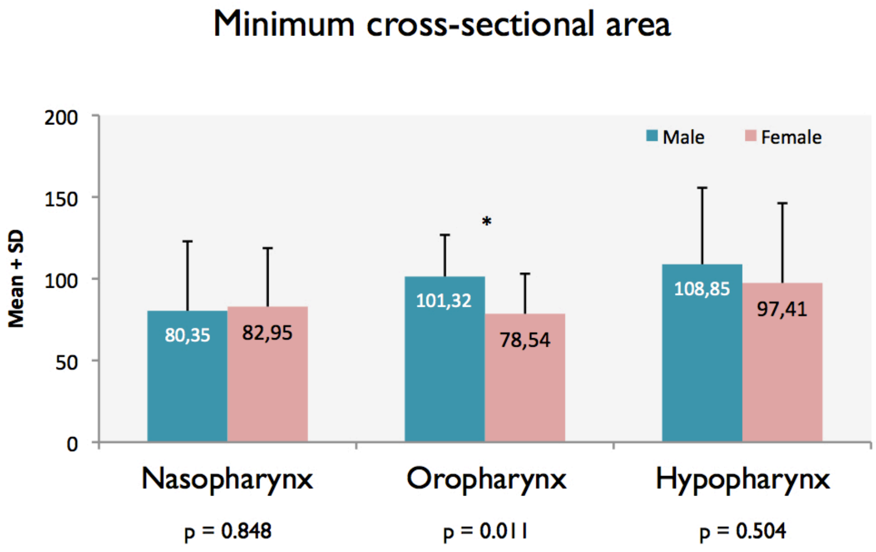


Figure 3.9

Sexual dimorphism analysis for volumes: Student's t test for independent samples

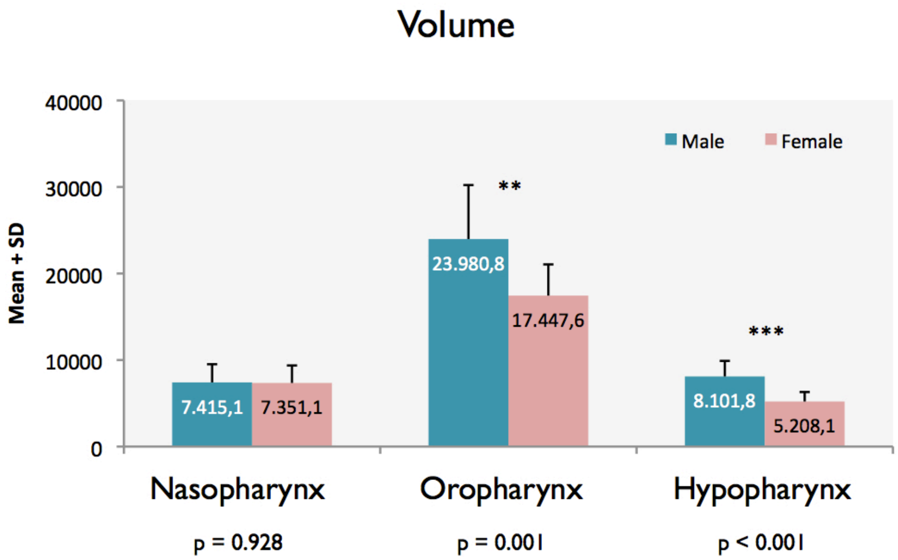


Table 3.5 summarizes the comparison between the three analysed subregions. Repeated measures ANOVA revealed the volume of the oropharynx was significantly greater (mean 20994.20 mm^3, SD 6104.37) than that of the nasopharynx (mean 7385.84 mm^3, SD 2035.17) and hypopharynx (mean 6654.92 mm^3, SD 2076.01). The volumetric superiority of the oropharynx was also confirmed separately on males and females. Cross-sectional area differences did not reach statistical significance, although they did show a marked trend (p=0.078). Paired comparisons suggested the most noticeable differences could be found between the nasopharynx and hypopharynx (p=0.059). In other words, while the minimum cross-sectional areas of the nasopharynx and oropharynx were similar, the nasopharyngeal area (slightly smaller according to the descriptive analysis) tended towards statistically significant inferiority compared to the hypopharynx.

Table 3.5

Comparison between the three anatomical subregions

		N	Mean	SD	p value
MINIMUM CROSS-SECTIONAL AREA IN TOTAL SAMPLE	**Nasoph.**	35	81.54	39.03	0.078 (F)
	Oroph.	35	90.90	27.23	
	Hypoph.	32	103.13	47.39	
MINIMUM CROSS-SECTIONAL AREA IN MALES	**Nasoph.**	19	80.35	42.52	0.269 (Fri)
	Oroph.	19	101.32	25.48	
	Hypoph.	16	108.85	46.79	
MINIMUM CROSS-SECTIONAL AREA IN FEMALES	**Nasoph.**	16	82.95	35.78	0.444 (Fri)
	Oroph.	16	78.54	24.52	
	Hypoph.	16	97.41	48.80	
VOLUME IN TOTAL SAMPLE	**Nasoph.**	35	7385.84	2035.17	**<0.001 (F)**
	Oroph.	35	20994.20	6104.37	
	Hypoph.	32	6654.92	2076.01	
VOLUME IN MALES	**Nasoph.**	19	7415.11	2101.63	**<0.001 (Fri)**
	Oroph.	19	23980.83	6241.83	
	Hypoph.	16	8101.75	1799.95	
VOLUME IN FEMALES	**Nasoph.**	16	7351.09	2021.33	**<0.001 (Fri)**
	Oroph.	16	17447.59	3604.90	
	Hypoph.	16	5208.09	1096.08	

N: Sample size

SD: Standard deviation

Nasoph.: Nasopharynx

Oroph.: Oropharynx

Hypoph.: Hypopharynx

F: Repeated measures ANOVA for comparisons in total sample

Fri: Friedman’s test for comparisons in males and females, respectively

Volumes are expressed in mm^3 and areas in mm^2.

Discussion

Currently, objective airway evaluation is possible by several techniques including CBCT, multidetector CT, MRI, cine-MRI, endoscopy and optical coherence tomography. However, due to its advantages over other routine imaging techniques such as multidetector CT (mainly in terms of lower radiation dose) and MRI (especially in terms of easier accessibility and lower costs), CBCT has become the method of choice for upper airway analysis. Recent research has confirmed its accuracy and reliability for this particular indication [1, 133].

The fact that systematized protocols for upper airway analysis with CBCT are still lacking in the clinical routine is due to the persistence of important obstacles. These include the following [1]: (1) impact of respiration phase, (2) influence of tongue position and mandible morphology, (3) longitudinal and cross-sectional 3D CBCT upper airway evaluation, and (4) 3D CBCT definition of the anatomical boundaries of the upper airway. Indeed, the lack of control of these variables hinders the definition of a methodical approach to upper airway evaluation. Substantial clinical research is needed in order to control systematic errors and enable unbiased comparisons between different studies.

Regarding the first two issues, most studies do not control or do not specify how respiration phase and lingual or mandibular position is managed during CBCT data acquisition [1]. This is surprising taking into account that qualitative and quantitative changes of the airway occur during different breathing stages [58, 59] and that the position of the mandible and tongue influence the shape and size of the oropharyngeal airway [101]. The patient should be instructed to avoid deglutition and any other movement during the CBCT scan, breathe lightly and maintain the mandible in a reproducible position, be it maximum intercuspation or centric relation [29]. If a wafer is to be used in order to stabilize the mandible, it is important that this wafer does not displace the tongue due to its shape or thickness such that the volume of the oropharyngeal airway is not distorted. If the latter methodology is respected, both inspiration and expiration contribute to the final airway volume, thereby introducing an error that is nevertheless systematic [29]. As newer scans reduce their acquisition times, respiratory phase control will become systematically practicable.

Another concern is the need to achieve an accurate 3D longitudinal and cross-sectional evaluation of the upper airway, both quantitatively and qualitatively. In this study, patients were scanned sitting upright in NHP because NHP is the recommended scanning posture for baseline assessment of upper airway morphology and dimensions [1]. However, it has been shown that slight variations in craniocervical extension (while in NHP) may affect the reliability of measurements in general [134] and modify the size of the pharyngeal airway in particular [112-114]. Head posture can be assessed by evaluating craniovertical orientation (i.e., the inclination of the SN plane to a true vertical line) or craniocervical orientation (i.e., the inclination of the SN plane to a line through the cervical vertebrae) [135]. The second option is preferred by most authors [113, 131] because it eliminates the need for an external reference. In addition, the anatomical cephalometric landmarks used to define it are precisely and easily identifiable on CBCT data and hence yield very reproducible results (Table 3). Post-processing of DICOM images by a third-party software permits virtual head reorientation in order to facilitate image superimposition when treatment outcome evaluation or growth assessment is intended. Virtual head orientation is also mandatory for accurate and reproducible individualized analysis of the upper airway subregions, since technical boundaries as defined in the presented methodology are based on well-defined planes. However, virtual head reorientation does not necessarily obviate bias in quantitative and qualitative analysis, since the dimensions and morphology of the upper airway are dependent on the patient's head position and craniocervical inclination during image acquisition. It is thus crucial to pay attention to adequate head orientation with the aid of proper patient instruction (e.g. a marking point at a distance, a laser beam or a mirror). According to the descriptive statistics of craniocervical inclination analysis (Table 3.4), the patient positioning protocol used in this study achieved highly homogeneous head extensions (mean 95.04°, SD 8.14°).

The precise 3D definition of the anatomical boundaries of the different pharyngeal airway subregions is a critical issue for upper airway analysis. Many studies tend to omit the definition of the specific anatomical limits used for a particular subregion [1]. Moreover, those studies that do report their chosen boundaries illustrate the great inconsistency that exists among authors. Indeed, the anatomical definitions of the airway subregions from the nasal and oral cavities to the larynx are exceedingly variable among different study groups. This is greatly a consequence of the lack of specific subregion definition in the scientific literature in general and in the anatomical literature in particular. Quantitative and qualitative comparisons among studies, even between those claiming to analyze the same particular subregion, are hence very problematic and prone to analysis bias. For example, while some studies take the plane parallel to the palatal plane that passes through the most anteroinferior point of C2 as the inferior limit of the oropharynx [103, 125], others use other anatomical landmarks such as the most anteroinferior point of C3 [82], the tip [14, 92, 101] or the base of the epiglottis [100]. Consequently, comparisons between studies are often methodologically impossible, and the combination of data in order to obtain normative values of the upper airway is extremely difficult.

In the light of the results of a SR about CBCT imaging and analysis of the upper airway [1], the present study tried to provide the scientific community with logical anatomical limits of the subregions of the upper (i.e. pharyngeal) airway. Furthermore, corresponding cephalometric landmarks that are easily and reliably defined on CBCT images were provided for consistent and reproducible analysis (Table 3.1). Standardisation of these anatomical limits would homogenize upper airway analysis and permit comparisons among future studies. The validation of these boundaries was performed on the Dolphin Imaging® software package on the grounds that it is a widespread third-party software for orthodontic analysis and orthognathic surgery planning. Moreover, its accuracy and reliability for airway assessment on CBCT have been adequately validated [133]. After following a pre-defined head orientation protocol, the chosen boundaries proved excellent intra- and inter-observer reproducibility for volumetric analysis of the individualized subregions. However, the reproducibility of minimum cross-sectional area measurements between both investigators and also for the same investigator at different time points was not as consistent. This combination of highly reproducible volumetric results and less reproducible area measurements requires specific clarification. From a methodological perspective, 3D head orientation during CBCT scan acquisition was adequately standardized as proven by the highly homogeneous craniocervical inclination values of the analyzed population sample. Similarly, virtual head reorientation based on the protocolized anatomical landmarks was also highly reliable in the light of the highly reproducible intra- and inter-observer volumetric results. The fact that the total study sample was preliminarily evaluated in order to determine a single threshold value (that was then manually defined by the investigator prior to automatic 3D and 2D calculations by the program) eliminates the potential source of error due to different threshold windows. Alves et al.[136] studied the most accurate threshold value for airway volume evaluation on an airway prototype and found that values between 70 and 75 showed no statistically significant differences compared to the gold standard (the actual physical volume of the prototype). Although our study was performed in vivo, our pre-calculated threshold value fell within this range. Finally, the high reproducibility of the volumetric measurements for the three subregions of the upper airway according to the predefined technical boundaries validates the latter. Since volumes are values of several thousand voxels (cubic millimetres) but areas are measured in pixels (tens of square millimetres), it is possible that slight variations in virtual head orientation give way to important modifications of the cross-sectional area and hence affect reproducibility significantly. Ghoneima and Kula [133] used CBCT DICOM data and Dolphin Imaging® to measure the volume and minimum cross-sectional area of an air-filled acrylic airway model and found no statistically significant differences between the manual and the digital measurements, thereby proving the software's high accuracy and reliability for both 2D and 3D analysis. However, the simplicity of the constructed airway model in comparison to the intricate anatomy of the airway in vivo was acknowledged [133]. Moreover, the airway model was installed in a human skull with a fixed craniocervical extension – hence, no need for a patient positioning protocol or virtual head orientation - and with no soft tissue movement due to deglutition or respiration, thereby creating the perfect scenario for the static evaluation of a structure that is in reality dynamic and, in addition, lodged in a mobile framework, the human's neck. The influence of these variables is critical in vivo and probably justifies the moderate reproducibility of 2D measurements found in the present study. Indeed, Dahlberg's value, which integrates systematic and random error [132], defined a low relative error for volumes but a moderate relative error for areas. The ICCs were above 0.98 for volumes in both intra- and inter-observer reproducibility analysis, but mostly below 0.90 for areas.

Considering the excellent reproducibility of the 3D calculations in particular, the results of this study are suitable to report preliminary normative volumetric data of the upper airway subregions of the Caucasian population. The reported normative values would correspond to a young (23-35 years of age) healthy adult population with a class I dental occlusion and class I facial profile without facial asymmetry. According to the study by Schendel et al. [137] on a wide population sample aged between 6 and greater than 56 years, the age frame of the patients in our study would correspond to the peak volume, cross-sectional area and airway length attained with human growth and development. Compared to the results of our study, Schendel et al. [137] found lower global airway volumes (average 14.77 for the age frame 21-25 years; average 15.59 for the age frame 26-30 years). Though the measurement unit was not specifically defined, it can be assumed it was 1000 mm^3. The authors used the 3dMD Vultus® software to measure the region comprised between PNS and the most anterior-superior edge of C4; no particular technical boundaries, head positioning protocol during CBCT scanning or subsequent virtual head orientation procedures were mentioned. According to our proposed anatomical classification, the upper airway region analysed by Schendel et al. [137] comprised the oropharynx and a part of the hypopharynx. Nevertheless, the reported volumetric values [137] were smaller than those found for the oropharynx in our study. These differences could respond to different CBCT settings or different threshold values in 3D airway software analysis. Unfortunately, the authors did not specify the latter parameters either. Quantitative comparisons of our results to other studies are difficult because many were performed in children [14, 100, 101, 131, 138] or orthognathic surgery patients [29, 35, 101, 139], and the limits of the analyzed upper airway regions were not specified or different to ours [14, 82, 99, 101, 103, 125]. Furthermore, results from studies that do not report CBCT settings and software threshold definition, use softwares that lack proper previous validation, or do not specify patient scanning conditions should be taken with caution [1].

In conclusion, there is a need to comprehensively define the subregions of the pharyngeal airway in order to standardize upper airway analysis and permit objective comparisons between different studies. The paired anatomical landmarks and subsequent technically defined boundaries proposed in this study are clinically reasonable, technically convenient and statistically reliable. The preliminary normative data for the upper airway subregions of healthy young Caucasian adults requires additional contrast with further studies following a similar methodology. Special attention must be paid to patient head positioning during CBCT scan acquisition and protocolized subsequent virtual reorientation in order to minimize the relative error in 2D measurements.

7. Discussion

7.1. RATIONALIZATION OF THE WORKFLOW FOLLOWED FOR THIS INVESTIGATION

At the time this PhD project was set up, several authors had studied pharyngeal airway and soft tissue changes after orthognathic surgery procedures using lateral cephalometry [30-33, 37, 38, 41-43] and CT [36, 39, 44, 51]. However, to our knowledge, there were no previous reports with CBCT evaluation. This particular scenario of increasing airway concern in a CBCT-dominated world inspired this PhD thesis.

The aims of the investigation were structured and justified as follows:

7.1.1. Paper one:

The onset of this PhD project was a SR about CBCT imaging and analysis of the upper airway [1]. The justification for this first article was our perception that, prior to the realization of any clinical work, a comprehensive literature review of the core subject was essential in order to get acquainted with the current and potential clinical indications of upper airway analysis with CBCT, investigate the technical parameters, anatomical boundaries and DICOM-processing softwares used by other authors in this particular context, and determine the accuracy and reliability of CBCT upper airway analysis as reported in the scientific literature.

7.1.2. Paper two:

Assuming that the preceding literature analysis led us to conclude that CBCT was indeed a valid method to analyze the upper airway, the next step would be the clinical application of a CBCT protocol for the preliminary analysis of upper airway changes after orthognathic surgery [29]. It must be emphasized that our prevailing treatment concept for orthognathic surgery comprises the triad occlusion-bone-soft tissue (“external and internal masks”). The consideration of the “internal mask” as a key component of our comprehensive approach leads us to steer away from isolated mandibular setback procedures in order to avoid an airway volume reduction. We try to associate mandibular setbacks with maxillary advancements, with or without anticlockwise rotations of the maxillomandibular complex. However, because the introduction of a rotational component would pose additional difficulties to the assessment of airway changes due to the variation of reference anatomical landmarks (in particular, the hard palate), we chose to evaluate pure sagittal advancements. For the same reason, procedures involving combined genioplasty or changes in the transversal dimension (in other words, segmented Le Fort I, SARPE, or mandibular midline expansion) were excluded too. In order to investigate the effect of advancement osteotomies in all regions of the upper airway (naso, oro and hypopharynx), and to compare the individual effect of each osteotomy on the airway volume, the studied sample was composed of three groups of patients: Group 1: Bimaxillary surgery (Le Fort I maxillary osteotomy and mandibular BSSO with maxillomandibular advancement); Group 2: Maxillary advancement (Le Fort I maxillary osteotomy); and Group 3: Mandibular advancement (BSSO).

7.1.3. Paper three:

Based on the results of the previous two papers, the last part of our investigation was aimed at providing clinical 3D anatomical limits for the upper airway subregions, translating them into accurate and reliable cephalometric landmarks in CBCT data, and validating the proposed measuring protocol [53]. This last paper should be considered the natural consequence of our previous theoretical (paper one [1]) and clinical (paper two [29]) work. Indeed, an unexpected finding of our literature review was the dramatic incongruity among study groups regarding the anatomical definition of the upper airway subregions. Moreover, many studies did not even specify the anatomical boundaries of the particular region of interest in their methodology. Subsequently, our preliminary clinical experience with upper airway analysis had thrown light to the technical and methodological difficulties of CBCT as a diagnostic tool and the upper airway as the target region of interest. The benefits, pitfalls and potentially improvable points of our initial protocol had become apparent to us. As a result, our third article was intended to be “the product” of the knowledge derived from the former two papers.

7.2. METHODOLOGICAL REMARKS

While the methodological procedure followed for our SR [1] is in agreement with the international guidelines for the execution of SR [140, 141] and requires no further discussion, we would like to clarify a couple of points regarding the method followed for our clinical investigation, in other words, papers two [29] and three [53].

7.2.1. Patient positioning during scan acquisition:

Similar patient positioning protocols were followed for both clinical papers: Patients were instructed to sit upright and position themselves in NHP with the help of a mirror and a laser beam. They were taught to rest the tongue in a relaxed position, breathe lightly and avoid any other motor reaction. It must be emphasized that patient training for adequate head orientation was considered a key requisite in our protocol.

In paper two, adequate head positioning during scanning was analyzed by checking the correspondence of the hard palate and cervical vertebrae between the pre and postoperative scans. It was established that if this correspondence was not achieved despite having followed our head posture protocol, the patient would be excluded from further evaluation. This technique was further refined for validation purposes in paper three. In this case, head position was checked by comparing the pre and post craniocervical inclinations. As the highly homogeneous values showed, patient positioning during scan acquisition was indeed adequately standardized.

The only difference between paper two and paper three was the fact that while patients' mandibles were kept in centric relation with the help of a wax bite in paper two, patients were taught to place the mandible in maximum intercuspation without the use of a wafer in paper three. Although the avoidance of any kind of wafer or wax bite is theoretically preferable in order to avoid any tongue displacement that could modify the dimensions of the oropharyngeal airway, the effect of thin wafers that do not invade the lingual aspect of the alveolar process is probably insignificant. Moreover, it must be emphasized that the patient sample of paper two were individuals with a dentomaxillofacial deformity in whom Orthognathic Surgery was planned. Hence, image acquisition in centric relation – maintained with the aid of a wax bite - was an important requirement for treatment planning. On the contrary, the studied sample of paper three was composed of normal individuals with no occlusal or esthetical abnormalities, in other words, they were not candidates for an orthognathic procedure and hence condylar position during image acquisition was irrelevant.

7.2.2. Threshold definition:

The threshold value controls the filling degree of the airway. During airway space analysis, after selecting the anatomical region of interest, the investigator chooses a threshold value and then the software fills in and displays the airway space automatically. Automatic segmentation of the airway is achieved by differentiating the densities between the airway and the surrounding soft tissues. This automatic segmentation is not realized slice by slice, as in manual segmentation, and thus does not allow delineation of all the tortuous anatomy of the airway. Consequently, the results of airway volume can vary according to the threshold chosen. An increase of the threshold value can result in an overflow of the volume into the surrounding soft tissues, and a decrease of the threshold can result in a smaller airway volume. At any rate, it is clear that the accuracy of airway measurements with CBCT can be strongly affected by the selected threshold value [13, 53, 136].

In paper two, the threshold value was individually determined for each patient. The procedure entailed selecting a distinctive high-contrast that depicted the airway region between PNS and the body of C4. Subsequently, undesired regions that became simultaneously highlighted, as well as any additional unwanted artifacts, were manually eliminated slice by slice. We acknowledge, indeed, that the increase or decrease of the threshold may result in a greater or smaller airway volume, respectively. This possible source of error was nevertheless systematic. And truth is we must not forget that the ideal threshold value for airway volume quantification has not yet been standardized.

With the aim to minimize this error and to try to systematize threshold definition as much as possible, we designed a new strategy for paper three. Prior to airway evaluation, all 40 CBCT databases were assessed in order to determine the most appropriate threshold value: The automatically fixed threshold value was manually increased for each dataset until the nasopharyngeal airway was adequately depicted. The average of all patients' threshold values thus defined was 70. This value was established as the reference threshold value for all patients included in the study. In our opinion, this method minimizes the potential source of error due to different threshold windows.

7.2.3. Virtual head orientation:

Post-processing of DICOM images permits virtual head reorientation. Both in paper two and paper three, the skull was reoriented to the FH. Our protocolized guidelines were specified in detail in paper three [53]. This step is crucial for accurate and reproducible analysis of the upper airway subregions, since technical boundaries as defined in paper three are based on well-defined planes. However, an important fact must be emphasized: Virtual head reorientation does not obviate bias in quantitative and qualitative analysis. The dimensions and morphology of the upper airway are dependent on the patient's head position - and hence, craniocervical inclination - during image acquisition. It is thus crucial to pay attention to adequate head orientation with the aid of proper patient instruction; subsequent virtual head orientation will not make up for incorrect patient positioning during scanning.

7.2.4. Third-party software:

For this investigation, two DICOM processing softwares were used:

- Paper two: SimPlant Pro Crystal (Materialise, Leuven, Belgium).
- Paper three: Dolphin Imaging v. 11.0 (Dolphin Imaging Systems, Chatsworth, CA).

Both softwares are widespread third-party softwares for orthodontic analysis and Orthognathic Surgery planning, and both proved to be practical for airway analysis. The only reason why one or the other was used was the fact that the clinical work for paper two was performed at the Institute of Maxillofacial Surgery and Implantology of the Teknon Medical Center (Barcelona, Spain), and the clinical work for paper three at the Department of Maxillofacial Surgery of the General Hospital St. Jan Bruges (Bruges, Belgium). In the first location, SimPlant Pro Crystal is the available DICOM viewer, while in the second location Dolphin Imaging is used.

7.2.5. Anatomical limits of the region of interest:

In paper two, the region of interest was delimited between the plane tangent to the hard palate plane and the plane tangent to the superior border of the body of C4. These limits were selected for the following reasons: First, the aim was to study the volumetric changes of the airway after mono- or bimaxillary advancement. Taking into account the design of the standard Le Fort I osteotomy, the hard palate is an appropriate upper limit to evaluate the effect of the forward movement of the maxilla. Second, the nasopharyngeal airway is the most tortuous region of the upper airway, and the definition of its boundaries is the most challenging. By establishing the upper limit of the region of interest at the plane tangent to the hard palate plane, manual airway segmentation is simplified substantially. Third, the complete body of C4 is often not completely visible in regular facial mode FOV. Hence, the plane tangent to the superior border of C4 is a “safer” inferior limit.

On the other hand, the aim of paper three was to provide appropriate 3D limits for the upper airway subregions. Therefore, despite the weight of the aforementioned arguments for paper two, the whole pharyngeal airway space had to be necessarily considered for paper three. Our study provided logical anatomical limits for the three subregions plus adequate corresponding technical landmarks that could be reliably used in CBCT studies. According to these limits, the studied region in paper two would approximately correspond to the oropharynx plus part of the hypopharynx as defined in paper three.

In paper three, the definition of the particular anatomical landmarks of each of the three airway subregions took into consideration the results of paper one - where the anatomical boundaries reported by other authors were recorded for comparative purposes -, clinical expertise, and the fact that every anatomical landmark had to give way to a matched technical reference point. According to these preconditions, the selected boundaries can be justified as follows:

- The upper limit of the nasopharynx – and upper limit of the whole pharyngeal airway – was set at the soft tissue contour of the pharyngeal wall in its most superior aspect.
- The subdivision between the nasopharynx and the oropharynx was set at a major reference landmark, the hard palate plane, more appropriately defined as the plane parallel to FH passing through PNS and extended to the posterior wall of the pharynx.
- The differentiation between the oropharynx and the hypopharynx was the most challenging, since it is not well defined in the anatomical literature and it is probably the most variable boundary among different study groups. With the aim to restrict the oropharynx to the pharyngeal airway related to the oral cavity and at the same time relate it to a major anatomical landmark, the inferior limit of the oropharynx was set at the plane parallel to FH plane passing through C3ai. Actually, C3ai tends to correspond to the level of the tip of the epiglottis in an opened position.
- The lower limit of the hypopharynx – and lower limit of the whole pharyngeal airway – was anatomically set at the plane parallel to FH connecting the base of the epiglottis to the entrance of the esophagus. In our opinion, this lower limit is a rational boundary with the esophagus and the laryngeal apparatus. Technically, the base of the epiglottis tends to correspond to C4ai, which is a reliable technical landmark.

It must be pointed out that these boundaries are not the only valid options. Others are probably acceptable too, as long as they are anatomically logical and, most importantly, adaptable to reliable technical landmarks in CBCT studies. At any rate, we believe the standardization of a proposed set of anatomical limits has the potential to homogenize upper airway subregion analysis and permit unbiased comparisons among studies.

7.3. KEY RESULTS

7.3.1. Paper one:

In agreement with other authors [16-18, 20-26, 63], the results of our SR led us to conclude that CBCT is indeed an accurate and reliable tool for upper airway analysis. Nevertheless, important problems were detected [1]. These problems can be grouped into two categories:

- Problems related to image acquisition:
    - There was great inconsistency in how authors reported the settings of the CBCT devices used in their studies. This fact had already been pointed out by previous studies [27].
    - Patient conditions during image acquisition were also very irregularly described and often unreported. These conditions refer to patient positioning, respiration phase control, tongue position control and mandibular position stabilization during scanning. The relevance of these conditions can be summarized as follows:
        - Patient positioning: While in some devices the patient is scanned in a supine position, other CBCT apparatus scan the patient in a vertical seated position. The upright position is closer to NHP and recommendable for baseline assessment of upper airway morphology and dimensions. Conversely, the supine position offers an incomplete representation of the upper airway but is very adequate for OSA research [1].
        - Respiration phase control: The fact that the airway's dimensions and shape change with every breathing phase is a well-acknowledged fact [58, 59, 118]. Most studies are performed with the patient breathing lightly, such that both inspiration and expiration contribute to the final airway volume. This introduces an error that is nevertheless systematic [29]. Newer scanners have reduced acquisition times to about 10 seconds, so respiratory phase control is currently feasible.
        - Tongue position control: Tongue position influences the shape and size of the oropharyngeal airway [101]. The patient should be instructed to avoid deglutition and any other movement during the

CBCT scan [1, 29]. If a wafer is to be used in order to stabilize the mandible, it is important that this wafer does not displace the tongue due to its shape or thickness such that the volume of the oropharyngeal airway is not distorted [1].

    - Mandibular position stabilization: The particular maxillomandibular relationship of the patient during scanning influences the shape and size of the oropharyngeal airway too [101]. A reproducible mandibular position (maximum intercuspation or centric relation) should be stabilized with the aid of a wafer or wax bite [1].

- Problems related to image processing and analysis:
  - Most papers included in our SR did not specify threshold definition in their methodology.
  - As many as 18 different software packages were reported for viewing and analyzing CBCT data of the upper airway. However, validation studies with a clear study design had only been performed for 4 of them (22%).
  - The anatomical definitions of the airway subregions from the nasal and oral cavities to the larynx were extremely variable among different authors. What is more, many studies included in the SR did not specify the anatomical boundaries of the particular region of interest in their methodology. As a result, it was very difficult to interpret quantitative analyses of the airway and to compare results between papers.

As far as the indications for CBCT imaging and analysis of the upper airway were concerned, our SR revealed four major clinical applications:

- Upper airway evaluation in normal subjects: Multidetector CT evaluation of the upper airway offers high-quality images, but due to its high radiation dose it is restricted to patients with severe cranio-maxillofacial deformities or undergoing craniofacial surgery [63]. The fact that radiation is significantly reduced with CBCT has widened the range of indications of upper airway analysis.
- Relationship between upper airway and dentomaxillofacial morphology: Cranio-maxillofacial abnormalities have been linked to the pathogenesis of OSA due to their repercussion on the dimensions of the upper airway.
- Relationship between upper airway and OSA: CBCT has significantly contributed to improve the understanding of the pathophysiology of OSA and the treatment planning of surgical and non-surgical interventions. Compared to conventional 2D

cephalometry, a 3D evaluation of the airway as provided by CBCT can better assess the cross-sectional and volumetric dimensions of the airway [18, 20, 26, 63, 82, 99-103].

- Evaluation of sinus anatomy and pathology: CBCT has become a useful alternative to traditional CT due to its high resolution, ease of use, low radiation, in-office clinical availability and comparatively low costs [15, 22-25].

7.3.2. Paper two:

Despite the important obstacles that our SR detected for upper airway analysis with CBCT, the key conclusion was that CBCT enables an accurate and reliable evaluation of the pharyngeal airway. This preliminary finding was an obligated requirement to justify any further investigation on this subject.

The evaluation of patients who underwent mono- or bimaxillary advancement revealed a statistically significant airway volume increase in all three groups [29]. On average, bimaxillary (group 1) and mandibular (group 3) advancement achieved a percentage increase in airway volume of 69.8% and 78.3%, respectively. Maxillary advancement (group 2) also increased the airway's volume but to a smaller extent (37.7%). These results suggest the influence of mandibular advancement on the posterior airway space's dimensions is greater than the effect of the forward movement of the maxilla. Anatomically, these findings can be explained by the advancement of the insertion of the following muscles:

- Genioglossus muscle.
- Suprahyoid group (Table 4).
- Pharyngeal constrictor group (Table 5).

The genioglossus, innervated by cranial nerve XII, is a fan-shaped muscle that originates from the superior mental spine of the mandible and inserts on the hyoid bone and tongue body. Within the suprahyoid muscle group, the geniohyoid and mylohyoid originate from the inferior mental spine and mylohyoid line, respectively, and insert on the hyoid bone (Figure 4). The superior and middle pharyngeal constrictors originate from different anatomical structures, which include the alveolar process of the mandible behind the mylohyoid line and the body of the tongue in the case of the superior constrictor, and the hyoid bone in the case of the middle component (Figure 5). Subsequently, in the context of Orthognathic Surgery, the advancement of the mandible causes a forward traction of the insertion of these muscles, which in turn pull directly from the tongue and hyoid bone, and indirectly from the soft tissue of the pharynx. The ultimate consequence is the expansion of the oropharyngeal space.

The fact that mandibular advancement alone caused a greater volumetric increase than bimaxillary advancement needs further deliberation. In our opinion, it is possible that group 3 patients underwent larger mandibular advancements (in absolute terms) than those in group 1. However, the possibility of a correlative relationship between the magnitude of skeletal forward movement and the subsequent increase in airway volume was not specifically investigated. The exploration of this parameter, together with an increase in sample size, should be taken into consideration for further studies.

As a result of pharyngeal volume enlargement, a relevant result of this study was the fact that four patients reported subjective significant postoperative improvement of OSA symptoms. Furthermore, one patient stopped requiring CPAP nocturnal support after a bimaxillary advancement procedure.

Table 4

Suprahyoid muscles

Muscle	***Origin***	***Insertion***	***Innervation***
Anterior belly of digastric	Digastric fossa of the mandible	Intermediate tendon	Mylohyoid nerve, branch of cranial nerve V_3
Posterior belly of digastric	Mastoid process of the temporal bone	Intermediate tendon	Cranial nerve VII
Stylohyoid	Styloid process of the termporal bone	Hyoid	Cranial nerve VII
Geniohyoid	Inferior mental spine of the mandibular symphysis	Hyoid	C_1 through cranial nerve XII
Mylohyoid	Mylohyoid line of the mandible	Hyoid	Mylohyoid nerve, branch of cranial nerve V_3

Table 5

Pharyngeal constrictor muscles

Muscle	*Origin*	*Insertion*	*Innervation*
Superior pharyngeal constrictor	Medial pterygoid plate and its hamulus Pterygomandibular raphe Alveolar process of the mandible above the posterior end of the mylohyoid line Lateral body of the tongue	Posterior median raphe Basilar part of the occipital bone	Cranial nerve X through the pharyngeal plexus
Middle pharyngeal constrictor	Hyoid Stylohyoid ligament	Posterior median raphe	
Inferior pharyngeal constrictor	Cricoid cartilage Thyroid cartilage	Posterior median raphe	

Figure 4

Suprahyoid muscles

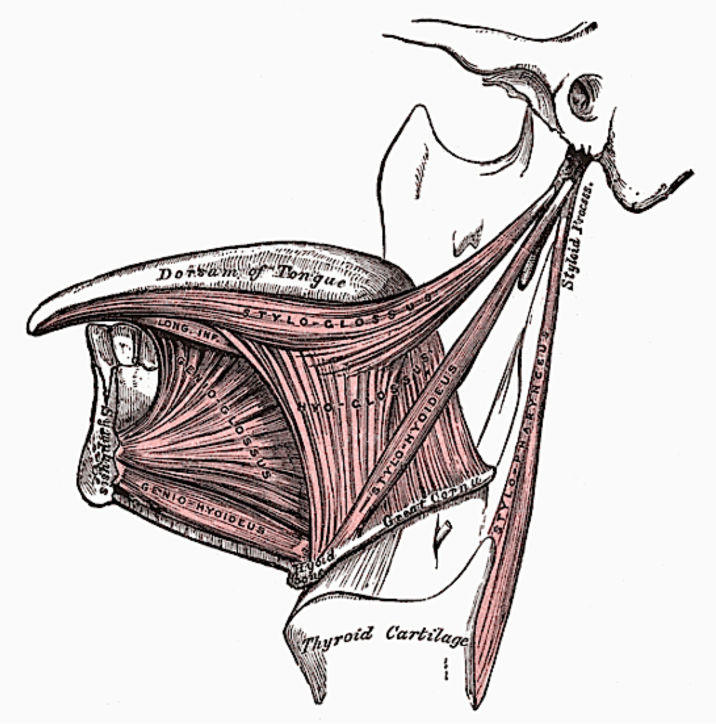
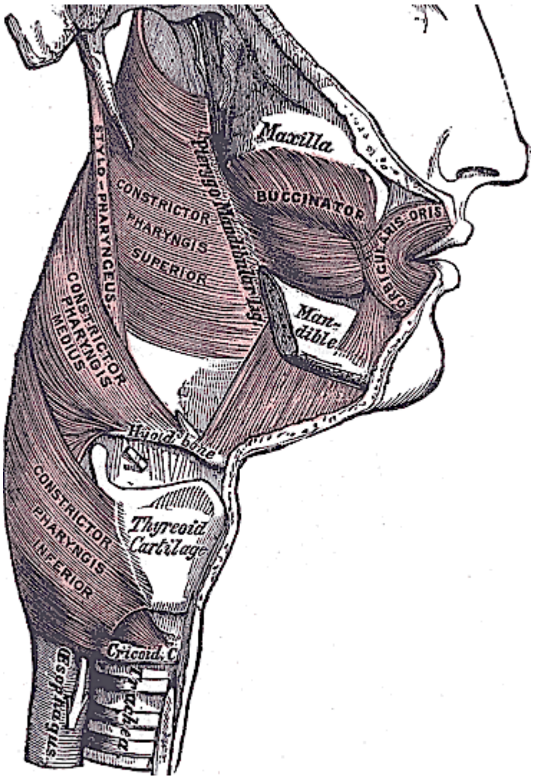


Figure 5

Pharyngeal constrictor muscles



Figures 4 and 5 belong to Gray's Anatomy's collection of medical images [142].

7.3.3. Paper three:

The fundamental finding of paper three was the fact that our proposed protocol for upper airway subregion analysis was anatomically logical, technically feasible, and statistically reliable. This statement is supported by the following individual facts:

- The anatomical landmarks used to demarcate the three subregions of the upper airway were based on clinical experience and previous work [1]. The superior limit of the nasopharynx – and of the total pharyngeal airway – was established at the soft tissue contour of the pharyngeal wall. The inferior limit of the hypopharynx – and of the total pharyngeal airway – was set at the plane parallel to FH connecting the base of the epiglottis to the entrance to the esophagus. In other words, the entire upper airway was thoroughly contemplated.

- The selected anatomical landmarks were effectively translated into technical boundaries that could be consistently located on CBCT studies.
- Craniocervical inclination measurements revealed excellent reproducibility. This means that the patient positioning protocol achieved highly homogeneous head extensions.
- The chosen boundaries of the individualized subregions showed excellent intra- and inter-observer reproducibility for volumes and acceptable intra- and inter-observer reproducibility for areas. This means that, besides an appropriate patient positioning protocol, virtual head reorientation based on the protocolized anatomical landmarks was also highly reliable. In addition, the fact that the total study sample was preliminarily evaluated in order to determine a single threshold value eliminated the potential source of error due to different threshold windows.

The combination of highly reproducible volumetric results and less reproducible area measurements is a finding requiring further discussion. Since volumes are values of several thousand voxels (cubic millimetres) but areas are measured in pixels (tens of square millimetres), it is possible that slight variations in virtual head orientation give way to important modifications in cross-sectional area and hence affect reproducibility significantly [53]. Indeed, while a low relative error was found for volumes, a moderate relative error was obtained for areas. ICCs were above 0.98 for volumes in both intra- and inter-observer reproducibility analysis, but mostly below 0.90 for areas.

8. Conclusions

The conclusions of this PhD investigation are the following:

1. According to contemporary scientific evidence, upper airway analysis can be accurately and reliably performed with CBCT.
2. Current clinical applications of CBCT upper airway analysis include upper airway evaluation in normal subjects, analysis of the relationship between upper airway and dentomaxillofacial morphology, analysis of the relationship between upper airway and OSA, and evaluation of sinus anatomy and pathology.
3. Airway evaluation entails inherent methodological difficulties that must be adequately controlled and systematically reported. These include patient conditions during image acquisition - head orientation, tongue and mandibular position, and respiration phase - and comprehensive 3D definition of the anatomical boundaries of the region of interest.
4. Pure sagittal mono- and bimaxillary advancement procedures increase the dimensions of the upper airway. The influence of mandibular advancement seems to be greater than the effect of the forward movement of the maxilla.
5. There is a need to comprehensively define the subregions of the pharyngeal airway in order to standardize upper airway analysis and permit objective comparisons between studies. The proposed subregion definition is anatomically reasonable, technically feasible and statistically reliable, especially for 3D calculations.
6. Special attention must be paid to patient head positioning during CBCT scan acquisition and protocolized subsequent virtual reorientation in order to minimize the relative error in 2D measurements.

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Appendix 1

Original published versions of the articles as they appear on their respective journals

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Invited Review Paper
Sleep Apnea

Cone-beam computerized tomography imaging and analysis of the upper airway: a systematic review of the literature

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R. Guijarro-Martínez, G. R. J. Swennen: Cone-beam computerized tomography imaging and analysis of the upper airway: a systematic review of the literature. Int. J. Oral Maxillofac. Surg. 2011; 40: 1227–1237. © 2011 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. A systematic review of the literature concerning upper airway imaging and analysis using cone-beam computed tomography (CBCT) was performed. A PubMed search (National Library of Medicine, NCBI; revised 9th January 2011) yielded 382 papers published between 1968 and 2010. The 382 full papers were screened in detail. 46 articles were considered clinically or technically relevant and were included in this systematic review. These were classified as articles on accuracy and reliability of CBCT imaging of the upper airway ($n = 4$), accuracy and reliability of DICOM viewers ($n = 2$), synopsis ($n = 10$), technical ($n = 7$) and clinical applications ($n = 27$). When one paper was considered related to two or more categories, it was assigned to each relevant group. Results indicate that three-dimensional (3D) analysis of the upper airway using CBCT can be achieved in an accurate and reliable manner. Important obstacles still need to be addressed, including the impact of respiration phase, influence of tongue position and mandible morphology, longitudinal and cross-sectional 3D CBCT upper airway evaluation, and 3D CBCT definition of the anatomical boundaries of the upper airway.

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Since its development in the 1990s, cone-beam computed tomography (CBCT) has become a well-accepted tool for oral and maxillofacial (OMF) diagnosis and treatment planning, mainly due to its advantages in lower effective radiation dose, lower costs, easy access and shorter acquisition times in comparison to conventional multidetector CT (MDCT) (also called multislice CT, MSCT)[29,47].

Interest in upper airway shape and dimensions has increased steadily during the past decades mainly due to the relationship between upper airway configuration and obstructive sleep apnea (OSA) as well as craniofacial morphology. According to the medical literature, airway evaluation can be performed with magnetic resonance imaging (MRI)[1,8,9,71], cine-MRI[28,34], MDCT[4,13,22,25,26,30,33,42,56–58,60,74], endoscopy[38] and optical coherence tomography[10]. Although CBCT is inferior to MDCT in discriminating between different soft-tissue structures,

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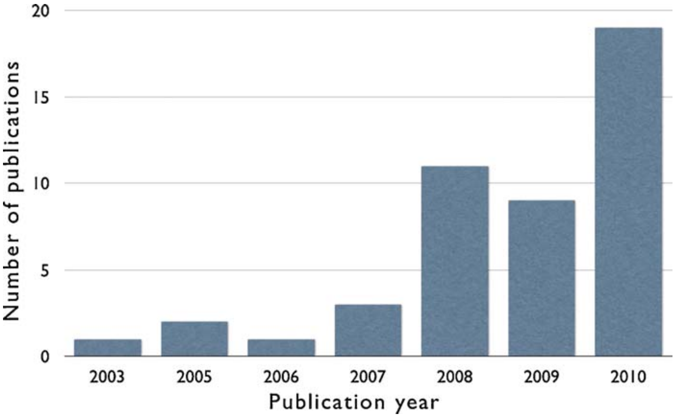

Fig. 1. Distribution of published articles on CBCT imaging and analysis of the upper airway yielded by the PubMed search (National Library of medicine, NCBI; updated 9th January 2011) and thoroughly analysed in this systematic review.

Table 1. Primary and secondary keywords used for the systematic research.

Primary keywords	Secondary keywords
1. Cone-beam	1. Air space
2. Conebeam	2. Airspace
3. CBCT	3. Airway
4. CB-CT	4. Upper airway
5. Digital volume tomography	5. Airflow
6. DVT	6. Pharynx
7. Compact computed tomography	7. Pharyngeal
8. Compact CT	8. Oropharynx
9. Volumetric computed tomography	9. Oropharyngeal
10. Volumetric CT	10. Nasopharynx
11. Ortho cubic	11. Nasopharyngeal
12. Flat panel	12. Hypopharynx
	13. Hypopharyngeal
	14. Larynx
	15. Laryngeal
	16. Nose
	17. Nasal
	18. Sinus
	19. Sinusal
	20. Obstructive sleep apnea syndrome
	21. Obstructive sleep apnea
	22. Sleep apnea
	23. OSA
	24. OSAS

it defines the boundaries between soft tissues and empty spaces with high spatial resolution[47,78]. Several studies have tested its accuracy and reliability and have confirmed its potential for the evaluation of the upper airway[2,5,15,39,45,53,61,62,66,70,73]. Post-processing of DICOM (Digital Imaging and Communications in Medicine) images by third-party software allows visualization and quantification of the airway in an unprecedented way. As a result, better understanding of the upper airway anatomy and physiology is to be expected[72].

The number of publications related to upper airway analysis with CBCT has increased during the last 5 years (Fig. 1). Although some articles[5,6,14,27,54] provide a synopsis of CBCT imaging of the OMF region and refer to the possibility of upper airway evaluation, a systematic review of CBCT imaging and analysis of the upper airway has not been published.

The purpose of this article was to conduct a systematic review of the literature on CBCT imaging and analysis of the upper airway in order to: (1) determine current and potential clinical indications of upper airway analysis with CBCT; (2) report technical parameters and verify the accuracy; and (3) reliability of CBCT for upper airway analysis according to the available studies.

Material and methods

A systematic review of the literature concerning upper airway imaging and analysis with CBCT was performed. A PubMed database (National Library of Medicine, NCBI) search was performed and updated on 9th January 2011. 12 primary keywords related to CBCT terminology were used in combination with 24 secondary keywords in order to restrict the search to CBCT evaluation of the upper respiratory tract relevant to the OMF region (Table 1). All possible combinations between one primary keyword and each secondary keyword were explored. The upper respiratory tract was considered to comprise the respiratory structures above the trachea from the nostrils to the larynx.

The initial search yielded 382 references. The full papers of all these references were analysed thoroughly and subsequent categorization produced the following clusters (Table 2): 155 references had no relevant relationship to CBCT or airway (upper/lower) analysis; 66 papers concerned the use of CBCT technology in the head and neck region for other purposes (e.g., dental implant imaging and planning, cephalometric analysis, temporomandibular joint evaluation, or radiotherapy treatment planning for head and neck cancer); upper airway evaluation with methods other than CBCT was described in 47 papers; and 68 articles concerned the evaluation of the lower airway. These four groups were excluded from further evaluation.

The remaining 46 articles were found clinically or technically relevant to the

Table 2. Articles yielded by the PubMed search (National Library of Medicine, NCBI) updated on 9th January 2011 using the primary and secondary keywords listed in Table 1.

Condition	Article types	Number of papers (n)
Excluded from the systematic review	1. No relevance to CBCT or airway analysis	155
	2. CBCT of the head and neck region for other purposes	66
	3. Upper airway evaluation with other methods	47
	4. Lower airway evaluation	68
Included in the systematic review	CBCT imaging and evaluation of the upper airway (Table 3)	46

Table 3. Classification of relevant papers that were analysed in detail for this study.

Category	Number of papers (*n*)	References	Percentage
1. Accuracy and reliability of CBCT imaging of the upper airway	4	2,3,47,73	8.7
2. Accuracy and reliability of DICOM viewers	2	29,62	4.3
3. Synopsis	10	5,6,14,18,32,43,54,68,69,77	21.7
4. Technical aspects	7	19,20,23,40,67,75,78	15.2
5. Clinical applications	27		58.7
• Upper airway evaluation in normal subjects	1	70	2.2
• Relationship between upper airway and dentomaxillofacial morphology	7	24,35,37,44,45,72,76	15.2
• Relationship between upper airway and obstructive sleep apnea	5	31,52,53,63,66	10.9
• Evaluation of sinus anatomy and pathology	14	11,12,15,17,18,21,35,39,43,59,61,64,75,78	30.4

subject of study and were included in this systematic review. According to their emphasis, these papers were categorized as follows (Table 3): accuracy and reliability of CBCT imaging of the upper airway; accuracy and reliability of DICOM viewers; synopsis; technical aspects; and clinical applications. The last category was subdivided according to the focus on upper airway evaluation of normal subjects, evaluation of sinus anatomy and pathology, or the relationship between the oropharyngeal airway and dentomaxillofacial morphology or OSA. When one paper was considered related to two or more categories, it was assigned to each relevant group. This explains why the total sum of articles in each group is larger than the total number of papers and why the sum of the separate percentages does not equal 100%.

Results

This systematic review comprised 46 papers. Table 3 shows the complete classification of the articles included in each category. An additional classification according to the specific anatomical region assessed is given in Table 4.

Accuracy and reliability of CBCT imaging of the upper airway

Two studies compared anatomic information on the nasopharyngeal airway between lateral cephalometric headfilms and CBCT[2,3]. The authors concluded that CBCT is an effective method to analyse the airway accurately, although they found high variability in the airway volume of patients with relatively similar airways on the lateral headfilm. Another paper[73] evaluated the reliability of CBCT measurements of the oropharyngeal airway compared with those obtained by MDCT and found the measurement of air spaces with CBCT reasonably accurate. The correlations between linear measurements, cross-sectional areas and volumes of the nasopharyngeal and oropharyngeal airways on CBCT datasets were evaluated in one paper[47]. The authors emphasized an adequate assessment of the airway requires the combination of linear measurements, area and volume.

Accuracy and reliability of DICOM viewers

One study[29] compared the accuracy and reliability of three commercially available DICOM viewers (Dolphin3D®, InVivoDental®, and OnDemand3D®) for measuring nasopharyngeal and oropharyngeal volumes. The three third-party softwares showed high correlation of results but poor accuracy, suggesting systematic errors. Another paper[62] analysed the accuracy and precision of one particular DICOM viewer (3dMD Vultus®) using an airway phantom in different orientations as a test standard. The software proved to be an accurate, reliable and fast method to evaluate the airway. The authors predicted that incorporation of upper airway imaging using CBCT will facilitate the screening and evaluation of anatomically related obstructed sleep disordered breathing.

Table 4. Classification of CBCT studies of the upper airway according to the specific anatomical region assessed.

Anatomical region	Number of papers (*n*)	References	Percentage
Nasal airway	5	15,24,35,45,78	10.9
Sinuses	Sphenoid: 1	17	2.2
	Ethmoid: 3	39,59,61	6.5
	Maxillary: 3	11,35,64	6.5
	Sphenoid, ethmoid and maxillary: 1	12	2.2
	Sphenoid, ethmoid, maxillary and frontal and osteomeatal unit: 4	15,18,21,43,78	8.7
Nasopharynx	2	2,3	4.3
Intraoral space	1	44	2.2
Oropharynx	8	31,52–54,63,72,73,76	17.4
Nasopharynx and oropharynx	4	29,37,45,47	8.7
Oropharynx and hypopharynx	2	67,70	4.3
Larynx	2	40,54	4.3

Synopsis

The systematic search yielded five papers that dealt with CBCT evaluation of the head and neck for maxillofacial and otorhinolaryngological purposes, which included, but did not focus on, upper airway evaluation[5,6,14,68,69]. One study[54] focused on airway assessment and offered a general overview of CBCT applications to improve airway management from an anaesthesiological perspective. Two papers[18,43] offered a general overview about imaging the paranasal sinuses. An editorial discussing the standards on which the definition of the field of view should be based in craniomaxillofacial studies[32] and a paper discussing the legal implications of CBCT imaging[77] were also assigned to this group.

Technical aspects

This group comprised two basic types of papers: those describing a methodology for detection and 3D reconstruction of the airway using CBCT data[19,23] and studies dealing with practical features that have relevant clinical implications in methodology and the interpretation of results[20,40,67,75,78]. One of these studies[67] analysed the response of oropharyngeal structures to gravity by comparing postural changes between sitting upright (assessed with CBCT) and lying down in a supine position (assessed with MDCT). The gravitational effect in response to postural changes caused relevant changes in the position of oropharyngeal structures. Another study[40] evaluated soft tissue image quality of a mobile C-arm with an integrated flat panel detector in comparison to MDCT and MRI. The conclusion was that integration of a flat panel detector improves soft tissue visualization. The possibilities and challenges of image superimposition of 3D CBCT models were addressed by another paper[20]. The authors emphasized the possibilities of 3D model superimposition and surface distance calculations to identify treatment outcomes and stability after treatment. The dose and image quality performance between a dedicated CBCT and MDCT scanner were compared in another study[75] for a sinus scanning protocol in a phantom model. CBCT proved comparable high-contrast resolution but inferior low-contrast resolution relative to MDCT. A study[78] comparing the quality of paranasal sinus CBCT imaging with different acquisition times was also assigned to this subgroup. The authors concluded image quality is directly related to scan time and accordingly radiation dose.

Clinical applications

Upper airway evaluation in normal subjects

Regarding upper airway evaluation in normal subjects, the oropharynx and hypopharynx of 10 healthy adults with normal class I occlusion were evaluated in one study[70]. The authors performed a 3D volumetric analysis of the airway and defined the area of maximum cross-sectional constriction, which was most frequently found in the oropharyngeal region.

Relationship between upper airway and dentomaxillofacial morphology

With respect to the relationship between upper airway and dentomaxillofacial morphology, 3 papers[37,44,45] emphasized the effects of respiratory function on craniofacial growth and morphology. One[45] compared the 3D volume of four predefined subregions of the upper airway in healthy children with a retrognathic mandible and those with normal craniofacial growth. As expected, retrognathic patients were found to have a decreased total airway volume. Another paper[44] focused on the oropharyngeal airway differences between children with class I malocclusion and children with class III malocclusion. In this case, class III malocclusion was associated with a larger and flatter oropharyngeal airway. One study[37] assessed nasopharyngeal and oropharyngeal airway volume and shape in non-growing patients (adolescents and adults) with different facial patterns. The authors found that airway shape and volume vary amongst different anteroposterior jaw relationships, whereas only airway shape differs with various vertical relationships.

The effects of surgical-orthodontic treatment of dentofacial anomalies on the upper airway were the subject of four papers[24,35,72,76]. Three[24,35,76] analysed the effects of rapid palatal expansion (RPE). One study[76] evaluated the effects of RPE on the volume of the oropharynx and found no evidence of oropharyngeal airway volume increase. The other two[24,35] evaluated the dimensional changes of the nasal cavity and maxilla after RPE. One[35] of the latter studies found a statistically significant decrease in maxillary sinus width. The effects of extraction versus non-extraction orthodontic treatments on oropharyngeal airway volume were analysed by one research group[72]. The extraction of four premolars with retraction of the incisors was not found to alter the volume of the oropharynx.

Relationship between upper airway and obstructive sleep apnea (OSA)

Regarding the relationship between the upper airway and OSA, the systematic review yielded 5 papers[31,52,53,63,66] focusing on the OSA–airway relationship. One[66] was a synopsis of diagnostic imaging of OSA, including CBCT and other techniques. Another study[63] used CBCT to investigate the correlation between retroglossal airway dimensions and body mass index, comparing OSA and non-OSA patients. Of all the studied parameters, only the ratio ‘airway cross-section area/square area’ showed statistically significant differences between both groups. Other studies compared the cross-sectional configuration of the oropharynx in OSA and non-OSA patients[53] and developed a prediction model for OSA based on CBCT features and sleep questionnaires[31]. Both studies[31,53] found a statistically significant smaller minimum cross-sectional area in OSA patients. Conversely, another study[52] found significant group differences regarding total airway volume and anteroposterior diameter of the smallest cross-sectional area. There were no significant differences with respect to the smallest cross-sectional area or its lateral dimension.

Evaluation of sinus anatomy and pathology

The group to which most papers were assigned ($n = 14$) was the one concerning CBCT assessment of sinus anatomy and pathology. Two papers[18,43] were synopses about imaging of the paranasal sinuses in general. The authors affirmed CBCT introduces a new era in the use of imaging for the evaluation of maxillofacial and otorhinolaryngologic pathology[18,43]. Whereas intraoperative CBCT seems to increase accuracy and safety, in-office use raises important issues related to patient and clinician convenience[18].

One research group evaluated the efficiency of CBCT as a diagnostic modality for the anterior skull base in general[15] and the olfactory cleft and olfactory fossa in particular[39,61]. The authors concluded that CBCT evaluation of these areas is accurate and extremely helpful for preoperative assessment[15,39,61]. Three other studies described CBCT intraoperative imaging based on a mobile C-arm to guide surgery of the frontal recess[59], sinuses in general and skull base[12,21].

Clinical aspects such as the relationship between maxillary sinusitis and the prevalence of concha bullosa and nasal septal deviation were evaluated in one paper[64], but no statistically significant association was detected. The effects of RPE on the maxilla were studied by one research group[35] who reported a statistically significant increase in nasal width and a decrease in maxillary sinus width. CBCT was also used to investigate the prevalence of sphenoid sinus hypoplasia and agenesis in the Turkish population[17] and the formation of the maxillary sinus in Japanese fetuses[11].

One study[78] compared the image quality and diagnostic accuracy of CBCT scanning with three different data acquisition times on paranasal sinus imaging in general and found that image quality was directly related to scan time and, consequently, radiation dose. Similarly, the comparison of dose and image quality performance between a dedicated CBCT and MDCT scanner in the context of a sinus scanning protocol[75] found CBCT had similar high-contrast resolution but inferior low-contrast resolution relative to MDCT with a matched radiation dose. The authors proposed that whilst CBCT may be comparable to MDCT for the assessment of bony anatomy or gross sinus

Table 5. Reported settings of different CBCT devices for the visualization and/or analysis of the upper airway.

Type of image detector	Image intensifier								Flat panel	
Scanner	NewTom 3G QR srl	NewTom QR-DVT 9000	NewTom 3G QA srl	PSR 9000N	Master 3D	Accu-I-Tomo F17	i-CAT	CB Mercuray	MiniCAT	Paxscan 4030 CB
Manufacturer	Quantitative Radiology, Verona, Italy	Quantitative Radiology, Verona, Italy	Quantitative Radiology, Verona, Italy	Asahi Roentgen Industry, Kyoto, Japan	Vatech, Seoul, Korea	Morita, Kyoto, Japan	Imaging Sciences International, Hatfield, Pennsylvania	Hitachi Medical Systems, Tokyo, Japan	Xoran Technologies, Ann Arbour, Michigan	Varian, Palo Alto, California
References	[20,31,47,63]	[20,3,17,52,53,63]	[76]	[11]	[45]	[15,39,61]	[20,24,37,62,64]	[20,29,44,54,67,70,72,73]	[75,78]	[40,59]
Tube voltage		110 kV, 14 mA[17]		60 kV, 4 mA[11]		80 kV, 8 mA[15,39,61]		120 kV, 2 mA[29,72] 100 kV, 10 mA[73] 120 kV, 15 mA[44,67] 120 kV, 10 mA[70]	125 kVp, 67.9 mAs[75]	100 kV, 2.3 mA[40]
Grayscale depth	4096[63]	256[52,63]						4096[29,70,72,73]		
Scan time (seconds)	12[47]	75–77[52,53]	36[76]			18[15,39,61]	40[62] 20–38[37] 10 and 20[24]	9.6[29,44,67] 10[70]	10[78] 20[78] 40[78]	≤60[59]
Rotation		360° [52]					360°			
Field of view (cm)		13[17]			12 in[45]	10[15,39,61]	13[62]	12[29,72] 15[67,73] 19[73]		20 × 20 × $15\ \mathrm{cm}^3$ [40,59]
Slice thickness (mm)		0.8–1[2] 1[53] 0.2 axial, 2 coronal, 2 sagittal[17]				0.08[15,39,61]		0.377[29] 0.3[73] 0.37[70]		
Slice number	360[63]	360[53]				580[15,39,61]		512[29,72]		200–500[59]
Voxel size	0.36 mm[47]	0.3 mm[2] 0.28 mm[3]		0.1 mm[11]	0.3 mm[45]		0.25 mm[62] 0.3 mm[37,64]	0.3 × 0.3 × 0.3 mm[67,73] 0.377 mm[44,72] 0.6 mm[70]		0.5 mm[40]
Scanned volume dimensions		150 × 150 mm[52,53]								40 × $30\ \mathrm{cm}^2$ [40]
Pixel set								1024 × 1024[29,72]		
Bits per pixel	12[63]	8[52,53]						12[29]		
Data output	DICOM[31,47]	DICOM[2,3]					DICOM[62]	DICOM[29,44]		
Patient positioning	Supine	Supine[2,3,52,53]	Supine[76]		Sitting upright[45]	Sitting upright[15,39,61]	Sitting upright[37]	Sitting upright[29,44,67,73]		

DICOM: Digital imaging and communications in Medicine. *The following settings were not reported: exposure control, exposure time, radiation source, exposure time per image, projections per rotation, detector type, amplification, cone beam angle, scanned volume height, scanned volume diameter, proprietary software, total filtration, front panel attenuation.

Table 6. Reported conditions in CBCT evaluation of the upper airway.

Head posture control	Yes	Frankfort plane perpendicular to the floor[31,53,76] Frankfort plane parallel to the floor[24,67] Natural head position[45,72] Craniocervical inclinations were examined to ensure they were between 90° and 110° [44] Head fixed in the operative position at the centre of the C-arm using a brace[59] After image acquisition, head was oriented so that it was straight with no cant[70] After image acquisition, head was oriented according to a line 6° down from the sella-nasion as the horizontal axis[37]
	Not specified	2,3,15,29,35,39,47,52,61,64
	Not relevant	11,12,18,21,40,43,62,73,75
Mandibular position control	Yes	In occlusion [47,67] In maximum intercuspation [45,72,76]
	No	2
	Not specified	3,24,29,31,37,44,52–54,70
	Not relevant	11,12,15,17,18,21,35,39,40,43,59,61,62,64,73,75
Tongue position control	Yes	The patient was asked not to swallow during the exposure[45,67,70]
	No	2
	Not specified	3,24,29,31,37,44,47,52–54,70,72,76
	Not relevant	11,12,15,17,18,21,35,39,40,43,59,61,62,64,73,75
Breathing stage control	Yes	Modified Muller test[54]
	No	37,70
	Not specified	2,3,24,29,35,37,44,45,47,52,70,72,73,76
	Not relevant	11,12,15,17,18,21,35,39,40,43,59,61,62,64,73,75
Threshold definition	Individually determined for each CBCT on the basis of a profile line and the correspondent vertical intersecting lines	47
	User-initialized 3D surface evolution	37
	Manual segmentation	53,67
	Automatic segmentation	52,76
	Not specified	2,3,11,12,15,17,18,21,24,29,35,39,40,43–45,59,61,62,64,70,72,75

pathology, current CBCT image quality is probably inadequate for the diagnosis and follow-up of certain neurosurgical conditions.

Table 7. Reported software used for viewing, measuring and analyzing the data from CBCT scanning of the upper airway.

Software	References
Mimics (version 12.13, Materialise Interactive Medical Image Control System, Leuven, Belgium)	47
3D Doctor (Able Software Corporation, Lexington, Massachusetts)	2,3
Dolphin 3D (Dolphin Imaging & Management Solutions, Chatsworth, California)	24,29,72
InVivoDental (version 4.0.70, Anatomage, San Jose, California)	29,45
OnDemand3D (version 1.0.1.8407, CyberMed, Seoul, Korea)	29
OrthoSegment (Department of Orthodontics, School of Medicine, Case Western University)	29
VGStudio MAX1.2.1 (Nihon Visual Science, Tokyo, Japan)	73,67
3dMDVultus (3dMD, Atlanta, Georgia)	62
InsightSNAP (version 1.4.0, Cognitica, Philadelphia, Pennsylvania)	37
INTAGE Volume Editor (KGT, Tokyo, Japan)	44
CBworks (Cybermed Inc., Seoul, Korea)	54,70
OsiriX Medical Imaging Software (Pixmeo, Geneva, Switzerland)	54,64
vWorks (Cybermed, Seoul, Korea)	31,63
Amira (Mercury Computer Systems/3D Viz group, San Diego, California)	52,53
ASAHI vision software (Asahi Roentgen Industry, Kyoto, Japan)	11
Micro AVS (KGT, Tokyo, Japan)	11
Idixel (Morita, Kyoto, Japan)	15,39,61
Syngo (Siemens Medical Solutions)	40
DICOM viewer not specified or not used	17,18,35,43,59,75

The settings of different CBCT devices for visualization and/or analysis of the upper airway as reported by the articles included in this systematic review are given in Table 5. Tables 6 and 7 summarize the conditions in CBCT evaluation of the upper airway and the software used for viewing, measuring and analysing, respectively. The anatomical limits of the upper airway in the sagittal plane as defined by each paper are illustrated in Table 8.

Discussion

The interest in dedicated CBCT scanners for the OMF region has increased exponentially since their introduction in the late 1990s[7,49]. As a result, new possibilities and applications for CBCT have arisen in the fields of OMF surgery, dentistry and otorhinolaryngology. Upper airway analysis in particular has become increasingly relevant mainly due to the relationship between morphological airway character-

Table 8. Anatomical limits of the upper airway (in the sagittal plane) as reported in the literature included in the systematic review (PubMed, National Library of Medicine, NCBI; search revised January 9th, 2011).

Nasal airway	Anterior limit: ANS (frontal plane perpendicular to the FH plane passing through ANS[45] Posterior limit: PNS (frontal plane perpendicular to the FH plane passing through PNS[45]
Oral airway	Anterior limit: Incisive canal and midline of the upper incisors[72] Posterior limit: not reported
Nasopharynx	Superior limit: *Last slice before fusion of the nasal septum with the posterior wall of the pharynx[29] *Intersection of the line PNS-So (midpoint of the sella-basion line) and the posterior wall of the pharynx[47] *Soft tissue contour of the posterior pharyngeal wall extending from the superior aspect of the pterygomaxillary fissure[2] *Plane perpendicular to the plane through PNS at the height of the pterygomaxillary fissure[3] *Highest point of the nasopharynx, coinciding with the posterior choanae[37] *Posterior nasal plane (frontal plane perpendicular to the FH plane passing through PNS[45] Inferior limit: *Palatal plane (ANS-PNS) extended to the posterior wall of the pharynx[2,3,29,44,72,76] *Plane including the PNS and the lower medial border of the 1st cervical vertebra[37] *Plane including the PNS and basion[67] *Plane parallel to the FH plane passing through PNS[31,45,53]
Oropharynx	Superior limit: ∼ inferior limit of the nasopharynx. Inferior limit: *Plane parallel to the palatal plane that passes through the most anteroinferior point of the 2nd cervical vertebra[29,52] *Plane parallel to the FH plane that passes through the most anteroinferior point of the 2nd cervical vertebra[31,53] *Horizontal line through the superior point of the epiglottis[47,67,76] *Horizontal line through the base of the epiglottis[44] *Plane tangent to the most caudal medial projection of the 3rd cervical vertebra perpendicular to the sagittal plane[37] *Plane extending from the most anteroinferior point on the body of the 3rd cervical vertebra to the base of the epiglottis[72] *Plane parallel to the FH plane passing through the superior margin of the epiglottis[45]
Hypopharynx/laryngopharynx	Superior limit: ∼ inferior limit of the oropharynx Inferior limit: Plane connecting the entrance to the oesophagus to the body of the hyoid bone and left and right greater horns of the hyoid[67]

FH: Frankfort horizontal; ANS: anterior nasal spine; PNS: posterior nasal spine.

istics and craniofacial growth, dentomaxillofacial pathology and OSA. Owing to its easy access, low cost and decreased radiation compared with MDCT and especially its capability to define the boundaries between soft tissue and empty spaces (air) accurately, CBCT has become an unprecedented diagnostic method to analyse the airway three dimensionally[47,78]. As a result, the number of publications related to upper airway evaluation with CBCT has increased significantly during the last few years (Fig. 1). Although a systematic review of the literature on CBCT imaging of the OMF region in general has already been performed[27], to the authors' knowledge this is the first on CBCT evaluation of the upper airway.

Objective airway evaluation is possible using several techniques including MDCT and MRI. There is still a lack of basic clinical research to quantify and analyse the upper airway with MDCT and MRI protocols in the clinical routine[23]. CBCT technology has emerged as a potential alternative for obtaining a thorough 2D and 3D evaluation of the upper airway at relatively modest costs, with easy access and a short scanning time compared with MDCT. Other major benefits of CBCT include the potential for vertical scanning in a natural seated position, easy handling, DICOM compatibility and high resolution[27]. Compared with standard MDCT, CBCT exposes the patient to substantially lower radiation[5,6,15,27,39,54,59,61,66]. Although MRI is still superior in soft tissue rendering[40], its use is limited by its cost and restricted accessibility[47].

After meticulous scrutiny, this systematic review included 46 relevant papers on CBCT imaging and analysis of the upper airway. As previously noted[27], there was great inconsistency and discrepancy in how authors reported the settings of the CBCT devices used in their studies (Table 5). The reported conditions of CBCT image acquisition and threshold definition were also irregular and often unreported (Table 6). De Vos et al.[27] recommended a minimum set of parameters for dedicated OMF scanners. Systematic reporting of these factors would reduce the reader's confusion and enable unbiased comparisons between different studies.

In particular, patient positioning during data acquisition is of major importance. Whilst the patient is scanned in a supine position in some devices, other CBCT apparatus scan the patient in a vertical, seated position (Table 5). The upright position is closer to the natural head position (NHP) and recommended for baseline assessment of upper airway morphology and dimensions. Moreover, it allows excellent visualization of the pharyngeal recess, the 'fossa of Rosenmüller', a frequent location of nasopharyngeal carcinoma[6,67]. The supine position offers incomplete representation of the upper airway but is adequate for OSA research. Sutthiprapaporn et al.[67] studied the response of oropharyngeal structures to gravity by comparing the position of key anatomical landmarks in patients sitting upright (using CBCT) versus supine position (using MDCT). The authors found the soft palate, epiglottis and entrance of the oesophagus moved caudally with a change from supine to sitting upright, and posteriorly when the position changed from upright to supine. The hyoid bone moved caudally but not posteriorly in response to the same postural changes. As anticipated, they found the cross-sectional area in the upright position was larger than in the supine position. These findings imply that morphological changes in the upper airway and related soft tissues should be expected as a result of gravity and posture. Other studies confirmed the size of the pharyngeal airway changes with different head positions[41,50,51]. In fact, a strong correlation between the posterior airway space and head posture defined by the craniocervical angulation at the uppermost part of the cervical spine has been reported[50]. The authors found that a change of 10 degrees in craniocervical angulation can produce a 4 mm change in posterior airway space. Another important issue is manipulation of head posture by stabilizing the patient's head during CBCT scanning (e.g., with a strap around the forehead or a chin platform) in order to optimize resolution by minimizing patient movement. The first generation iCAT devices enabling vertical scanning of the patient required the technician to position the patient with a strap around the forehead and a chin support. A prominent chin was prone to cause extension of the head, whilst less prominent chins caused the opposite[37]. The new generation iCATs advocate only the strap around the forehead but no longer the chin platform for airway studies. Other CBCT apparatus furnishers propose to avoid a forehead strap and to orientate the patient towards NHP with the aid of a mirror or a laser beam. The variability of NHP between individuals and also at different time points for the same subject is controversial and direct reproducibility continues to be questionable[55,65]. Comparisons of qualitative and quantitative studies of the upper airway should systematically involve an evaluation of how head posture was controlled since it may affect the results.

As far as software is concerned, numerous software packages are dedicated to manage and analyse DICOM records. Many of them have incorporated tools to segment and measure the airway. In their study to compare the accuracy and reliability of three different DICOM viewers, El et al.[29] found calculation of upper airway volume with three commercially available viewers (Dolphin3D®, InVivoDental® and OnDemand3D®) to be reliable. Results showed a high correlation but nevertheless poor accuracy, suggesting systematic errors. Table 7 lists the 18 different software packages that were reported for viewing and analyzing CBCT data of the upper airway according to this systematic review. Unfortunately, validation studies with a clear study design were only performed in 4 (22%) of the software packages. Consequently, the results of some studies are scientifically questionable and comparisons amongst papers become prone to analysis bias. Decent studies assessing the accuracy and reliability of current and new software packages have to be conducted before these applications can be implemented for airway analysis.

One important software-related issue is thresholding. The 3D image of a CBCT scan is the result of surface or volume rendering of the DICOM data. In volume rendering each grey value of the volume image is assigned a colour and opacity, whilst in surface rendering a threshold filter, defined by the user, is applied[36]. Manual segmentation based on surface rendering seems to be more accurate but is significantly more time-consuming and not practical for clinical purposes[2,29]. The automation of image-analysis procedures has the advantage of being less prone to observer error[20]. Most studies in this systematic review did not specify the threshold definition in their methodology. Lenza et al.[47] reported the use of a single threshold value to segment the airway in each patient's CBCT scan. This approach may generate errors especially in volume analysis, but it is certainly more reproducible than the use of a dynamic threshold.

Although the advent of CBCT allows clinicians to avoid the limitations of conventional cephalometrics, other problems that need to be solved include: the influence of the respiration phase; the influence of tongue position and mandibular morphology; longitudinal and cross-sectional upper airway evaluation; and 3D CBCT definition of the anatomical boundaries of the upper airway. Regarding the first two issues, changes in airway dimensions and shape depending on the breathing stage have been acknowledged[1,13,48]. However, there are no normative data currently available[72]. Newer scanners have reduced acquisition times to about 10 s, so respiratory phase control is practicable. This enables, for example, the performance of a Muller test during data acquisition. With this manoeuvre and modified variants, volumetric measurements can be performed under different negative inhalation pressures, thereby measuring the plasticity of the airway and its tendency to collapse[54]. This systematic review revealed that most studies did not control respiratory phase during data acquisition and/or did not refer to it in the *materials and methods* section (Table 6). Similarly, the position of the mandible and tongue, which have been shown to influence the shape and size of the oropharyngeal airway[76], were not specified by most papers (Table 6). As far as longitudinal and cross-sectional upper airway evaluation is concerned, there is still a need to allow comparison of CBCT to conventional cephalograms[20]. In order to compare CBCT images with 2D data, virtual cephalograms and multiplanar slices can be reconstructed out of the CBCT data by mathematical algorithms[36,47]. Linear accuracy of CBCT virtually reconstructed lateral cephalograms has meanwhile been validated[16,46]. Subsequent superimposition of 2D and 3D data becomes feasible theoretically for the evaluation of treatment outcome and growth assessment. The patient's head could be virtually oriented to a position that permits image superimposition. In the context of upper airway analysis, intra- and inter-individual comparisons are dependent on the patient's head posture during CBCT data acquisition. Virtual head orientation cannot obviate this problem and only includes analysis bias. Therefore, in CBCT upper airway assessment it is crucial to consider and report patient positioning properly to avoid erroneous conclusions[20,67,72]. Another important obstacle to comparison amongst studies is the 3D definition of the different anatomical regions of the upper airway. This systematic review showed that anatomical definitions of the airway from the nasal and oral cavities to the larynx were extremely variable (Table 8). As a result, the boundaries of a particular region of interest should be carefully defined in the *materials and methods* section in order to allow accurate interpretation of quantitative analyses of the airway and permit comparison between papers.

As far as the indications for CBCT imaging and analysis of the upper airway are concerned, this review revealed 4 major groups: craniofacial growth and morphology; effect of combined orthodontic-surgical treatment on airway; OSA; and sinus pathology. The relationship between respiratory function and craniofacial growth and morphology has been studied for decades. There is a vast amount of literature on this topic, although most studies are 2D. MDCT evaluation of the upper airway offers high-quality images, but due to its high radiation dose it is restricted to patients with severe craniofacial deformities or undergoing orthognathic surgery[45]. The fact that radiation is significantly reduced with CBCT has widened the range of indications for upper airway analysis. CBCT is able to provide accurate measurements of cross-sectional areas and volumes[2,5,15,39,45,53,61, 62,66,70,73]. This systematic review included 3 papers emphasizing the effects of respiratory function on craniofacial growth and morphology based on CBCT studies[37,45,76]. According to these, it seems 3D airway measurements do not exhibit sexual dimorphism[37,45,76]. Conversely, volumetric measurements of the airway are significantly correlated to anteroposterior and vertical cephalometric variables[44,45]. Recent studies have shown airway volume and shape vary significantly amongst patients with different anteroposterior jaw relationships[37,44,45]. Some authors report healthy pre-adolescent children with retruded mandibles have decreased total pharyngeal airway volumes[45], whilst others find class III malocclusion in this age group is associated with a larger oropharyngeal airway and intraoral space[44]. When comparing various vertical jaw relationships, it is airway shape but not volume that differs[37].

Changes in airway volume and shape after surgical-orthodontic treatment of dentofacial anomalies have also been assessed with CBCT[24,35,72,76]. Craniofacial abnormalities have been linked to the pathogenesis of OSA due to their repercussion on the dimensions of the upper airway. In particular, there is a concern that maxillary constriction leads to inferior repositioning of the tongue, which can result in oropharyngeal airway narrowing. Studies have shown growing patients with maxillary constriction have a smaller retropalatal airway volume than age- and sex-matched controls[76]. An increase in nasal width and maxillary basal bone width has been shown after RPE[24,76]. There is no evidence that RPE increases the oropharyngeal volume[76]. No statistically significant oropharyngeal airway volume changes have been found between cases treated with premolar extractions versus non-extraction treatments, despite anticipated changes in the angulation and position of the incisors and subsequent tongue repositioning[72].

Significant anatomical differences between OSA patients and normal subjects have been reported regarding mandible size and position, posterior airway space morphology and dimensions, tongue size and position, and soft palate morphology[31,52,53,63,66]. In children and young adults, adenotonsillar hypertrophy has been emphasized as a major risk factor of OSA[31,45,66]. Similarly, the turbinates can protrude significantly into the nasopharyngeal airway space and cause severe airway restrictions[2]. Craniofacial skeletal abnormalities are another acknowledged risk factor for OSA in children and non-obese adults[31,37,44,45,53,63,76]. Since its introduction, CBCT has significantly contributed to improve the understanding of the pathophysiology of OSA and aid in treatment planning for surgical and non-surgical interventions. Compared with conventional 2D cephalometry, a 3D evaluation of the airway as provided by CBCT can better assess the cross-sectional and volumetric dimensions of the airway[2,31,37,44,45,52,53,66,72,76]. A major disadvantage of cephalometric measurements is that the patient is scanned in an upright posture (which is not a natural sleeping position), whilst OSA events typically occur when the patient is asleep supine. The Newtom device, which is currently the only commercially available CBCT that images the patient in the supine position, is ideal for OSA studies[31]. In these, the most common measurements to compare the static morphology of the upper airway between OSA patients and healthy controls are the minimum surface area of the oropharynx and the anteroposterior and lateral dimensions of this area[31,53,63]. Research has shown the minimum cross-sectional area of the upper airway is significantly smaller in OSA patients[31,52,53,63] and has been described at the dorsum of the tongue to the posterior pharyngeal wall on the bisected occlusal plane[47,66,67,70] or at the most posteroinferior point of the soft palate to the line perpendicular to Frankfort horizontal passing through porion[47,53,66,67]. In addition, the morphology of the upper airway in OSA patients is more spherical or elliptical than in non-OSA subjects[31,53]. No statistically significant differences between the airways of male and female OSA patients have been found[63].

Focusing on the radiological display of the paranasal sinuses, CBCT has become a useful alternative to traditional MDCT due to its high resolution, ease of use, low radiation, in-office clinical availability and comparatively low costs[5,15,39,61,78]. It seems the quality of CBCT imaging of the sinuses is directly related to the scan time and radiation dose[78]. With correct patient positioning, a selected volume of 10 × 10 cm is sufficient to display the nasal cavity, lateral nasal wall, paranasal sinuses and adjacent vital structures[15]. Various studies have tested the efficiency of CBCT as a diagnostic modality of the anterior skull base[15,39,61]. In this context, CBCT has proved to be a valuable tool to assess the olfactory area. Preoperative, bilateral evaluation of the latter region is mandatory in order to avoid complications during sinus surgery[15,39,59,61]. Intraoperative CBCT guidance during paranasal sinus surgery is also a possibility. It is especially desirable in areas that are close to vital anatomical structures, distorted anatomy, revision sinus surgery, extensive sino-nasal polyposi and increased risk of intraoperative bleeding[12,59].

In conclusion, the results of this systematic review confirm CBCT is an accurate and reliable tool for upper airway evaluation[2,5,15,39,45,53,61,62,66,70,73]. This includes the assessment of the paranasal sinuses[5,6,15,17,39,59,61]. Lateral headfilms offer limited information about the airway, with the inherent errors of a 2D representation of a 3D structure and the lack of information about cross-sectional area and volume[2,3,15,31,37,44,45,47,53,76]. The advent of CBCT has provided the opportunity to assess the cross-sectional area and volumetric depiction of the upper airway precisely with an accessible, rapid, noninvasive, and low-radiation scan. Important obstacles still need to be addressed, including: the influence of the tongue position and mandible morphology; the impact of the respiration phase; longitudinal and cross-sectional 3D CBCT upper airway evaluation; and 3D CBCT definition of the anatomical boundaries of the upper airway. Authors should make an effort to overcome the inconsistency reported in CBCT settings and conditions, DICOM software and assessed regions in order to facilitate the integration of information and permit unbiased comparison amongst studies.

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None declared.

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Effect of Mono- and Bimaxillary Advancement on Pharyngeal Airway Volume: Cone-Beam Computed Tomography Evaluation

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Purpose: To evaluate pharyngeal airway volume changes after forward movements of the maxilla or mandible, or both, using cone-beam computed tomography.

Patients and Methods: A retrospective evaluation of 30 patients who underwent maxillomandibular advancement, maxillary advancement, or mandibular advancement was performed. Three groups of 10 subjects each were established: group 1, bimaxillary surgery (Le Fort I maxillary osteotomy and mandibular bilateral sagittal split osteotomy with maxillomandibular advancement); group 2, maxillary advancement (Le Fort I maxillary osteotomy); and group 3, mandibular advancement (bilateral sagittal split osteotomy). Pre- and postoperative cone-beam computed tomography scans were taken in each case, and the changes in pharyngeal airway volume were compared.

Results: A statistically significant increase in the pharyngeal airway volume occurred systematically. The average percentage of increase was 69.8% in group 1 and 78.3% in group 3. Group 2 exhibited a lower magnitude of increase (37.7%).

Conclusion: Cone-beam computed tomography provides a new method for airway evaluation using a noninvasive, rapid, low-radiation, cost-effective scan. It seems the influence of mandibular advancement on the pharyngeal airway volume is greater than the effect of the forward movement of the maxilla.
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Orthognathic surgery aims to restore proper dental occlusion and facial harmony through the modification of the position, shape, and size of the facial bones. Bone movement implies secondary positional and tensional changes in the attached soft tissues. These new soft tissue relationships introduce significant changes in the facial appearance and, in addition, in the pharyngeal airway space (PAS) dimensions, especially when a significant anteroposterior component is present.[1]

The tongue, soft palate, hyoid bone, and related musculature are directly or indirectly attached to the maxilla and mandible; therefore, the dimensions of the oral cavity and pharyngeal airway will change depending on the direction and magnitude of the skeletal movements.[1-3] Several investigators have reported the induction of sleep-related breathing disorders after isolated mandibular setback procedures.[4-7] Research has shown postoperative narrowing of the retrolingual and hypopharyngeal airway[1,4,5,7-10] and posteroinferior displacement of the hyoid bone and tongue.[10-12] This is an issue receiving increasing attention during the past 2 decades owing to the potentially serious adverse systemic consequences of obstructive sleep apnea (OSA).

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In contrast, favorable improvement of OSA can be achieved with maxillomandibular advancement.[2,13-18] An increase in the PAS is achieved by the advancement of the skeletal attachment of the suprahyoid and velopharyngeal muscles and tendons.[13,16,17,19] Moreover, when a counterclockwise rotation of the maxillomandibular complex is performed in patients with high occlusal plane morphology, the genial tubercles move forward more than the teeth, thereby maximizing the advancement of the hyoid bone, base of the tongue, and related soft tissues.[15,20]

In the medical field, airway evaluation is possible using several techniques, including magnetic resonance imaging,[21] cine-magnetic resonance imaging,[22] computed tomography (CT),[23] endoscopy,[24] and optical coherence tomography.[25] However, the advent of cone-beam CT (CBCT) has provided the chance to evaluate the airway using a noninvasive, rapid, low-radiation scan. In their study to measure the human airway with CBCT, Tso et al[26] demonstrated this appliance achieves highly correlative linear, cross-sectional area and volumetric measurements in addition to morphometric analysis of the airway. They found the narrowest region in an awake subject, sitting upright and breathing quietly, is located chiefly in the oropharynx.[26] Although several investigators have studied pharyngeal airway and soft tissue changes after orthognathic surgery procedures using lateral cephalometry[4-9,11,12,27] and CT,[10,13,19,28] no previous studies have reported on CBCT evaluation. To our knowledge, this is the first study to assess the effects of orthognathic surgery, in particular mono- and bimaxillary advancement, on the PAS using CBCT.

Patients and Methods

A retrospective analysis of 30 patients who underwent orthognathic surgery during 2009 at the Institute of Maxillofacial Surgery and Implantology, Teknon Medical Center (Barcelona, Spain) was performed. The Helsinki Declaration guidelines were followed. As a retrospective analysis, the study was exempt from institutional review board approval. The patients were randomly selected from the Institute's database according to the orthognathic procedure performed. Three groups of 10 subjects each were established: group 1, bimaxillary surgery (Le Fort I maxillary osteotomy and mandibular bilateral sagittal split osteotomy with maxillomandibular advancement); group 2, maxillary advancement (Le Fort I maxillary osteotomy); and group 3, mandibular advancement (bilateral sagittal split osteotomy). Patients undergoing procedures involving changes in the transverse dimensions (ie, segmented Le Fort I osteotomy, surgically assisted rapid palatal expansion, mandibular midline expansion) or isolated or combined genioplasty, were excluded for evaluation with the aim of analyzing "pure" sagittal advancements without changes in hard palate inclination. All patients provided written informed consent. All procedures were performed by the same surgeon using rigid fixation and postoperative box elastics for 2 to 6 weeks. The patients received routine preoperative and postoperative orthodontic treatment.

Every patient underwent pre- and postoperative CBCT with the IS i-CAT, version 17-19 (Imaging Sciences International, Hatfield, PA). A 7-second scan was taken with the patient breathing quietly and sitting upright, with the clinical Frankfort horizontal plane parallel to the floor, the tongue in a relaxed position, and the mandible in centric relation with a wax bite in place. The radiologic parameters used were 120 kV and 5 mA. The axial slice distance for each scan was 0.300 mm^3. The facial mode with the 23-cm field of view was used. Primary images were stored as 576 Digital Imaging and Communications in Medicine data files.

Each CBCT scan was processed using the SimPlant Pro Crystal software (Materialise, Leuven, Belgium). Special attention was paid to the correspondence of the hard palate and cervical vertebrae between the pre- and postoperative scans to minimize the influence of the head and cervical posture on the airway evaluation. It was established that if this correspondence was not achieved despite having followed our head posture protocol, the patient would be excluded from evaluation.

To digitally excise the airway, a distinctive high-contrast border was defined using threshold segmentation. In the resulting set of masks (highlighted areas representing the region of interest within each slice), the areas occupied by air corresponded to a range of CT units below the ranges for the denser soft tissue and bone. The threshold limits were modified to an appropriate range that adequately captured all spaces filled by air within the volume of each particular CBCT scan. Therefore, other areas, in addition to the PAS, were defined, including the oral cavity, maxillary sinuses, nasal cavity, and trabecular matrix within dense bones. These undesired structures, together with any artifacts or background scatter, were eliminated manually from each slice by using the tools "Edit Mask in Single Slice" and "Edit Mask in Multiple Slices." Similarly, the air space above the palatine plane and below the plane tangent to the superior border of the body of the fourth cervical vertebra was eliminated from the evaluation (Fig 1).

The volume of the segmented region was calculated from the "Masks List Window." A 3-dimensional display of the excised area was attained. Thus, a pair of values (pre- and postoperative PAS volume) and the

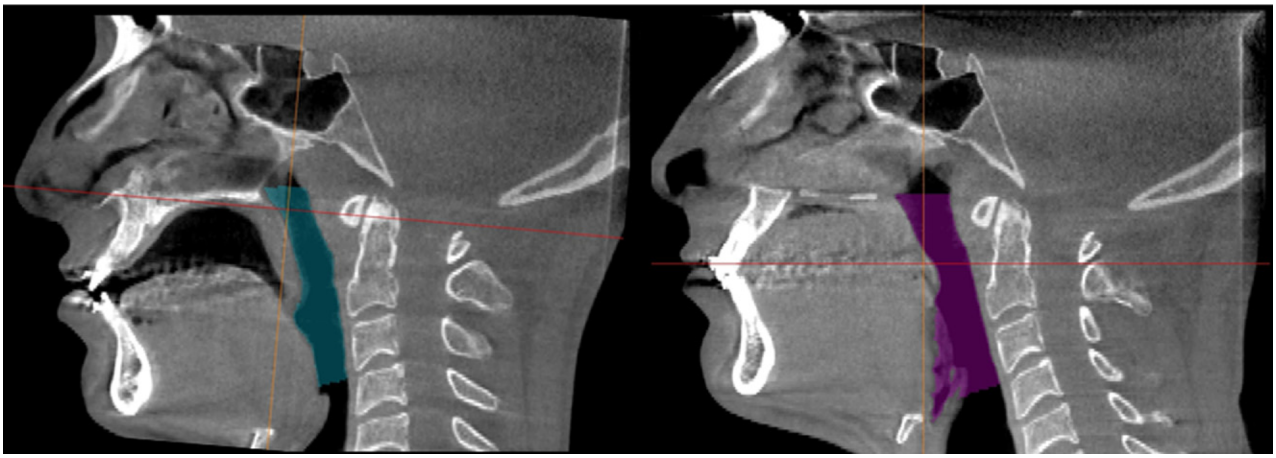

FIGURE 1. Digital excision of the pharyngeal airway space in patient 3 (bimaxillary surgery). Pre- (*left*) and postoperative (*right*) CBCT scans.

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corresponding pair of airway reconstructions was obtained for each patient (Fig 2).

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 15.0.1 (SPSS, Chicago, IL). Descriptive statistics were used for quantitative analysis. Each patient's percentage of variation in volume was calculated as follows: (postoperative volume × 100/preoperative volume) − 100. Student t test for paired samples was used to compare pre- and postoperative PAS volumes. The α level was set at 0.05.

Results

The studied sample included 22 women and 8 men (ratio 2.75:1), with a median age at surgery of 32 years. Preoperative scans were taken the day before surgery. The average period elapsed between the pre- and postoperative scans was 146.3 days for group 1, 132.9 days for group 2, and 121.4 days for group 3 (average for all 3 groups 133.5 days).

The pre- and postoperative volumetric measurements and percentage of variation in the airway volume in each group are presented in Figure 3 and Table 1. The average variation was positive in all 3 groups (ie, an average increase in airway volume occurred systematically). The average increase was 68.4% in group 1 and 78.3% in group 3. Group 2 exhibited a lower magnitude of increase (37.7%). For an α level of 0.05, these positive variations were statistically significant ($t_o = 8.07$, 29 degrees of freedom).

Discussion

To our knowledge, the present study is the first to evaluate the changes in the PAS after orthognathic surgery using CBCT technology. Cephalometric radiography has been commonly used to evaluate the postoperative pharyngeal airway and soft tissue changes.[4-9,11,12,27] This method was chosen because it is an essential imaging tool for orthodontic treatment

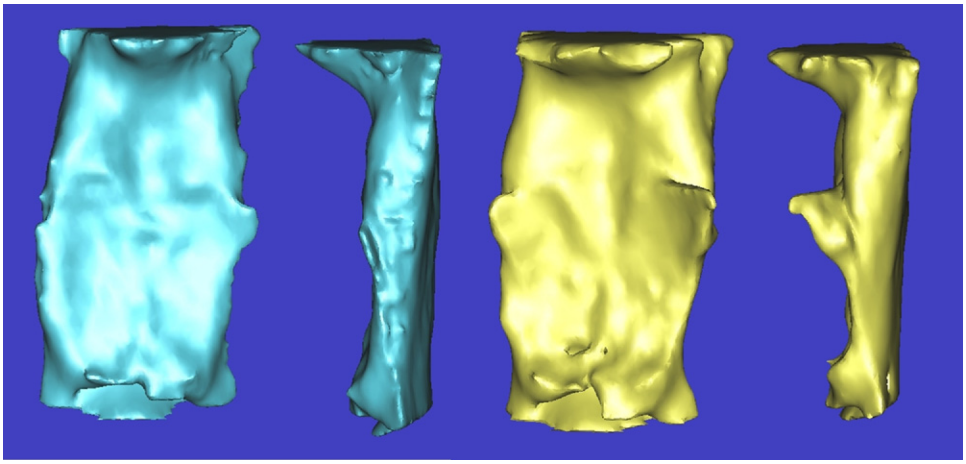

FIGURE 2. Three-dimensional pharyngeal airway space of patient 3 (bimaxillary surgery). Pre- (*left*) and postoperative (*right*) volumes.

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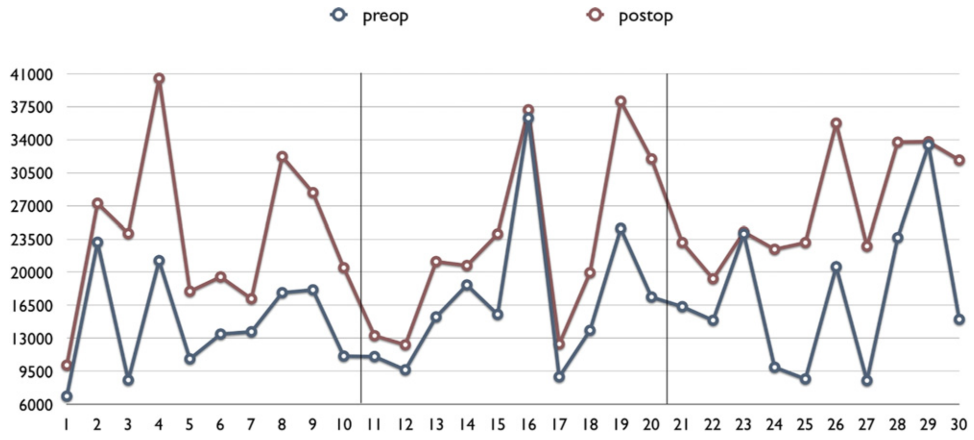

FIGURE 3. Pre- and postoperative volumetric measurements and percentage of variation in airway volume in the studied sample.

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planning and follow-up.[10] Although airway changes are only assessed 2-dimensionally, a significant correlation between the PAS measured on the cephalographs and the volume of the airway calculated from the CT studies was demonstrated.[2,29] Therefore, the results are still relevant. However, it is difficult to evaluate the airway 3-dimensionally using conventional cephalometric radiography, and the hard tissue structures often overlap.[10] In contrast, CT, especially with 3-dimensional reconstruction, permits excellent visualization of the pharyngeal airway without hard tissue superimposition and can create various types of images repeatedly.[10,13,18,19,28]

Table 1. PRE- AND POSTOPERATIVE MEASUREMENTS AND PERCENTAGE OF VARIATION IN AIRWAY VOLUME

Pt. No.	Preoperative Volume (mm^3)	Postoperative Volume (mm^3)	Percentage of Variation (%)
1	6,851.61	10,136.67	47.9
2	23,173.56	27,270.36	17.7
3	9,077.91	24,296.35	167.6
4	21,225.29	40,517.03	90.9
5	10,803.17	17,975.48	66.4
6	13,439.98	19,508.32	45.2
7	13,683.65	17,190.77	26.6
8	17,832.68	32,224.76	80.7
9	18,131.64	28,395.94	56.6
10	11,100.53	20,478.20	84.5
11	11,051.06	13,265.68	20.0
12	9,644.50	12,301.71	27.6
13	15,260.35	21,125.43	38.4
14	18,647.53	20,711.63	11.1
15	15,526.51	24,050.31	54.9
16	36,309.92	37,187.14	2.4
17	8,905.06	12,381.79	39.0
18	13,831.24	19,953.76	44.3
19	24,620.72	38,109.47	54.8
20	17,371.64	31,979.38	84.0
21	16,345.32	23,145.30	41.6
22	14,904.35	19,313.97	29.6
23	24,058.36	24,264.57	0.9
24	9,918.28	22,432.04	146.3
25	8,677.63	23,141.80	166.7
26	20,580.04	35,766.55	73.8
27	8,504.14	22,756.92	167.6
28	23,662.25	33,746.96	42.6
29	33,442.49	33,792.43	1.0
30	14,996.70	31,847.19	112.4

Abbreviation: Pt. No., patient number.

Group 1, bimaxillary advancement, patients 1-10; group 2, maxillary advancement, patients 11-20; group 3, mandibular advancement, patients 21-30.

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Recently, CBCT has proved to be a practical technique for the quantitative assessment of the PAS, with important advantages over other current scanning systems. It is a noninvasive, low-radiation, fast scanning (<60-second) technique that is more cost-effective than other systems such as spiral CT or magnetic resonance imaging.[26,30] The system is highly accurate in its measurements, the images are not distorted, and the relative range of the CT units for different tissues provides a method to rapidly segment the airway.[26]

However, CBCT does have some inherent deficiencies, in particular its static evaluation of the PAS. Airway imaging studies have shown that the airway dimensions change at different levels with breathing,[21,23] especially in the lateral dimension.[31] One weakness of our study was that the patient was scanned while breathing normally, suggesting that both inspiration and expiration contribute to the final calculated airway volume. It is essential that the patient does not swallow, cough, speak, or do any motor response other than breathe quietly during the scanning process.[26] Accordingly, in addition to standardizing a repeatable head posture protocol in our study, the patient was carefully instructed to breathe normally during the 7-second scan and to avoid any other motor reaction.

Muto et al[32] reported a strong correlation (r = 0.807) between the PAS and the head posture, defined as the craniocervical angulation at the uppermost part of the cervical spine. A change of 10° in craniocervical angulation produced a 4-mm change in the PAS.[32] Taking into account these findings, the head posture correspondence between each patient's pre- and postoperative CBCT scans was checked before airway volume measurement in our study. Using the SimPlant software, it was ensured that the hard palate plane and cervical vertebrae coincided at the superimposed sagittal midline in the pre- and postoperative scans. No significant discrepancy was found to exclude any subject from evaluation. A possible explanation to this is that particular care was taken to correctly position the patient for the scan (patient sitting upright, with the clinical Frankfort horizontal plane parallel to the floor, tongue in a relaxed position, and mandible in centric relation with the help of a wax bite).

Our results support other investigators' findings that maxillomandibular advancement can achieve an increase in the PAS.[13,16,17,19] A systematic increase in the PAS volume occurred in all cases. On average, bimaxillary and mandibular advancement achieved an increase in the airway volume of 69.8% and 78.3%, respectively. Maxillary advancement also increased the PAS volume but to a lesser extent (37.7%). These results suggest the influence of mandibular advancement on the PAS is greater than the effect of the forward movement of the maxilla. Thus, the advancement of the skeletal attachment of the suprahyoid muscles and tendons could play a major role in the widening of the PAS. An ongoing study will seek to determine whether any correlation exists between the magnitude of skeletal forward movement and the increase in PAS volume.

A possible limitation of the present study was that the hypothetical influence of substantial postoperative weight loss on the dimensions of the PAS was not evaluated. Although this possibility has not been confirmed, it should be considered for future investigation.

The relationship between OSA and a narrow PAS has been emphasized by numerous studies.[4-7] Patients with OSA have a retropositioned mandible and maxilla, short mandibular body length, and long anterior facial height compared with age- and gender-matched controls.[33,34] These craniofacial abnormalities can be minimized with maxillomandibular advancement, thereby improving OSA symptoms.[2,13-18] In the present study, patients 1, 3, 10, and 25 reported subjective significant improvement of OSA symptoms postoperatively. Moreover, patient 10 stopped requiring continuous positive airway pressure nocturnal support after a bimaxillary advancement procedure. Therefore, forward movements of the mandible and/or maxilla in the context of orthognathic surgery procedures can be aimed at correcting malocclusion, restoring facial harmony, and improving OSA symptoms because of PAS volume enlargement.

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Three-dimensional cone beam computed tomography definition of the anatomical subregions of the upper airway: a validation study

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Abstract. The exact boundaries of the upper airway subregions remain undefined. Consequently, anatomical limits vary greatly among different research groups and impede unbiased comparisons. The aim of this study was to provide clinical three-dimensional anatomical limits for the upper airway subregions, translate them into accurate and reliable cephalometric landmarks in cone beam computed tomography (CBCT) data, and validate the proposed measuring protocol. The upper airway of 40 normative individuals aged 23–35 years was evaluated with Dolphin Imaging® software. An appropriate grey-scale threshold value was pre-calculated. After adapting specific head positioning and virtual orientation protocols, the volume and minimum cross-sectional area of the nasopharynx, oropharynx, and hypopharynx, as previously defined by the authors, were calculated. Intra- and inter-observer reliability was excellent for volumes and moderate for areas. The sexual dimorphism analysis revealed a significantly greater oropharyngeal volume, hypopharyngeal volume, and minimum cross-sectional oropharyngeal area in males than in females. In conclusion, the proposed subregion definition showed technical feasibility and statistical reliability, especially for three-dimensional calculations. The reliability of two-dimensional calculations may be increased with improved head positioning during CBCT scanning and subsequent virtual head orientation. Standardization of the proposed anatomical limits has the potential to homogenize upper airway subregion analysis and permit comparisons among future studies.

Keywords: cone beam computed tomography; CBCT; upper airway; pharyngeal airway; subregions.

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During the past decade, cone beam computed tomography (CBCT) has become a widely acknowledged tool for oral and maxillofacial diagnosis and treatment planning. Besides its irrefutable advantages of a lower effective radiation dose, lower costs, easy access, and shorter acquisition times in comparison to conventional multidetector CT (MDCT), its high spatial resolution between soft tissue and empty space provides an unprecedented method to analyse the airway three-dimensionally.[1–5]

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Recently, a systematic review of the scientific literature on CBCT imaging and analysis of the upper airway was performed.[1] It was found that three-dimensional (3D) analysis of the upper airway using CBCT is accurate and reliable, although important obstacles still need to be addressed. These include the impact of respiration phase, influence of tongue position and mandible morphology, longitudinal and cross-sectional 3D CBCT upper airway evaluation, and 3D CBCT definition of the anatomical boundaries of the upper airway. Regarding the latter aspect, it was found that the anatomical definitions of the airway subregions from the nasal and oral cavities to the larynx were extremely variable among different authors. What is more, many studies included in the systematic review did not specify the anatomical boundaries of the particular region of interest in their methodology. As a result, comparisons among studies, even between those claiming to analyse the same airway subregion, is often difficult and prone to error.

In this context, the objectives of this paper were the following: (1) to provide 3D anatomical limits for the different subregions of the upper (pharyngeal) airway; (2) to precisely translate these anatomical limits into cephalometric landmarks that can be used reliably in CBCT analysis; and (3) to validate a measuring protocol for the predefined subregions of the upper airway using widespread third-party software.

Materials and methods

The study protocol obtained local ethics review board approval. CBCT scans from 40 healthy individuals (20 females and 20 males) were prospectively obtained. Inclusion criteria were the following: (1) Caucasian; (2) age between 23 and 35 years; (3) Angle Class I molar relationship; (4) class I facial profile and no clinically obvious facial asymmetries; (5) normal body mass index (BMI); (6) no prior surgery in the head and neck. Individuals at risk of sleep-disordered breathing according to the Epworth Sleepiness Scale, and with congenital or acquired craniofacial anomalies were excluded from the evaluation.

Scans were performed using a standardized scanning protocol (i-CAT^{TM}, Imaging Sciences International, Inc., Hatfield, PA, USA) between March and May 2011. The period of data acquisition was strictly limited to these dates in order to ensure the same calibration parameters. In addition, calibration of the CBCT apparatus was checked daily during the data acquisition period. Vertical scanning was performed in ‘extended field’ modus (field of view (FOV) 17 cm diameter, 22 cm height; scan time 2×20 s; voxel size 0.4 mm) at 120 kV (according to DICOM field 0018,0060 KVP) and 48 mA (according to DICOM field 0018,1151 X-ray tube current). Special attention was paid to proper patient positioning for the scan: patients were instructed to sit upright and position themselves in a natural head position (NHP)[6,7] with the help of a mirror and a laser beam. They were also taught to place the mandible at maximum intercuspation without the use of a wafer in order to avoid tongue displacement. They were asked to rest the tongue in a relaxed position, breathe lightly, and avoid any other motor reaction.

The DICOM (Digital Imaging and Communications in Medicine) data were processed using third-party software (Dolphin Imaging®, version 11.0, Chatsworth, CA, USA). Prior to airway evaluation, all 40 CBCT databases were preliminarily assessed in order to determine the most appropriate threshold value for upper airway analysis in this study. The automatically fixed threshold value was manually increased for each dataset until the nasopharyngeal airway was adequately depicted. The average threshold value of all the patients thus defined was 70 (range 48–81) and was established as the reference threshold for this study.

Subsequently, all CBCT datasets were evaluated separately by the two investigators of this study (RGM, GRJS) in order to determine the inter-observer error. In addition, each patient was reassessed separately by each investigator 4 weeks after the first evaluation with the aim of establishing the intra-observer error. Separate spreadsheets were used to record the first and second measurements in order to avoid analysis bias from the first results.

On multiple planar reconstruction images, the skull was reoriented to the Frankfort horizontal (FH) using the following guidelines: (1) In the frontal view, the mid-sagittal plane was fixed through the centre of the anterior nasal spine (ANS) and the axial plane was constructed through both infraorbitale skeletal landmarks. When a bifid ANS was encountered in the frontal view, the mid-sagittal plane was established at the midpoint between the two bony prominences. (2) In the right sagittal view, the axial plane was placed through the right porion and right infraorbitale landmarks. For standardization, the left sagittal view was not processed in order to avoid orientation problems due to asymmetrically positioned porions. (3) In the transversal view (patient facing down or endocranial view), the mid-sagittal plane was constructed through crista galli and basion. In the opposite transversal view (patient facing up or exocranial view), it was ensured that no ‘yaw’ (transversal rotation) of the mandible or the zygomatic arches was present. Figure 1 illustrates the coronal, sagittal, and axial reconstruction slices after head orientation in a male patient.

In the sagittal view, the cranial base angle and cranio-cervical inclination were also measured. The cranial base angle of the analysed population sample was used for descriptive purposes; the cranio-cervical inclination was evaluated in order to test the homogeneity of head inclination during scanning, and hence the effectiveness of our head positioning protocol. The cranial base angle was measured between the points nasion, sella and basion, as described by Enlow (Fig. 2). Following other author recommendations,[8,9] the cranio-cervical inclination was measured as the angle between the line formed by connecting C2od (tangent point at the most superior–posterior point of the odontoid process of C2) and C2ip (the most inferior–posterior point of the body of C2) and the SN line (sella–nasion) (Fig. 3).

The process of airway segmentation was systematized as follows: A virtual marker for the region-of-interest definition, referred to in the software as the ‘seed point’, was placed in the airway region immediately anterior to C2ia (the most inferior–anterior point of the body of C2). The automatic threshold thus determined by the program was manually increased to the value of our predefined airway sensitivity (70). Subsequently, the limits of the nasopharynx, oropharynx, and hypopharynx were outlined by the investigator. Within each separate region, the software calculated the total airway volume (mm^3) and minimum cross-sectional area (mm^2) automatically. The anatomical limits of each subregion were established by the authors according to clinical experience and previous work.[1] The ensuing technical boundaries were determined with the aim of defining reproducible limits based on reliable anatomical cephalometric landmarks that are easily identifiable on CBCT studies. Table 1 details the anatomical and technical boundaries of each subregion of the upper airway. Figures 4–6 exemplify the independent evaluation of the nasopharynx, oropharynx, and hypopharynx according to these limits. In the case of the hypopharynx, care was taken to add a second

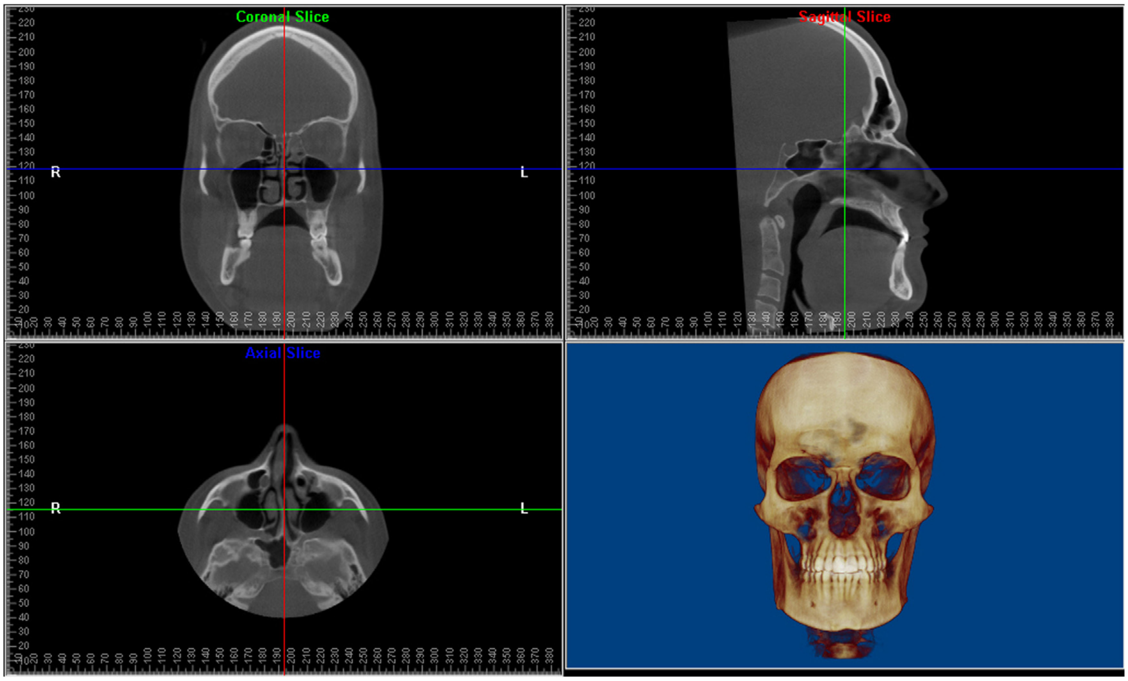

Fig. 1. Coronal, sagittal, and axial reconstruction slices after head orientation.

virtual 'seed point' when the epiglottis was positioned halfway across the air space of the airway, in order to adequately include all the air within the predefined limits (Fig. 7).

The statistical analysis was performed using SPSS for Windows, version 19.0 (SPSS, Chicago, IL, USA). Reproducibility was evaluated by calculating the inter- and intra-observer error with Dahlberg's formula.[10] Intraclass correlation coefficients (ICC) were obtained. A descriptive analysis was used to obtain preliminary normative data for the sample as a whole and also when stratified by gender. After corroborating the normal distribution of the sample with the Kolmogorov–Smirnov test, a Student's t-test for independent samples was used to compare the sex groups. Repeated measures analysis of variance (ANOVA) was used to compare the three subregions of the upper airway. Friedman's test was used to stratify the analysis by gender. Statistical significance was fixed at $\alpha = 0.05$.

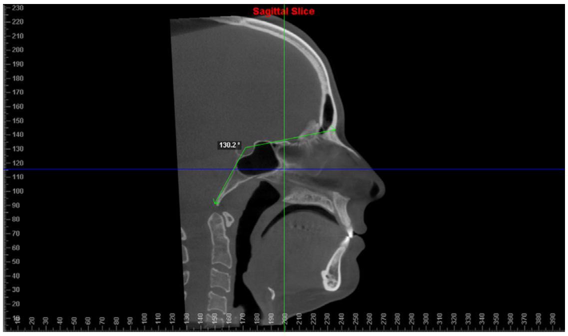

Fig. 2. Cranial base angle.

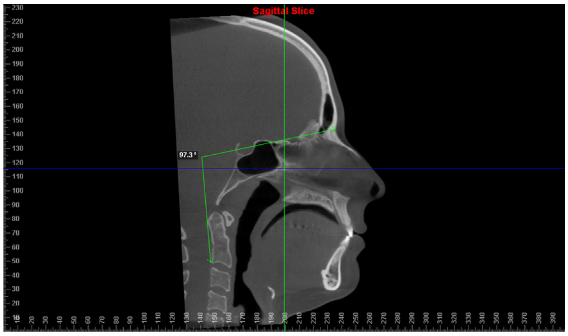

Fig. 3. Cranio-cervical inclination.

Results

Of the initial 40 patients whose CBCTs were analysed, one male and one female were excluded because of inadequate localization of the crista galli for skull orientation purposes, and three females were excluded for pathological findings on radiology (hypertrophic adenoids in one case and inadequately ventilated sinuses in the two others). Thus, the studied sample comprised 35 subjects, of whom 19 were male (54.3%) and 16 female (45.7%). Adequate hypopharyngeal analysis was impossible for three of the 19 males because the FOV did not include the most anterior–inferior point of the body of C4 (C4ai); hence, only the nasopharynx and oropharynx were quantified for these three male patients.

Tables 2 and 3 summarize the intra- and inter-observer reproducibility analysis, respectively. Whereas the intra-observer error for volumetric calculations was below 4% for both investigators, it ranged

Table 1. Anatomical and technical limits of the upper airway.

Region	Limits	Anatomical	Technical
Nasopharynx	Anterior	Frontal plane perpendicular to FH passing through PNS	=
	Posterior	Soft tissue contour of the pharyngeal wall	Frontal plane perpendicular to FH passing through C2sp
	Upper	Soft tissue contour of the pharyngeal wall	Transversal plane parallel to FH passing through the root of the clivus
	Lower	Plane parallel to FH passing through PNS and extended to the posterior wall of the pharynx	=
	Lateral	Soft tissue contour of the pharyngeal lateral walls	Sagittal plane perpendicular to FH passing through the lateral walls of the maxillary sinus
Oropharynx	Anterior	Frontal plane perpendicular to FH passing through PNS	=
	Posterior	Soft tissue contour of the pharyngeal wall	Frontal plane perpendicular to FH passing through C2sp
	Upper	Plane parallel to FH passing through PNS and extended to the posterior wall of the pharynx	=
	Lower	Plane parallel to FH plane passing through C3ai	=
	Lateral	Soft tissue contour of the pharyngeal lateral walls	Sagittal plane perpendicular to FH passing through the lateral walls of the maxillary sinus
Hypopharynx	Anterior	Frontal plane perpendicular to FH passing through PNS	=
	Posterior	Soft tissue contour of the pharyngeal wall	Frontal plane perpendicular to FH passing through C2sp
	Upper	Plane parallel to FH plane passing through C3ai	=
	Lower	Plane parallel to FH connecting the base of the epiglottis to the entrance to the oesophagus	Plane parallel to FH connecting the base of the epiglottis to C4ai
	Lateral	Soft tissue contour of the pharyngeal lateral walls	Sagittal plane perpendicular to FH passing through the lateral walls of the maxillary sinus

FH, Frankfort horizontal; PNS, posterior nasal spine; C2sp: superior–posterior extremity of the odontoid process of C2; C3ai, most anterior–inferior point of the body of C3; C4ai, most anterior–inferior point of the body of C4.

between 11% and 20% for minimum cross-sectional area calculations. In terms of ICC, volumetric measurements ranged between 0.981 and 0.999 and thus were highly reproducible, but area measurements ranged between 0.780 and 0.937 and hence were moderately reproducible. The fact that all confidence intervals included 0, ruled out a bias tendency when performing the second measurement for both investigators. The inter-observer error analysis revealed excellent reproducibility for cranial base angle and craniocervical inclination measurements (ICC 0.983 and 0.992, respectively), good reproducibility for volumetric calculations (ICC between 0.986 and 0.998), and again moderate reproducibility for cross-sectional area calculations (ICC between 0.837 and 0.876).

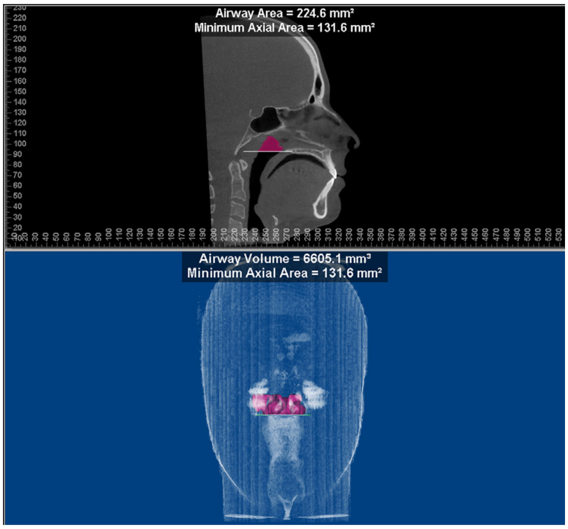

Fig. 4. Evaluation of the nasopharyngeal airway.

Table 4 shows the descriptive variables for the whole sample and for males and females separately. When analysing sexual dimorphism with the Student's *t*-test for independent samples, males showed a significantly greater oropharyngeal volume ($P = 0.001$) and hypopharyngeal volume ($P < 0.001$) than females (Fig. 8). In addition, the minimum cross-sectional area for the oropharynx was significantly greater in males than in females ($P = 0.011$) (Fig. 9).

Table 5 summarizes the comparison between the three analysed subregions. Repeated measures ANOVA revealed the volume of the oropharynx was significantly greater (mean 20,994.20 mm^3, SD 6104.37) than that of the nasopharynx (mean 7385.84 mm^3, SD 2035.17) and hypopharynx (mean 6654.92 mm^3, SD 2076.01). The volumetric superiority of the oropharynx was also confirmed separately in males and females. Cross-sectional area differences did not reach statistical significance, although they did show a marked trend ($P = 0.078$). Paired comparisons suggested the most noticeable differences could be found between the nasopharynx and hypopharynx ($P = 0.059$). In other words, while the minimum cross-sectional areas of the nasopharynx and oropharynx were

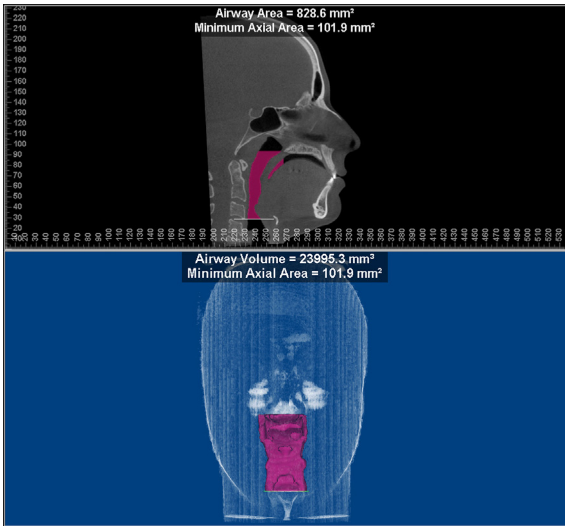

Fig. 5. Evaluation of the oropharyngeal airway.

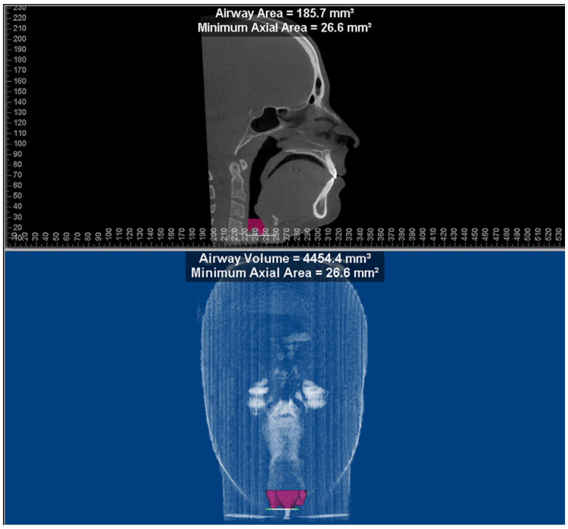

Fig. 6. Evaluation of the hypopharyngeal airway.

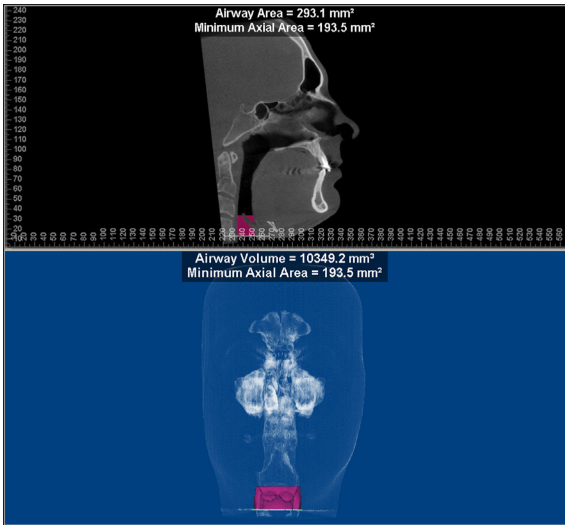

Fig. 7. If the epiglottis was positioned halfway across the hypopharynx, thereby determining a secluded air space, a second virtual ‘seed point’ was added in order to include this area/volume within the region of interest.

similar, the nasopharyngeal area (slightly smaller according to the descriptive analysis) tended towards statistically significant inferiority compared to the hypopharynx.

Discussion

Currently, objective airway evaluation is possible using several techniques including CBCT, MDCT, magnetic resonance imaging (MRI), cine-MRI, endoscopy, and optical coherence tomography. However, due to its advantages over other routine imaging techniques such as MDCT (mainly in terms of lower radiation dose) and MRI (especially in terms of easier accessibility and lower costs), CBCT has become the method of choice for upper airway analysis. Recent research has confirmed its accuracy and reliability for this particular indication.[1,11]

The fact that systematized protocols for upper airway analysis with CBCT are still lacking in the clinical routine is due to the persistence of important obstacles. These include the following[1]: (1) impact of respiration phase, (2) influence of tongue position and mandible morphology, (3) longitudinal and cross-sectional 3D CBCT upper airway evaluation, and (4) 3D CBCT definition of the anatomical boundaries of the upper airway. Indeed, the lack of control of these variables hinders the definition of a methodical approach to upper airway evaluation. Substantial clinical research is needed in order to control systematic errors and enable unbiased comparisons between different studies.

Regarding the first two issues, most studies do not control or do not specify how respiration phase and lingual or mandibular position is managed during CBCT data acquisition.[1] This is surprising taking into account that qualitative and quantitative changes of the airway occur during different breathing stages[12,13] and that the position of the mandible and tongue influence the shape and size of the oropharyngeal airway.[14] The patient should be instructed to avoid deglutition and any other movement during the CBCT scan, breathe lightly, and maintain the mandible in a reproducible position, be it maximum intercuspation or centric relation.[15] If a wafer is to be used in order to stabilize the mandible, it is important that this wafer does not displace the tongue due to its shape or thickness so that the volume of the oropharyngeal airway is not distorted. If the latter methodology is respected, both inspiration and expiration contribute to the final airway volume, thereby introducing an error that is nevertheless systematic.[15] As

Table 2. Intra-observer error analysis.[a]

		Difference between first and second measurement		95% CI for the difference		Dahlberg's *d*	Relative error (%)	ICC
		Mean	SD	Inferior limit	Superior limit			
OBS 1	Minimum cross-sectional area of the nasopharynx	3.76	22.07	−3.56	11.08	15.61	19.74	0.848
	Nasopharyngeal volume	59.61	394.51	−71.23	190.44	278.16	3.73	0.981
	Minimum cross-sectional area of the oropharynx	−3.15	20.62	−9.98	3.69	14.54	15.92	0.780
	Oropharyngeal volume	5.94	459.72	−146.52	158.40	320.42	1.53	0.997
	Minimum cross-sectional area of the hypopharynx	−1.89	21.18	−8.91	5.14	14.82	14.60	0.904
	Hypopharyngeal volume	−31.95	220.01	−104.92	41.01	154.99	2.33	0.994
OBS 2	Minimum cross-sectional area of the nasopharynx	3.30	14.84	−1.62	8.22	10.60	12.11	0.937
	Nasopharyngeal volume	−33.67	259.65	−119.78	52.44	182.52	2.49	0.992
	Minimum cross-sectional area of the oropharynx	1.19	17.23	−4.53	6.90	12.04	13.45	0.825
	Oropharyngeal volume	42.29	308.55	−60.04	144.61	217.10	1.03	0.999
	Minimum cross-sectional area of the hypopharynx	2.32	17.46	−3.47	8.11	12.28	11.70	0.936
	Hypopharyngeal volume	−50.71	167.05	−106.12	4.69	121.82	1.84	0.996

OBS 1, observer 1; OBS 2, observer 2; SD, standard deviation; CI, confidence interval; ICC, intraclass correlation coefficient.

[a] Means, SD, and CI for volumes are expressed in mm^3; means, SD, and CI for areas are expressed in mm^2.

newer scans reduce their acquisition times, respiratory phase control will become systematically practicable.

Another concern is the need to achieve an accurate 3D longitudinal and cross-sectional evaluation of the upper airway, both quantitatively and qualitatively. In this study, patients were scanned sitting upright in the NHP because NHP is the recommended scanning posture for baseline assessment of upper airway morphology and dimensions.[1] However, it has been shown that slight variations in cranio-cervical extension (while in NHP) may affect the reliability of measurements in general[16] and modify the size of the pharyngeal airway in particular.[9,17,18] Head posture can be assessed by evaluating cranio-vertical orientation (i.e., the inclination of the SN plane to a true vertical line) or cranio-cervical orientation (i.e., the inclination of the SN plane to a line through the cervical vertebrae).[19] The second option is preferred by most authors[8,9] because it eliminates the need for an external reference. In addition, the anatomical cephalometric landmarks used to define it are precisely and easily identifiable on CBCT data and hence yield very reproducible results (Table 3). Post-processing of DICOM images by third-party software permits virtual head reorientation in order to facilitate image superimposition when treatment outcome evaluation or growth assessment is intended. Virtual head orientation is also essential for accurate and reproducible individualized analysis of the upper airway subregions, since technical boundaries as defined in the presented methodology are based on well-defined planes. However, virtual head reorientation does not necessarily obviate bias in quantitative and qualitative analysis, since the dimensions and morphology of the upper airway are dependent on the patient's head position and cranio-cervical inclination during image acquisition. It is thus crucial to pay attention to adequate head orientation with the aid of proper patient instruction (e.g., a marking point at a distance, a laser beam, or a mirror). According to the descriptive statistics of the cranio-cervical inclination analysis (Table 4), the patient positioning protocol used in this study

Table 3. Inter-observer error analysis.[a]

	Difference between OBS 1 and OBS 2		95% CI for the difference		Dahlberg's *d*	Relative error (%)	ICC
	Mean	SD	Inferior limit	Superior limit			
Cranial base angle	0.37	1.04	0.03	0.72	0.77	0.58	0.983
Cranio-cervical inclination	0.16	1.51	−0.34	0.66	1.06	1.11	0.992
Minimum cross-sectional area of the nasopharynx	−8.71	18.36	−14.80	−2.62	14.20	18.40	0.876
Nasopharyngeal volume	77.95	337.98	−34.14	190.04	241.92	3.26	0.986
Minimum cross-sectional area of the oropharynx	3.99	15.97	−1.31	9.29	11.48	12.36	0.837
Oropharyngeal volume	−30.91	435.79	−175.43	113.62	304.50	1.45	0.998
Minimum cross-sectional area of the hypopharynx	−0.99	27.18	−10.00	8.03	18.95	18.48	0.839
Hypopharyngeal volume	42.02	219.91	−30.91	114.95	156.11	2.34	0.994

OBS 1, observer 1; OBS 2, observer 2; SD, standard deviation; CI, confidence interval; ICC, intraclass correlation coefficient.

[a] Means, SD, and CI for volumes are expressed in mm^3; means, SD, and CI for areas are expressed in mm^2.

Table 4. Descriptive analysis.[a]

Measurement		*n*	Mean	SD	Typical error	95% CI for the mean		Min	Max	Median
						Inferior limit	Superior limit			
Cranial base angle	Total	35	131.61	4.12	0.70	130.19	133.03	123.05	140.30	131.65
	Male	19	131.02	4.58	1.05	128.80	133.22	123.05	140.30	131.15
	Female	16	132.33	3.51	0.88	130.45	134.19	126.35	138.15	133.18
Cranio-cervical inclination	Total	35	95.04	8.14	1.38	92.24	97.83	77.95	113.85	96.60
	Male	19	96.38	8.97	2.06	92.05	100.70	78.20	113.85	96.95
	Female	16	93.45	6.97	1.74	89.73	97.16	77.95	103.60	95.25
Minimum cross-sectional area of the nasopharynx	Total	35	81.54	39.03	6.60	68.12	94.94	16.00	158.63	74.40
	Male	19	80.35	42.52	9.75	59.85	100.84	16.00	144.90	83.70
	Female	16	82.95	35.78	8.94	63.88	102.01	36.80	158.63	72.14
Nasopharyngeal volume	Total	35	7385.84	2035.17	344.01	6686.73	8084.94	3842.85	11,503.28	6859.18
	Male	19	7415.11	2101.63	482.15	6402.15	8428.05	4242.20	11,503.28	6859.18
	Female	16	7351.09	2021.33	505.33	6273.99	8428.17	3842.85	10,459.83	6981.99
Minimum cross-sectional area of the oropharynx	Total	35	90.90	27.23	4.60	81.55	100.25	36.25	141.73	91.20
	Male	19	101.32	25.48	5.84	89.03	113.59	40.80	141.73	104.28
	Female	16	78.54	24.52	6.13	65.47	91.60	36.25	115.53	81.19
Oropharyngeal volume	Total	35	20,994.20	6104.37	1031.83	18,897.27	23,091.12	9297.43	39,481.75	19,306.43
	Male	19	23,980.83	6241.83	1431.97	20,972.35	26,989.29	16,008.13	39,481.75	24,510.53
	Female	16	17,447.59	3604.90	901.23	15,526.66	19,368.50	9297.43	23,991.90	17,593.58
Minimum cross-sectional area of the hypopharynx	Total	32	103.13	47.39	8.38	86.04	120.21	15.78	216.43	107.35
	Male	16	108.85	46.79	11.70	83.01	133.78	15.78	177.00	111.78
	Female	16	97.41	48.80	12.20	71.40	123.41	27.55	216.43	98.95
Hypopharyngeal volume	Total	32	6654.92	2076.01	366.99	5906.44	7403.40	3341.73	10,477.70	6366.20
	Male	16	8101.75	1799.95	449.99	7142.62	9060.87	3341.73	10,477.70	7949.74
	Female	16	5208.09	1096.08	274.02	4624.03	5792.15	3706.75	7711.85	4995.26

n, sample size; SD, standard deviation; CI, confidence interval; Min, minimum; Max, maximum.

[a] Angles and inclinations are measured in degrees; volumes are expressed in mm^3 and areas in mm^2.

achieved highly homogeneous head extensions (mean 95.04°, SD 8.14°).

The precise 3D definition of the anatomical boundaries of the different pharyngeal airway subregions is a critical issue for upper airway analysis. Many studies tend to omit the definition of the specific anatomical limits used for a particular subregion.[1] Moreover, those studies that do report their chosen boundaries illustrate the great inconsistency that exists among authors. Indeed, the anatomical definitions of the airway subregions from the nasal and oral cavities to the larynx are exceedingly variable among different study groups. This is greatly a consequence of the lack of a specific subregion definition in the scientific literature in general and in the anatomical literature in particular. Quantitative and qualitative comparisons among studies, even between those claiming to analyse the same particular subregion, are hence very problematic and prone to analysis bias. For example, while some studies take the plane parallel to the palatal plane that passes through the most antero-inferior point of C2 as the inferior limit of the oropharynx,[3,20] others use other anatomical landmarks such as the most antero-inferior point of C3,[21] the tip[2,14,22] or the base of the epiglottis.[23] Consequently, comparisons between studies are often methodologically impossible, and the combination of data in order to obtain normative values of the upper airway is extremely difficult.

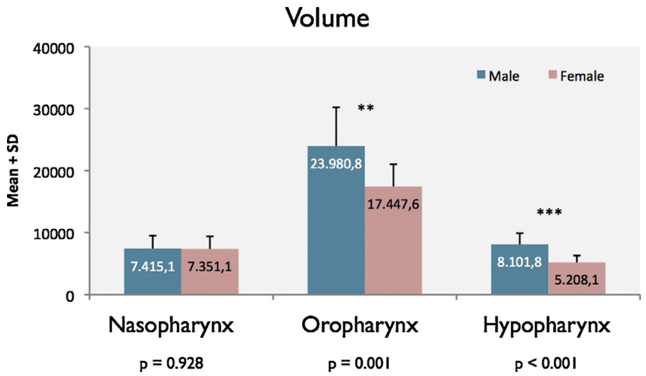

Fig. 8. Sexual dimorphism analysis for volumes: Student's *t*-test for independent samples.

In light of the results of a systematic review on CBCT imaging and analysis of the upper airway,[1] the present study tried to provide the scientific community with logical anatomical limits for the subregions of the upper (i.e., pharyngeal) airway. Furthermore, corresponding cephalometric landmarks that are easily and reliably defined on CBCT images were provided for consistent and reproducible analysis (Table 1). Standardization of these anatomical limits would homogenize upper airway analysis and permit

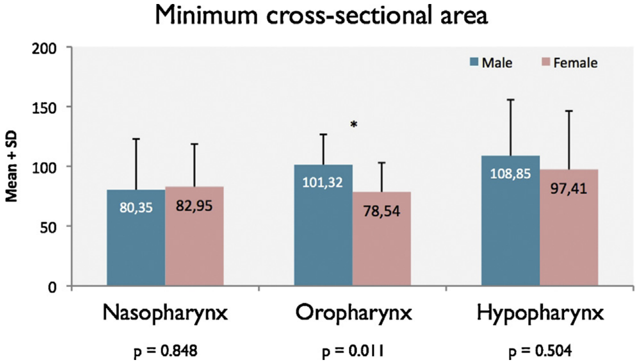

Fig. 9. Sexual dimorphism analysis for minimum cross-sectional areas: Student's *t*-test for independent samples.

comparisons among future studies. The validation of these boundaries was performed using the Dolphin Imaging software package on the grounds that this third-party software is used widely for orthodontic analysis and orthognathic surgery planning. Moreover, its accuracy and reliability for airway assessment on CBCT have been adequately validated.[11] After following a predefined head orientation protocol, the chosen boundaries showed excellent intra- and inter-observer reproducibility for volumetric analysis of the individualized subregions. However, the reproducibility of minimum cross-sectional area measurements between the two investigators and also for the same investigator at different time points was not as consistent. This combination of highly reproducible volumetric results and less reproducible area measurements requires specific clarification. From a methodological perspective, 3D head orientation during CBCT scan acquisition was adequately standardized, as proven by the highly homogeneous cranio-cervical inclination values for the analysed population sample. Similarly, virtual head reorientation based on the anatomical landmarks of the protocol was also highly reliable in light of the highly reproducible intra- and inter-observer volumetric results. The fact that the total study sample was preliminarily evaluated in order to determine a single threshold value (that was then manually defined by the investigators prior to automatic 3D and two-dimensional (2D) calculations by the program) eliminates the potential source of error due to different threshold windows. Alves et al.[24] studied the most accurate threshold value for airway volume evaluation on an airway prototype and found that values between 70 and 75 showed no statistically significant differences compared to the gold standard (the actual physical volume of the prototype). Although our study was performed in vivo, our pre-calculated threshold value fell within this range. Finally, the high reproducibility of the volumetric measurements for the three subregions of the upper airway according to the predefined technical boundaries validates the latter. Since volumes are values of several thousand voxels (cubic millimetres) but areas are measured in pixels (tens of square millimetres), it is possible that slight variations in virtual head orientation give way to important modifications of the cross-sectional area and hence affect reproducibility significantly. Ghoneima and Kula[11] used CBCT DICOM data and Dolphin Imaging to measure the volume and minimum cross-sectional area of an air-filled acrylic airway model and found no statistically significant differences between the manual and the digital measurements, thereby proving the software's high accuracy and reliability for both 2D and 3D analysis. However, the simplicity of the constructed airway model in comparison to the intricate anatomy of the airway in vivo was acknowledged.[11] Moreover, the airway model was installed in a human skull with a fixed cranio-cervical extension – hence, no need for a patient positioning protocol or virtual head orientation – and with no soft tissue movement due to deglutition or respiration, thereby creating the perfect scenario for the static evaluation of a structure that is in reality dynamic and, in addition, lodged in a mobile framework, the human neck. The influence of these variables is critical in vivo and probably explains the moderate reproducibility of 2D measurements found in the present study. Indeed, Dahlberg's value, which integrates systematic and random error,[10] defined a low relative error for volumes but a moderate relative error for areas. The ICCs were above 0.98 for volumes in both the intra- and inter-observer reproducibility analyses, but mostly below 0.90 for areas.

Table 5. Comparison between the three anatomical subregions.[a]

		n	Mean	SD	*P*-value
Minimum cross-sectional area in total sample	Nasopharynx	35	81.54	39.03	0.078 (F)
	Oropharynx	35	90.90	27.23	
	Hypopharynx	32	103.13	47.39	
Minimum cross-sectional area in males	Nasopharynx	19	80.35	42.52	0.269 (Fri)
	Oropharynx	19	101.32	25.48	
	Hypopharynx	16	108.85	46.79	
Minimum cross-sectional area in females	Nasopharynx	16	82.95	35.78	0.444 (Fri)
	Oropharynx	16	78.54	24.52	
	Hypopharynx	16	97.41	48.80	
Volume in total sample	Nasopharynx	35	7385.84	2035.17	<0.001 (F)
	Oropharynx	35	20,994.20	6104.37	
	Hypopharynx	32	6654.92	2076.01	
Volume in males	Nasopharynx	19	7415.11	2101.63	<0.001 (Fri)
	Oropharynx	19	23,980.83	6241.83	
	Hypopharynx	16	8101.75	1799.95	
Volume in females	Nasopharynx	16	7351.09	2021.33	<0.001 (Fri)
	Oropharynx	16	17,447.59	3604.90	
	Hypopharynx	16	5208.09	1096.08	

n, sample size; SD, standard deviation; F, repeated measures ANOVA for comparisons in total sample; Fri: Friedman's test for comparisons in males and females, respectively.

[a] Volumes are expressed in mm^3 and areas in mm^2.

Considering the excellent reproducibility of the 3D calculations in particular, the results of this study are suitable to report preliminary normative volumetric data of the upper airway subregions of the

Caucasian population. The reported normative values would correspond to a young (23–35 years of age) healthy adult population with a Class I dental occlusion and Class I facial profile without facial asymmetry. According to the study by Schendel et al.[25] on a wide population sample aged between 6 and greater than 56 years, the age frame of the patients in our study would correspond to the peak volume, cross-sectional area, and airway length attained with human growth and development. Compared to the results of our study, Schendel et al.[25] found lower global airway volumes (average 14.77 for the age frame 21–25 years; average 15.59 for the age frame 26–30 years). Though the measurement unit was not specifically defined, it can be assumed it was 1000 mm^3. The authors used the 3dMD Vultus® software to measure the region – between PNS and the most anterior–superior edge of C4; no particular technical boundaries, head positioning protocol during CBCT scanning, or subsequent virtual head orientation procedures were mentioned. According to our proposed anatomical classification, the upper airway region analysed by Schendel et al.[25] comprised the oropharynx and a part of the hypopharynx. Nevertheless, the reported volumetric values[25] were smaller than those found for the oropharynx in our study. These differences could be the result of different CBCT settings or different threshold values in 3D airway software analysis. Unfortunately, the authors did not specify the latter parameters either. Quantitative comparisons of our results with those of other studies are difficult because many were performed in children[2,14,23,8,26] or orthognathic surgery patients,[14,15,27,28] and the limits of the analysed upper airway regions were not specified or were different to ours.[2,3,14,20,21,29] Furthermore, results from studies that do not report CBCT settings and the software threshold definition, use software that lacks proper previous validation, or do not specify patient scanning conditions should be taken with caution.[1]

In conclusion, there is a need to comprehensively define the subregions of the pharyngeal airway in order to standardize upper airway analysis and permit objective comparisons between different studies. The paired anatomical landmarks and subsequent technically defined boundaries proposed in this study are clinically reasonable, technically convenient, and statistically reliable. The preliminary normative data for the upper airway subregions of healthy young Caucasian adults require additional contrast with further studies following a similar methodology. Special attention must be paid to patient head positioning during CBCT scan acquisition and the subsequent virtual reorientation protocol in order to minimize the relative error in 2D measurements.

Funding

None to declare.

Competing interests

None to declare.

Ethical approval

Ethical approval was obtained from the local Ethics Review Board of the General Hospital St-Jan Bruges (Bruges, Belgium).

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Appendix 2

11.1. ***Approval of the PhD Thesis project by the UIC***

11.2. ***Approval of the PhD Thesis project by the Teknon Medical Center Ethics Committee on Clinical Investigation (Comité Ético de Investigación Clínica, CEIC)***

11.3. ***Approval of the PhD Thesis project by the Ethics in Research Committee (Comité d'Ética de Recerca, CER)***

11.4. ***Approval of the PhD Thesis project by the Health Sciences Doctoral Academic Committee***

Universitat
Internacional
de Catalunya

FACULTAD DE ODONTOLOGÍA
Comisión científica

La comisión de doctorado del Departamento de Odontología de la Universitat Internacional de Catalunya, CERTIFICA que

El presente proyecto de Tesis Doctoral titulado: "**Evaluación mediante CBCT (cone-beam computerized tomography) de los efectos de la cirugía ortognática de avance sobre la via aérea superior**", cuyos directores son el Dr. Federico Hernández Alfaro y el Dr. Gwen R. J. Swennen y cuyo investigador principal es el doctorando **Raquel Guijarro Martínez**

ha sido evaluado satisfactoriamente y es apto para entrar en el programa de doctorado.

Firmado en Sant Cugat del Vallès, a 23 de Febrero del 2011.

Universitat Internacional
de Catalunya
Facultat d'Odontologia

Dr Lluís Giner Tarrida
Director de la comisión de doctorado de Odontología

Título:	**Evaluación mediante CBCT (cone-beam computerized tomography) de los efectos de la cirugía ortognática de avance sobre la via aérea superior**
Investigador principal:	**Raquel Guijarro Martínez**
Director de la tesis:	**Dr. Federico Hernández Alfaro; Dr. Gwen R. J. Swennen**
Número de estudio:	**CIR-ECL-2011-01-NF**

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APROBACIÓN DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

D. Josep Maria Payà i Padreny, Presidente del Comité Ético de Investigación Clínica de Centro Médico Teknon de Barcelona,

CERTIFICA

Que este Comité ha evaluado la propuesta de tesis doctoral correspondiente al estudio titulado: **"Evaluación mediante CBCT (Cone-Beam-Computerized Tomography) de los efectos de la cirugía ortognática de avance sobre la vía área superior"** y considera que:

> Se cumplen los requisitos éticos, metodológicos y de idoneidad del protocolo en relación con los objetivos del estudio.
>
> La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

Y que este Comité acepta que este estudio sea realizado en Centro Médico Teknon por el Dr. Federico Hernández Alfaro como Director de la tesis doctoral contando como doctorando a la Dra. Raquel Guijarro. A la vez que solicita formalmente al Dr. Federico Hernández Alfaro, Director e investigador principal, información de seguimiento cada 6 meses e informe final.

En Barcelona, a 06 de febrero de 2012

Fdo. Dr. Josep Maria Payà i Padreny

CMT-57

CER Comitè d'Ètica de Recerca
Universitat Internacional de Catalunya

CARTA DE CONFORMITAT DEL CER PER A PROJECTES AVALUATS I APROVATS PER UN CEIC

Codi de l'estudi:CIR-ECL-2011-01-NF
Versió del protocol:1.0
Data de la versió:12/02/13
Títol:"Evaluación mediante CBCT (cone-beam computerized tomography) de los efectos de la cirugía ortognática de avance sobre la vía aérea superior"

Sant Cugat del Vallès,14 de febrer de 2013

Investigadora: Raquel Guijarro Martínez

Titol de l'estudi: :"Evaluación mediante CBCT (cone-beam computerized tomography) de los efectos de la cirugía ortognática de avance sobre la vía aérea superior"

Benvolgut (da),

Valorat el projecte presentat, el CER de la Universitat Internacional de Catalunya, considera que, des del punt de vista ètic, reuneix els criteris exigits per aquesta institució i, per tant, ratifica l'aprovació dels CEICs aportada, d'acord amb el reglament vigent.

Em permeto recordar-li que si en el procés d'execució es produís algun canvi significatiu en els seus plantejaments, hauria de ser sotmès novament a la revisió i aprovació del CER.

Quedo a disposició per a qualsevol dubte o aclaració al respecte.

Atentament,

Dr. Josep Argemí
President CER-UIC

Universitat
Internacional
de Catalunya
Escola
de Doctorat

Barcelona, 25 de noviembre de 2013

Sra. Raquel Guijarro Martínez
Paseo Porta Coeli, 12
46530 Puzol - Valencia

Estimada Sra.

Por la presente, le comunico que la Comisión Académica del Doctorado en Ciencias de la Salud, en la su sesión del 12 de noviembre de 2013, y una vez estudiada su Tesis ha acordado:

Se aprueba el depósito en la CQ3C de la Tesis elaborada por Raquel Guijarro Martínez titulado "Cone-beam computerized tomography (CBCT) evaluation of the upper airway in the context of orthognathic surgery" dirigida por Federico Hernández Alfaro y Gwen R. J. Swennen.

Aprovecho la oportunidad para saludarla cordialmente,

Jaime Oliver Serrano
Secretario Comisión Académica
Doctorado en Ciencias de la Salud

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de Catalunya
VICERECTORAT DE RECERCA