THIRD MOLAR MANAGEMENT

MYRTHEL VRANCKX

ERUPTION, REMOVAL AND ASSOCIATED RISKS

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THIRD MOLAR MANAGEMENT: ERUPTION, REMOVAL AND ASSOCIATED RISKS

TOWARDS EVIDENCE-BASED TREATMENT GUIDELINES

Myrthel VRANCKX

Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

Jury:
Promoter: Prof. dr. Reinhilde JACOBS
Co-promoter: Prof. dr. Constantinus POLITIS
Chair examining committee: Prof. dr. Steven DYMARKOWSKI
Chair public defense: Prof. dr. Tania ROSKAMS
Jury members: Prof. dr. Antoon DE LAAT
Prof. dr. Wim TEUGHELS
Prof. dr. Michael BORNSTEIN
Prof. dr. Ivo LAMBRICHTS

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Jury:
Promotor: Prof. dr. Reinhilde JACOBS
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Voorzitter leescommissie: Prof. dr. Steven DYMARKOWSKI
Voorzitter openbare verdediging: Prof. dr. Tania ROSKAMS
Juryleden: Prof. dr. Antoon DE LAAT
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Prof. dr. Ivo LAMBRICHTS

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PREFACE

This doctoral thesis consists of 7 research chapters, proceeded by a scientific introduction and concluded by a general discussion. The research chapters follow the standard scientific IMRAD structure (Introduction, Methods, Results and Discussion), and were based on the following peer-reviewed publications:

Chapter 1:

Vandeplas C, **Vranckx M**, Hekner D, Politis C, Jacobs R. Pathologies associated with retention of asymptomatic third molars: a systematic review. *J Oral Maxillofac Surg.* 2020;S0278-2391:30588–7. (shared first-authorship)

Chapter 2:

Vranckx M, Ockerman A, Coucke W, Claerhout E, Grommen B, Miclotte A, Van Vlierberghe M, Politis C, Jacobs R. Radiographic prediction of mandibular third molar eruption and mandibular canal involvement based on angulation. *Orthod Craniofac Res.* 2019;22:118–23.

Chapter 3:

Vranckx M, Van Gerven A, Willems H, Vandemeulebroucke A, Leite AF, Politis C, Jacobs R. Artificial Intelligence (AI)-driven molar angulation measurements to predict third molar eruption on panoramic radiographs. *Int J Environ Res Public Health.* 2020;17:3716.

Chapter 4:

Vranckx M, Fieuws S, M3BE research group, Jacobs R, Politis C. Prophylactic vs. symptomatic third molar removal: effects on patient postoperative morbidity. *Under review*

Chapter 5:

Vranckx M, Fieuws S, Jacobs R, Politis C. Surgeon's inexperience has limited effect on postoperative morbidity following third molar removal. *Under review*

Chapter 6:

Vranckx M, Lauwens L, Moreno Rabie C, Politis C, Jacobs R. Radiological risk indicators for persistent postoperative morbidity after third molar removal. *Under review*

Chapter 7:

Moreno Rabie C, **Vranckx M**, Rusque Ignacia M, Deambrosi C, Ockerman A, Politis C, Jacobs R. Anatomical relation of third molars and the retromolar canal. *Br J Oral Maxillofac Surg.* 2019;57:765–70.

Chapter 8:

Vranckx M, Geerinckx H, Gaêta-Araujo H, Leite AF, Politis C, Jacobs R. Do anatomical variations of the mandibular canal pose an increased risk of inferior alveolar nerve injury after third molar removal? *Under review*

Chapter 9:

General discussion, conclusions and future perspectives.

PERSONAL ACKNOWLEDGEMENTS

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Table of Contents

List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AAOMS	American Association of Oral and Maxillofacial Surgeons
AI	Artificial intelligence
ALARA	As Low As Reasonably Achievable
BMC	Bifurcations of the mandibular canal
CBCT	Cone-beam computed tomography
CI	Confidence interval
CNN	Convolutional neural network
D3	Postoperative day 3
D10	Postoperative day 10
ERR	External root resorption
GA	General anesthesia
GLMM	Generalized linear mixed model
HR	Hazard ratio
HTA	Health Technology Assessment
IAN	Inferior alveolar nerve
ICC	Intraclass correlation coefficient
ICH-GCP	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use: Guideline for Good Clinical Practice
KCE	Belgian Health Care Knowledge Centre Federaal Kenniscentrum voor de Gezondheidszorg
KIMO	Knowledge Centre for Oral Health (The Netherlands) Kennisinstituut Mondzorg
LA	Local anesthesia
LN	Lingual nerve
LOA	Limits of agreement
LR+	Positive likelihood ratio
LR–	Negative likelihood ratio
M2D	Distal side of the second molar
M3	Third molar

MZP	Mariaziekenhuis Pelt
NHS	National Health Service (United Kingdom)
NICE	National Institute of Health and Care Excellence (United Kingdom)
NPV	Negative predictive value
OAC	Oroantral communication
OMFS	Oral and Maxillofacial Surgery
OR	Odds ratio
PAN	Panoramic radiograph(y)
PD	Probing depth
PPV	Positive predictive value
PTTN	Posttraumatic trigeminal neuropathy
P&G	Pell & Gregory classification
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering
RMC	Retromolar canal
R&S	Rood & Shehab classification
SBD	AZ Sint-Blasius Dendermonde
SED	Procedural sedation
SIGN	Scottish Intercollegiate Guidelines Network
UZL	University Hospitals Leuven
VAS	Visual analogue scale
ZOL	Ziekenhuis Oost-Limburg Genk

CHAPTER 1
General introduction
Aims & Hypotheses

This chapter was partly based on:

Does retaining third molars result in the development of pathology over time?
A systematic review.

Vandeplas C.[1]
Vranckx M.[1] (shared first-authorship)
Hekner D.[2]
Politis C.[1]
Jacobs R.[1,3]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]Department of Oral and Maxillofacial Surgery, Radboud University Medical Center, Nijmegen, The Netherlands.

[3]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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1. Evolution of craniofacial dimensions has led to increasing third molar impaction

Throughout evolution, the dimensions of the human cranium have changed considerably. The size of the neurocranium has increased, while the size of the viscerocranium, including the jawbones, has reduced. The *phylogenetic theory* states that the transition of human nutritional habits from rough uncooked food to a much softer diet has led to a lack of masticatory stimulus, and thus growth stimulus, for our jaws.[1] The number, sizes and shapes of the 32 permanent teeth, however, have remained constant. The third molars or wisdom teeth are the last teeth to erupt, usually between the age of 17–25 years. As a consequence, there is insufficient space left in the dental arch to properly accommodate the teeth.

The failure to reach a normal functional position is termed “impaction” and is mainly dependent on two factors: aberrant orientation of the third molar (follicle) and insufficient space for its eruption posteriorly in the dental arch (Figure 1.1). McCoy (2012) defined impaction as: *“An impacted tooth is one that either fails to erupt into its natural position or one that is hindered from eruption by adjacent teeth, dense bone, or an overgrowth of soft tissue”*.[2]

Third molar impaction prevalence numbers vary among studied samples, populations, diagnostic tools and ages.[3] Carter et al. (2016) found a worldwide third molar impaction prevalence of 24.4% (95% CI 19.0–30.8%), with the odds of impaction being 60% higher in the mandible than in the maxilla.[4] The number was based on radiographic examinations. A radiographic study by Celikoglu et al. (2010) in 20 to 26 year olds reported that 35.9% of subjects had at least one impacted third molar.[5] The UK National Third Molar project (1997), a cross-sectional survey study, reported on average 25% of maxillary and 51% of mandibular third molar being impacted.[6] A study by Kruger et al. (2001) in a non-patient sample of young adults, it was found that only 15% of maxillary and 20% of mandibular third molars were erupted.[7] A Finnish report reported 90% of 20 year olds have at least one impacted, partially erupted or completely unerupted third molar.[8] Deducing one third molar impaction number or prevalence is impossible, but it is readily apparent that it is a frequently occurring and widely described phenomenon.

Third molar impaction is associated with pain and discomfort. And in case of eruption, a third molar levelled with the other teeth does not necessarily equal good function and health. Moreover, third molar impaction can have implications on the second molar's health and periodontal tissues. All things considered, it is well clear that impacted third molars are a common oral health concern.

Figure 1.1. *Panoramic radiograph of a patient with 32 permanent teeth. The four third molars are impacted.*

2. Pathologies and complications associated with third molar impaction

Though impaction itself is not considered a pathology, it is associated with several symptoms and diseases that might indicate the removal of the teeth, a very common oral procedure. Among these indications for removal are infections, non-restorable carious lesions, periodontal pathology, root resorption, pericoronitis, cysts and tumors. Pathologies are often accompanied by pain and discomfort, severely affecting the patient's quality of life. Dodson et al. (2012) reported that only 29% of subjects in a non-patient volunteer sample presented with all third molars asymptomatic and disease-free, and this number reduced to only 12% in a patient sample referred for third molar evaluation.[3] Age is thought to be the number one risk indicator for third molar pathology.[9] Moreover, third molar position and orientation play a significant role in the onset of third molar disease. In order to critically assess the pathologies associated with retention of impacted third molars, Vandeplas & Vranckx et al. (2020) conducted a systematic review of the available scientific evidence.[7] Three biomedical libraries were searched (PubMed (MEDLINE), Embase and Cochrane Library), and more than 8000 records were screened. The review was designed to answer the following research question: **What are the pathologies associated with retention of impacted third molars?**

Articles that met the following criteria were included to be reviewed:

- Studies investigating a human population presenting with at least one third molar in a longitudinal or cross-sectional study design;
- Studies investigating the prevalence and/or incidence of pathology related to the presence of third molars by clinical and/or radiographic evaluation;
- Studies reporting sufficient information to extract data on the measured outcomes.

In total, 37 eligible records were identified.[7] The primary outcome measures were prevalence, incidence and relative risks of pathologic conditions associated with third molar retention. The reviewed pathologies were dental caries of the third molar or the distal side of the second molar, periodontal pathology of the third molar or distal to the second molar, external root resorption of the second molar, and pathological widening of the third molar's pericoronal space (Figure 1.2).

Figure 1.2. *Radiographic representation of the four assessed pathologies associated with third molar impaction and retention. (a) dental caries; (b) alveolar bone loss distal to the second molar as a result of periodontal pathology; (c) second molar root resorption; and (d) pathological widening of the third molar's pericoronal space.*

Dental caries

Dental caries was by far the most observed pathology in retained third molars. Because of their distal position in the mouth, third molars are difficult to maintain clean. Consequently, accumulation of dental plaque and oral bacteria can cause the tooth enamel and dentine to demineralise. Prevalence ranged from 24% to 80%, depending on the age of the subjects.[10–12] As demonstrated by Shugars et al. (2005), mandibular third molars were significantly more affected by caries than maxillary third molars.[13] Several prevalence studies also demonstrated that third molars (M3) have an increased risk of developing caries in case of partial third molar eruption (both upper and lower jaw), and in the case of mesial third molar inclination in the mandible.[11,14–17] Moreover, an association was demonstrated between the presence of a third molar and the risk of caries on the distal side of the second molar (M2D).[18] In a 3-year follow-up of 416 persons (age 28–76 years), Nunn et al. (2013) found that the presence of an erupted third molar increased the risk of caries on M2D by 2.5-fold, compared with the risk in absence of an adjacent third molar.[18] Similar results were found by Pepper et al. (2017) who investigated a younger population (age 17–18.9 years).[19] They reported a significant increase in M2D caries prevalence when a partially erupted third molar was present (7%) compared with its absence (3%). A split-mouth study by Chou et al. (2017) on 70 elderly patients showed that caries in the third molar region (M3 and M2D) was significantly more frequent in a subsample of patients presenting with third molars, than in the non-third molar group.[20] The authors concluded that presence of a third molar is a risk factor that may negatively impact oral health well into later life.

Periodontal pathology

Periodontal pathology or periodontitis is a chronic inflammation of the gums, causing degeneration of the periodontal membrane and resorption of the alveolar bone. The distal surface of the second molar is especially prone for this pathological entity, resulting in clinical attachment loss of the periodontal ligament and alveolar bone loss in the area surrounding the second and third molar.[21] Age, and thus third molar retention time, appeared to have a significant relation to periodontal disease prevalence.[22–25] The Blakey and White series of follow-up studies showed progressively increasing third molar periodontal probing depths (PD) with increasing age and retention time.[22–25] During 4 years of follow-up, 38% of patients showed PDs of ≥4mm in the third molar region, even when PDs were low or non-existing at baseline.[24] Similarly, Ahmad et al. (2008) reported a 51% prevalence of third molar PDs of 4mm or more at baseline in a population aged 18 to 20 years, with a 10% increase 5 years later.[26] The overall prevalence of periodontal disease in the included papers ranged from 33–61% for the M3 and 17–50% for the M2D. Fisher et al. (2012). noted that third molars were more affected by periodontal pathology than first or second molars (56% vs. 50%, respectively).[27] The mandible was significantly more affected than the maxilla.[12,22,24,28] Moreover, the periodontal health of the second molar was shown to be negatively affected by retention of the adjacent third molar, both in young and older populations.[29,30] Two studies by Elter et al. (2004 and 2005), examining 5831 young patients (age 18–34 years) and 6793 older patients (age 52–74 years), reported that the odds of PDs >5mm on the distal side of the second molar were (respectively) 2 and 1.5 times higher when the adjacent third molar was present.[29,30] The odds also increased with increasing age. This association between third molar presence and occurrence of M2 periodontal disease was also observed by Chou et al. (2017) and Nunn et al. (2013).[18,20] Over a follow-up period of more than 25 years, the latter authors found significant differences in the relative risks for second molar pathology in patients with all kinds of third molar impaction, agenesis or third molar absence due to earlier removal.[18] Using the absence of third molars as a reference, the relative risk of having M2D PD >4mm was 1.87 for erupted third molars, 6.41 for soft tissue impacted third molars and 1.60 for bony impacted third molars. In addition, the relative risk of having ≥20% M2D alveolar bone loss was 1.49 for erupted third molars, 9.15 for soft tissue impacted third molars and 3.09 for bony impacted third molars.

Second molar external root resorption

As a result of persistent direct contact of an impacted third molar with the adjacent second molar, resorption of the second molar's root can occur. Several cross-sectional studies on **second molar external root resorption** (M2 ERR) in the presence of a third molar were identified. In general, increasing age, third molar impaction status and impacted depth were significantly associated with the prevalence of M2 ERR. Differences in M2 ERR prevalence were observed between studies investigating patients with mean age below or above 25 years: 40–49%[5,31] vs. 0.5–50%[32–36], respectively. Also differences between maxilla and mandible were reported. Li et al. (2019) concluded that M2 ERR is significantly more prevalent in the mandible (53%) than in the maxilla (33%); a finding contradicted by Sejfija et al. (2019), where maxillary M2s showed significantly more severe degrees of resorption.[15,35] The latter authors also found that mesial angulation and impaction depth of the third molar are significantly associated with M2 ERR. Similar significant findings in terms of age and third molar orientation were reported by Schriber et al. (2019), with the most significant increase in M2 ERR prevalence when the third molar was transversely oriented.[34]

Pathological widening of the third molar's pericoronal space

Clinical pericoronitis is a mild to moderate inflammation of the soft tissues surrounding or overlying an impacted third molar. Radiographically, this often translates as a pericoronal radiolucent area around the third molar. In the included papers, a widely varying range of results was reported on the prevalence of a **widened third molar pericoronal space**. Studies investigating pericoronal pathology in erupted, partially erupted and impacted third molars revealed prevalences of 0.7% to 13%.[5,33,35] These studies included patients ranging from 18 to 92 years, and large differences were observed in cut-off values for widened pericoronal space on panoramic radiographs (2.5mm to 4mm). This can be illustrated by the study of Sejfija et al. (2019) examining mostly young patients (mean age 29 years) reporting a prevalence of 1.2% using a 4mm cut-off on panoramic imaging.[35] In contrast, Eliasson et al. (1989), with a very similar study design, though older subjects (mean age 43 years) and using a 2.5mm cut-off, reported a prevalence of 4%.[32] Mandibular third molars were more affected than maxillary third molars.[32] Of all included papers, only Ventä et al. (2019) attributed the presence of pericoronal pathology to the position of the third molar (aberrant orientation and impaction depth).[36]

Other pathologies or conditions associated with third molar impaction

Other pathologies associated with impacted and retained third molars are **cystic changes** of the third molar follicle, that can in rare cases result in malignant tumors.[37,38] Yildirim et al. (2008) histologically examined pathological cystic changes in extracted third molar follicles and detected budding of 14.1% dentigerous cysts, 6.6% calcifying odontogenic cysts and 2.5% odontogenic keratocysts.[39] Moreover, partial third molar eruptions can cause accumulation of bacteria and food residues, resulting in **acute abscesses** in the third molar area. Also, **systemic inflammation** as a result of third molar retention is described.[40] Other conditions reported being associated with third molar retention, although not really of pathological origin, are **mandibular angle fractures** and crowding of the anterior incisors and canines.[41–43] The latter has long been considered a consequence of third molar retention, however, it is now understood that third molars cannot exert such an anterior force during eruption and distort the dental alignment to this degree.[44–47]

The results showed that the incidence of third molar pathology increases with increasing age of the patient. In such instances, removal of the affected third molars is indicated. However, as we grow older, our ability to recover from surgical interventions reduces and the risk of intra- and postoperative complications increases.[48,49] Among these complications are hemorrhage, edema and iatrogenic nerve injury. Complication rates are increased because of deteriorated systemic physiologic conditions, increased difficulty of the procedure, and extended operation time.[50–52] Changes in bone physiology cause the bone to become less elastic and resilient at older age. Consequently, in rare cases, the application of excessive force or bone removal can cause fracturing of the alveolar bone or even the complete mandible.[49] Moreover, tooth ankylosis can impede smooth extraction.[49] Additionally, older aged patients are often on anticoagulants, which increases the risk of excessive peri- and postoperative hemorrhage.

Although general agreement exists that third molars should be removed when signs or symptoms of disease are present, it remains difficult to predict whether disease-free and asymptomatic third molars will eventually develop pathological changes if they are retained.[53] Systematic reviews have been conducted to assess the risk of pathology and rivers of ink have flown on the eventual justification of prophylactic removal.[53–55] Estimation of the risk of pathology associated with retention of impacted third molars would help the timely treatment of non-functional third molars, and would avoid delayed healing and complications in case of extraction at older age.[49] The combination of clinical observation and radiological assessment is key to determining the risk of pathology in impacted third molars. Panoramic radiographs and cone-beam computed tomography (CBCT) images are indispensable in this process.

3. Dentomaxillofacial radiology as an indispensable tool in diagnosis, treatment planning and prediction of eruption and diseases

Panoramic radiography is considered the standard of care in the preoperative radiological assessment and diagnosis of third molars. Panoramic radiographs allow the 2D visualization of several anatomical structures, including the mandible and maxilla, and provides an overview of all teeth in the dental arches. The low cost and low radiation dose are clear advantages. Panoramic radiographs are used to determine the state of impaction, identify a potential close relationship of the third molar roots and the mandibular canal, and detect the presence of pathologies. However, with its 2D rendition of 3D facial structures, panoramic radiography is obviously subject to effects of magnification distortion, superimposition of structures, and incorrect patient positioning.[10] Moreover, in the absence of cross-sectional information, panoramic radiographs can leave room for misinterpretation. In these cases, the surgeon can opt for additional evaluation with CBCT imaging.

With its 3D rendition of the facial skeleton, CBCT provides a more accurate and reliable visualization of anatomical structures, including location, shape and relationship with adjacent structures.[5,23] CBCT images come as multiplanar, thin-sliced images that are not tainted by superimposition. Important concerns with the use of CBCT are the higher radiation doses and costs.[56] Its use should therefore be reserved for selected cases with clear clinical indications.

Since CBCT renders a 100% realistic representation of the 3D reality, the true extent of pathologies can be determined (e.g. M2D external root resorption, cysts and tumors (Figure 1.3)). Moreover, CBCT is superior in visualization and exploration of third molar's relation with the mandibular canal, and the presence of potential side branches of the canal containing neurovascular bundles. Moreover, it provides information in buccolingual view and allows determination of the exact number and positions of third molar roots.

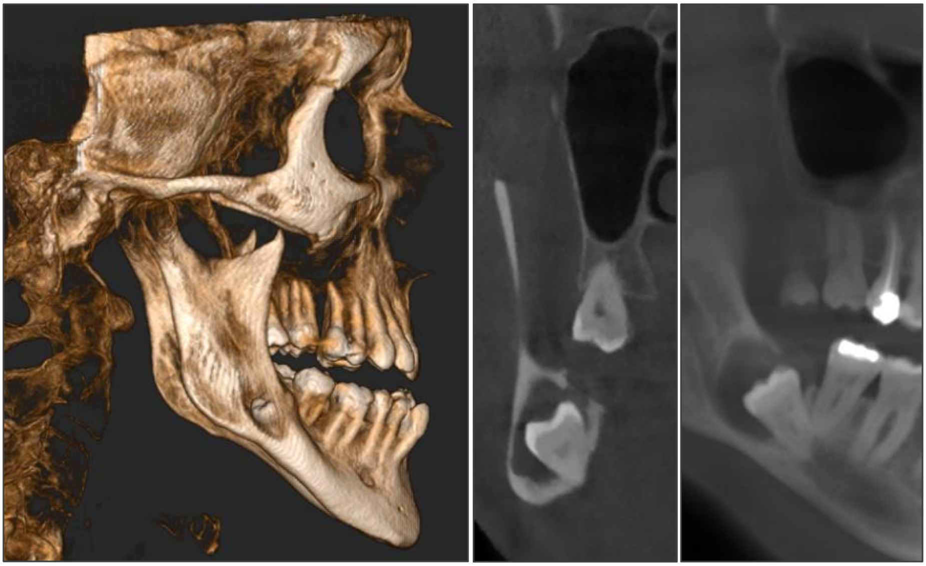

Figure 1.3. *Patient presenting with a coronal cyst of the lower right third molar. The real 3D extent of the cyst can only be determined by the use of CBCT.*

Some dental practitioners and experts advocate intraoral radiographs as first-line radiographic imaging modality, especially among dentists.[57] Intraoral radiographs are widely accessible in dental practices, however panoramic imaging machines are also drastically gaining ground. Intraoral scans provide more detail on the periodontal health of the third molars and distal side of the second molars, as well as the potential presence of (interproximal) caries. However, it is limited in its field of view and might miss deep third molar impactions (Figure 1.4).

Figure 1.4. *Intraoral radiograph.*

Dentomaxillofacial radiology is indispensable in all stages of the treatment process, from diagnosis and treatment planning, to prediction of eruption and/or risk of disease.[58,59] The broad availability of (digital) radiographic images in many modalities are a gift to the recent developments and radiological applications of artificial intelligence (AI). Where dentomaxillofacial imaging was an analogue process until two decades ago, the digital revolution in dentistry has largely automated the conventional dental workflow and drastically reshaped the field. The availability of digital 2D and 3D imaging data has led to the development of many AI applications, and allowed for deep learning algorithms or convolutional neural networks (CNN) to rapidly emerge in the field of dentomaxillofacial radiology.[60] By mimicking human cognition in terms of learning and problem solving, CNNs prove to be as accurate as human observers, if not more, and most importantly, they allow highly time-efficient and precise evaluations.[61] Besides applications in diagnostics and classification of diseases, such as caries staging[62], root fracture detection[63], cancer screening[64,65], and diagnosis of periodontal disease[66]; in this thesis, the first CNN to help estimating the third molar's eruption potential will be presented.[67] AI tools will smoothen and accelerate the daily practice and create an important ease-of-use for the dental practitioner.[68]

4. International differences in third molar management

The common practice of prophylactic third molar removal has been called into question by some authorities and practitioners. Because every surgical intervention poses a risk of intra- and postoperative complications, prophylactic extraction of third molars might put patients unnecessarily at risk, without clear evidence available that the benefits of removal would outweigh the associated risks. Commonly observed postoperative complications after third molar removal are infection, alveolar osteitis or dry socket, hemorrhage, excessive edema, and iatrogenic nerve injury, causing temporary or permanent sensory dysfunction of the inferior alveolar nerve (IAN) or lingual nerve (LN). Moreover, a surgical procedure comes with the need for local and/or systemic anesthesia, which in its turn poses a risk of adverse events or complications.

Many countries have implemented national treatment guidelines on third molar management. All of these guidelines are based on the available international peer-reviewed literature. Yet treatment approaches vary widely across countries. The conclusions reached differ because of varying governmental resources, availability of health insurance and reimbursements, surgical treatment environment, and culture.[69] As a result, some guidelines advocate a conservative approach of lifelong active surveillance or "watchful monitoring", while others stand by prophylactic removal of impacted third molars to avoid pathology later in life. Both approaches have a limited evidence base, but in general, third molar treatment remains a matter of debate.[70–72] The main goal is to find the delicate balance of offering the best possible care for the patient, without unnecessarily exploiting the health care system and the expenditure of resources.[69]

Back in 2000, the **National Institute of Health and Care Excellence (NICE) in the United Kingdom** published their Guidance on the Extraction of Wisdom Teeth.[73] The guidelines stated that the practice of prophylactic removal of pathology-free impacted third molars should be discontinued in the National Health Service (NHS). Healthy wisdom teeth (free from disease), should not be operated on. Unnecessary exposure to the risks and possible complications of surgery should be avoided when no clear evidence on the benefits is available. Surgical removal of impacted third molars should be limited to patients with signs or symptoms of pathology. Patients with asymptomatic impacted wisdom teeth should be monitored during annual check-up visits.

Similar to NICE, the **Scottish Intercollegiate Guidelines Network (SIGN)** also published recommendations regarding the removal of third molars in 2000.[74] It was stated that there is no need for routine removal of asymptomatic third molars. In addition, they provided a clear list of indications for justified removal and gave advice on the clinical and radiographic assessment of third molars.

In 2012, the **Belgian Health Care Knowledge Centre (KCE)** published a national report on the management of third molars.[75] Based on an extended literature review, their advice was to only extract impacted third molars with signs or symptoms of pathology. Impacted, but asymptomatic disease-free, third molars should be monitored by yearly dental evaluation instead of being prophylactically removed. They concluded that currently no scientific evidence is available on the benefits of prophylactic interventions on third molars. Their main priority is to adhere to the *"primum non nocere"* principle.

Conservative treatment guidelines might affect the daily practice to some extent. However, studies have shown that the NICE guidelines did not affect the volume of third molar care over a decade after implementation.[76] The introduction of the new treatment strategy caused an immediate drop in patient admissions (2000–2003); however, after 2003, numbers started to increase again. Overall, the total number of patients in need for third molar removal did not decrease in a 10-year period. In fact, the patients' age at the time of removal climbed from 25 to 32 years, and diagnoses such as pericoronitis and caries on third and/or second molars increased drastically.[76] Accordingly, there is increasing evidence available that a conservative treatment attitude will result in a delay of inevitable surgeries, with an increase of the mean patient age at time of the extraction, and no aimed reduction in the total number of surgeries. Many of the conservative treatment guidelines were based on the lack of high-quality evidence to substantiate prophylactic removal, despite showing no evidence to suggest that third molars would remain disease-free when retained. They thus conclude that retention automatically outperforms prophylactic extraction, but in the striking lack of evidence, does this - on its turn - justify the cease of practice as well? It is a two-way street.

With their 2007 White Paper on Third Molar Data, the **American Association of Oral and Maxillofacial Surgeons (AAOMS)** advocated a more interventional approach in favor of prophylactic third molar removal.[77] Their guideline was based on a systematic review of over 200 records, weighing the indications for and against third molar removal, and they concluded that *"predicated on the best evidence-based data, third molar teeth that are associated with disease, or are at high risk of developing disease, should be surgically managed"*.[77] Given the pathologies associated with third molar impaction, impacted third molars should preferably be treated as soon as it is apparent that they will not erupt into functional position. In the absence of significant risk of disease, active clinical and radiographic surveillance is indicated, and is supposed to pick up early signs of pathology in order to prevent further complications.[77]

Similarly, the **Finnish Current Care guidelines**, with their most recent update in 2014, recommend *"elective preventive removal of third molars"*, also defined as removal of symptomless third molars before the development of anticipated problems, in four specific situations: risk of IAN injury, risk of pericoronitis, risk of bone defects, and risk of caries.[69] Removal is advocated before the age of 25. Their conclusions were based on several studies from Ventä et al. reporting that, ultimately, third molars are subject to removal at some point in the patient's life.[12,36,78]

The **Swedish Västra Götalandsregionen** conducted a Health Technology Assessment (HTA) (2010) on the removal of impacted wisdom teeth.[79] Their conclusion was that despite the absence of symptoms or disease, prophylactic removal can be justified to prevent possible future complications. They add that in the absence of scientific evidence to either support or refute routine prophylactic removal of asymptomatic impacted third molars, the practice is continued to be frequently performed in Sweden.[79]

The **Knowledge Centre for Oral Health (KIMO) in The Netherlands** recently prescribed a more interventional approach as well.[80] Soft tissue impacted mandibular third molars with no chances of eruption are indicated for removal, especially before the age of 30 years, without the prerequisite of presence of symptoms or disease. Moreover, non-functional (maxillary) third molars are advised to be removed as well. Bony impacted third molar are better left untouched.

In general, and in all guidelines, the following contraindications for removal are put forward:

- Erupted and functional mandibular or maxillary third molars that can be maintained clean;
- Unerupted, disease-free, symptomless third molars totally covered in bone (and with no contact to adjacent teeth), and;
- When removal or associated anesthesia constitutes an unreasonable risk to the health of the patient.

Given the economic and personal costs involved, it is understandable how the validity of prophylactic third molar removal has been called into question over the last decades. The clinician’s treatment decision should be based on his/her expertise, on the individual needs of the patient and on the best research available. However, it is evident that the literature does not have a clear answer available and that there is a regular need to update current prevailing positions according to the best available research. In absence of evidence-based treatment guidelines, the decision to remove asymptomatic third molars remains individualized, rather than generalized.

5. Societal costs of third molar removal or retention

In the second half of the 20st century, early prophylactic removal of pathology-free impacted third molars was a widely performed oral intervention. The 2000 NICE guidance report, however, suggested that 22% to 44% of wisdom teeth removals and prophylactic surgery may have been inappropriate in the past.[73] Other studies reported that worldwide in 18% to 50% of the third molar removals, no clinically urgent indication or sound justification for surgery was present.[81–83] Considering this, from a cost implication point-of-view, it appeared not to be unwise to discourage the common practice of prophylactic third molar removal and continue to only remove teeth with appropriate clinical indications.[81] Yet, it is hard to convert the cost of prophylactic removal versus lifelong active surveillance into hard numbers.

It starts with getting a clear overview of the current practice in Belgium. Unfortunately, transparent numbers for Belgium do not exist. Third molar removal is not coded with a specific intervention number, so the numbers get lost in the umbrella intervention group of “surgical dental extractions” at the reimbursement authority Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV). In addition, non-surgical dental extractions in the patient group aged 18–53 years - interventions often performed by dentists - are not reimbursed. Accordingly, the RIZIV cannot quantify the exact need for third molar removal in Belgium. Although, no reliable numbers on the total picture are present, it is estimated by experts in the field that 40% of the RIZIV expenditure in OMFS goes to third molar extractions.

In the period 1994–1995, a few years before the introduction of the NICE guidelines, the NHS (UK) reported more than 36000 inpatient and 60000 day-case admissions for surgical third molar removal, accounting for nearly £50 million of the NHS expense per year.[84] In 2012, McArdle et al. investigated the effects of the NICE guidelines over a ten-year period after implementation.[76] They reported that in the implementation of the NICE guidelines caused a quick and steep drop in day-case admissions from 60000 in the 1990s to 40000 in 2003; however, since 2003, the numbers have increased again, raising up to 65000 in 2009–2010.

A recent UK HTA report by Hounsome et al. (2020) assessed the clinical effectiveness and cost-effectiveness of prophylactic removal of impacted mandibular third molars and compared it with retention of the teeth.[85] They reviewed four cohort studies, nine systematic reviews, and two cost-effectiveness studies, of which the latter two studies concluded that, *“to their knowledge, there is currently no economic evidence to support the prophylactic removal of impacted mandibular third molars”.* Still, the authors of the HTA report calculated that prophylactic removal may be the more cost-effective strategy in the end. Their economic model based on peer-reviewed observational studies suggested that many patients with impacted third molars will eventually have the teeth removed at some point in life, and that *“although prophylactic removal is probably more costly than a watchful waiting strategy, the improvements in health-related quality of life from a reduction in impacted mandibular third molar symptoms suggest that prophylactic removal may be a cost-effective strategy for the NHS”.*[85]

In the United States, approximately 10 million third molars in 5 million people are removed every year.[86] This makes third molar removal the most commonly performed oral intervention. The intervention constitutes the largest expenditure for any surgical procedure by the Blue Cross Blue Shield (health insurance), representing 50% of the cost spent to all oral surgery.[81,87] Besides the cost of the surgical intervention itself, economic consequences such as patients being unfit for work and the costs of recovery time and conceivable postoperative complications must be considered as well. Therefore, it was expressed that operating on patients without clinical indications involves unwarranted expenditure of resources, unnecessary costs to the patient (time and money), and the risk of legal claims against practitioners for complications inflicted during surgery.[81]

On the other hand, evidence is mounting that retention of wisdom teeth might lead to higher costs in the long run. It seems that retention of third molars might cost society more because of dental control visits and potential absence from work in case of eventual extraction, as compared with prophylactic removal during adolescence or early adulthood. A few days of school leave are considered economically less costly than work leave. Additionally, when surgery is performed at older age, the intervention might take longer, healing can be delayed, and the higher risk of complications can result in multiple postoperative hospital visits.[50,51] Moreover, lifelong active surveillance of third molars implies expenditure as well. Together with the possible cost of extraction at some point in life, it might not be as advantageous to retain third molars as one might think at first sight.[88] Ultimately, a trade-off must be made between prophylactic removal and retention of third molars, but all in all, the socioeconomic costs associated with prophylactic third molar removal might in the end be lower than the costs of lifelong active surveillance and eventual extraction at older age.[88]

Aims and Hypotheses

Third molar removal is one of the most commonly performed procedures in oral and maxillofacial surgery. Because of the often-prophylactic nature of the intervention, it is important to carefully consider the risks and benefits associated with it. Yet, high-quality prospective and/or longitudinal data on the topic is lacking. The overarching aim of this PhD project was to provide clear view on the common practice of surgical third molar removal and the indications and postoperative morbidity associated with this type of oral surgery. **The general hypothesis was that prophylactic third molar removal is indicated in case of impaction in order to avoid morbidity and neurosensory complications later in life.**

This doctoral thesis is divided into three main parts, each with its respective aims and objectives.

PART 1 Eruption prediction

Active evaluation of the third molars' eruption potential at adolescent age may help estimating the risk of impaction and thereby guide the orthodontist, dentist or oral and maxillofacial surgeon in their decision concerning the timely removal of third molars. To this end, panoramic radiographs acquired at the end of orthodontic treatment may serve not only for diagnosis and follow-up of the orthodontic treatment, but also for prediction of third molar eruption.

The objectives were:

- To identify and predict patients at risk of impeded mandibular third molar eruption and a potential close relation between the third molar roots and the mandibular canal, based on the molar angulations measured on panoramic radiographs, and;
- To automate this prediction by use of a deep learning network that segments the mandibular molars on panoramic radiographs and measures the molars' angulations.

The hypothesis was that:

> *"Severely angulated third molars will not erupt into a functional position and have a higher risk of developing a relation with the mandibular canal containing the inferior alveolar nerve."*

PART 2 Third molar removal

Prophylactic removal of impacted third molars can prevent the development of pathologies and complications associated with retention of the teeth. However, no clear evidence is available that the benefits associated with this oral intervention would outweigh the risks of it. This part of the thesis addresses the gap of large-scale prospective data on the indications for third molar removal, the effect of age, and the risks of postoperative morbidity. Panoramic radiographs are indispensable in this process and might contain more information than currently exploited. The obtained results may ultimately form a basis for updated treatment guidelines.

The objectives were:

- To gain insight into the indications for third molar removal, the postoperative recovery process and the incidence of neurosensory complications associated with this type of oral surgery;
- To assess the effect of age on the recovery of the patient;
- To study the effect of the surgeon's level of experience on postoperative morbidity, and;
- To identify radiological risk indicators for persistent postoperative morbidity after third molar removal.

The hypotheses were that:

> *"Removal of symptomatic third molars is associated with more and/or longer postoperative discomfort as compared with prophylactic third molar extractions, and postoperative discomfort and extraction-related morbidity is increased and prolonged with increasing age of the patient at the time of surgery. Moreover, deep third molar impactions, difficult extractions and/or the presence of pre-existing third molar pathology are risk factors for persistent postoperative morbidity."*

PART 3 Nerve complications

Anatomical variations of the mandibular canal, such as bifurcations and loops, might be more frequently present than expected. The most important mandibular canal variation in third molar area is the retromolar canal. It contains a side branch of the inferior alveolar neurovascular bundle, in which relies its clinical importance. Mandibular canal variations should be carefully considered before and during the surgical procedure in order to avoid neurosensory complications.

The objectives were:

- To study the prevalence of anatomical variations of the mandibular canal in vivo and ex vivo, by direct anatomical observations, panoramic radiographs and CBCT imaging, and;
- To correlate the presence of mandibular canal variations with the postoperative occurrence of (temporary) neurosensory disturbances of the inferior alveolar nerve following third molar removal.

The hypotheses were that:

> *"The prevalence of anatomical variations of the mandibular canal is higher than reported in the literature, and the presence of these variations is associated with an increased risk of postoperative neurosensory disturbances of the inferior alveolar nerve after third molar removal."*

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ERUPTION PREDICTION

1 ERUPTION PREDICTION

CHAPTER 2

Radiographic prediction of mandibular third molar eruption and mandibular canal involvement based on angulation

Vranckx M.[1]
Ockerman A.[1]
Coucke W.
Claerhout E.[1]
Grommen B.[1]
Miclotte A.[2]
Van Vlierberghe M.[1]
Politis C.[1]
Jacobs R.[1,3]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]Department of Oral Health Sciences – Orthodontics, KU Leuven, and Department of Dentistry, University Hospitals Leuven, Leuven, Belgium.

[3]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: The aim of our study was to identify and predict patients at risk of impeded mandibular third molar eruption and potential relation between the third molar roots and the mandibular canal, based on molar angulations in an early development stage.

Methods: We analyzed pre-eruptive rotational changes and root development of mandibular third molars on 2022 panoramic radiographs (two time points) of 1011 adolescent orthodontic patients. Five variables were evaluated: third molar eruption level, development stage, risk of relation between the third molar and the mandibular canal, the molar angulations and orthodontic treatment. The relation between early third molar angulation and mean annual angulation change was assessed using a linear mixed model. Logistic regression was applied to investigate a potential correlation of the radiographic variables with the eruption potential and risk of developing a relation between the third molar and the mandibular canal.

Results: Mandibular third molar follicles with an initial angulation exceeding 27.0° relative to the second molar tend to progressively increase their angulation during further development. A significant correlation was found between the mandibular molar angulations and the probability of eruption ($p<0.0001$). The second to first molar angulation was predictive for potential development of a relation with the mandibular canal ($p=0.005$).

Conclusion: From the present data, it appears that severely angulated mandibular third molars (>27.0°) have a minimal chance of future full eruption and a maximal risk of developing a relation with the mandibular canal.

Key words: angulation, orientation, mandibular canal panoramic radiograph, third molar, wisdom teeth

Introduction

Evolutionary arisen lack of space in the dental arch often results in impaction of the last teeth to erupt, the third molars. Along with frequent aberrant follicle orientation, this leads to increasing third molar impaction prevalence, with numbers varying from 17% to 32%.[1–3]

Although Ricchardson et al. suggested in 1978 that third molars are not static in development, it remains unclear to which extent pre- and peri-eruptive rotational changes enhance the eruption potential of third molars.[4,5] Many factors are known to influence the eruption process. Primarily, the anatomy of the mandible often embodies a narrow retromolar eruption space between the second molar and the anterior border of the ramus of the mandible, which can result in third molar impaction.[6,7] On the other hand, orthodontically indicated premolar extractions are proven to enlarge the retromolar space.[8,9] Notwithstanding this, studies aiming to elucidate the association between mandibular molar angulations and the third molars' eruption potential in a fully dentate jaw are scarce. Since the majority of adolescents in Western society is subjected to orthodontic treatment at relatively early age, orthodontically requested panoramic radiographies may serve not only for diagnosis and follow-up, but also for prediction of third molar eruption.[10] Active evaluation of the third molar's eruption potential at the end of orthodontic treatment may help estimating the risk of impaction and thereby guide the orthodontist and oral and maxillofacial surgeon in their decision concerning third molar removal.[11]

In this light, the aim of the study was to identify and predict patients at risk of impeded mandibular third molar eruption and potential relation between the third molar roots and the mandibular canal, based on molar angulations in an early development stage.

Materials and Methods

After receiving ethical approval from the Ethics Committee Research of the University Hospitals of Leuven (Belgium) (B322201525552), a retrospective longitudinal study was carried out upon 2022 panoramic radiographs of 1011 Caucasian subjects (444 males and 567 females). Patients were selected from the Department of Orthodontics at the University Hospitals Leuven and two private orthodontic practices. Two orthodontic follow-up panoramic radiographs with at least a one-year time-interval were selected per patient file. Only patients with complete and fully erupted (except for the third molars) mandibular dentition were included. Patients having supernumerary elements and patients suffering from odontomas, craniofacial or syndromic anomalies were excluded. The radiographs were generated with the following panoramic X-ray machines: Veraviewepocs 2D (Morita, Kyoto, Japan), Cranex Tome (Soredex, Tuusula, Finland), ProMax (Planmeca, Helsinki, Finland) and PaX-i (Vatech, Fort Lee, America).

Four parameters were evaluated. First, the **molar angulations** were measured with GIMP 2.0 Ink software (University of California, Berkeley, USA). The angles were defined as the intersections of the longitudinal axes of the hemimandibular molars (Figure 2.1). The longitudinal axis of each molar was defined based on two reference points: the most apical point of the pulp cavity and the midpoint of the mesiodistal crown width. In case of third molars in premature development stage, the longitudinal axis was drawn perpendicularly through the midpoint of the mesiodistal crown width.

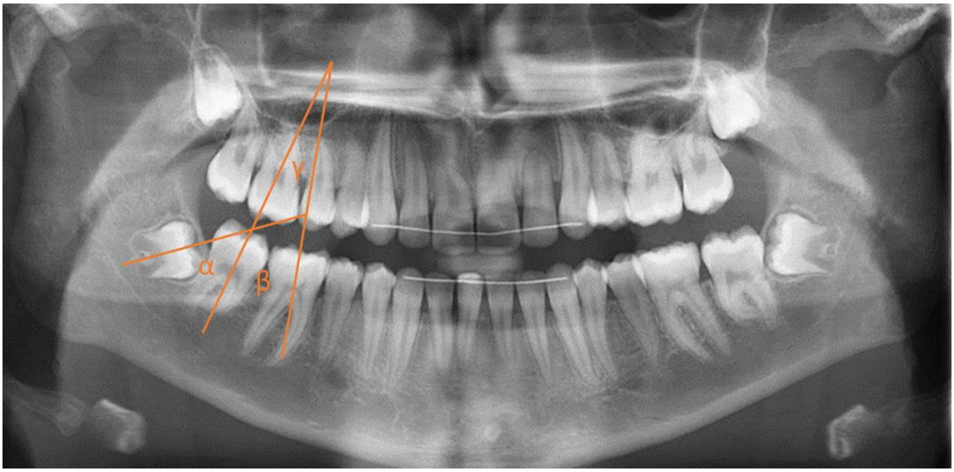

Figure 2.1. *Measurement of the mandibular molar angulations on panoramic radiographs: α represents the third to second molar angulation, β the third to first molar angulation, and γ the second to first molar angulation.*

The **Pell & Gregory classification** was used to assess vertical eruption level of the third molars (Appendix A).[8] The third molar was classified as fully erupted, partially erupted or unerupted, in case the occlusal plane of the third molar was at the same level as the occlusal plane of the second molar, between the occlusal plane and the cervical line of the second molar, and below the cervical line of the second molar, respectively. The third molar's development stage was recorded based on a shortened version of **Demirjian's classification** (Appendix A).[12] Three categories were used: follicles without root formation (Demirjian stages A–D), third molars with starting root bifurcation (stage E), and third molars with root length equal or greater than the crown height (stages F–H). Lastly, the third molars were classified according to their risk of being in relation with the mandibular canal based on the presence of **Whaites' nerve relation** markers (Appendix A).[12,13]

Two independent observers were trained and calibrated to score the radiographic parameters. The orthodontic treatment of each patient was scored as orthodontic appliances (braces), additional functional appliances stimulating mandibular jaw growth (activator), and maxillary treatment only. These categories accounted for 572, 328 and 111 patients, respectively.

Statistical analyses were performed in S-plus for Linux 8.0 (Tibco, Palo Alto, CA). Inter- and intraobserver reliability was calculated based on 10% of the sample using Fleiss' kappa and the intraclass correlation coefficient (ICC). The relationship between the initial angulation of a third molar follicle and its mean annual angulation change was assessed using a linear mixed model. Additionally, a survival analysis for eruption was run based on the mandibular molar angulations. The probability of eruption and developing a relation with the mandibular canal was modelled using logistic regression analysis based on the mandibular molar angulations. These models were based on the patients in the sample with at least 3 years between T1 and T2 to avoid the chance of non-eruption due to a too narrow time-interval. The level of significance was set at $p<0.05$.

Results

The sample of 1011 patients accounted for 2022 mandibular third molars evaluated at two time points, resulting in 4044 parameter scores. Fleiss' kappa and ICC values for inter- and intraobserver reliability ranged from 0.76 to 1 and 0.72 to 1, respectively. The average time-interval between T1 and T2 was 3.0 (± 1.4) years.

The average age of the patients was 13.0 (± 1.4) years at T1 (range 10–20 years) and 15.9 (± 1.8) years at T2 (range 12–23 years).

It was observed that third molars do make pre- and peri-eruptive rotational changes (Figure 2.2). The angulation measurements at T1 ranged from -10.5° to 83.6°, with an average angle of 29.2° (± 13.4). At T2, the angulations ranged from -23.3° to 81.9°, with an average angle of 27.1° (± 13.9). This results in an average angulation decrease of 2.1° (± 13.8). A negative angulation represented a distoangular orientation.

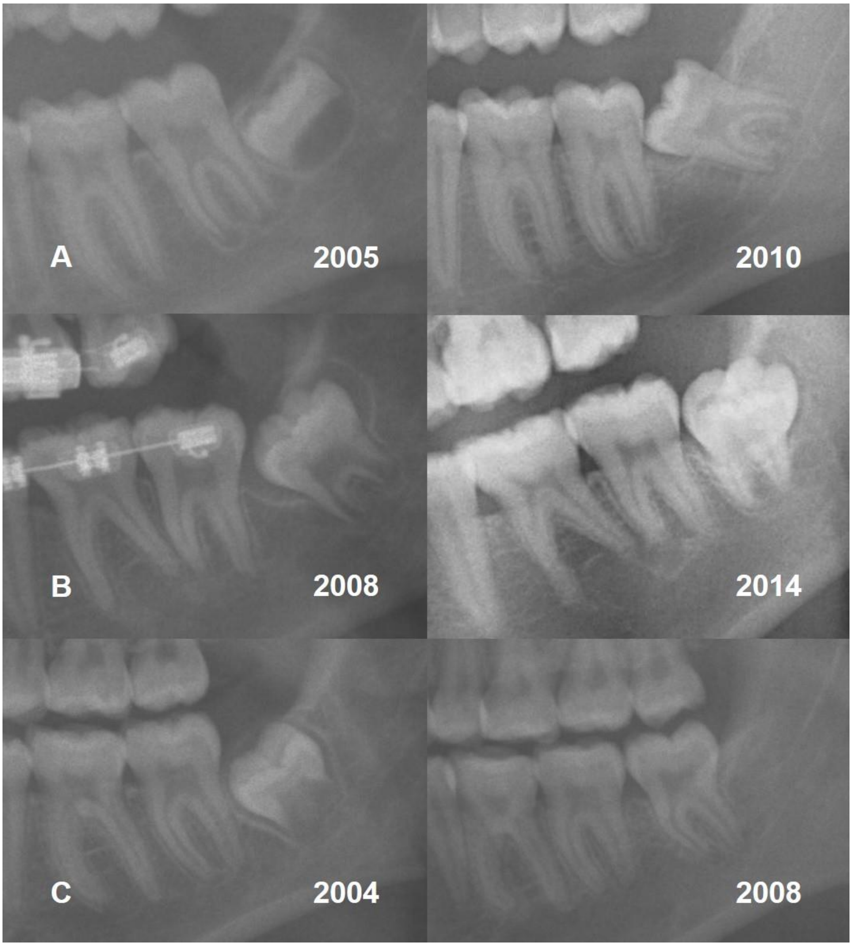

Figure 2.2. *Third molar angulation changes over time. (A) impaction because of aberrant orientation; (B) impaction because of lack of space; and (C) eruption.*

Depending on the direction of the rotational changes (uprighting or tilting), the third molar's eruption potential altered. However, in the majority of cases, the pre- and peri-eruptive rotational changes were not to the extent that they benefited the eruption potential of the third molars. At T2, more than half of the third molars (1052/2022; 52.0%) were partially erupted (Table 2.1).

Table 2.1. *Eruption levels of the third molars at T1 and T2.*

	T1	T2
No eruption	1893	926
Partial eruption	121	1052
Full eruption	8	44

2.1. Relation between the initial angulation of a third molar follicle and its mean annual angulation change

The relation between the initial third molar angulation and its mean annual angulation change was assessed for third molars in the earliest development stage (follicles without root formation; Demirjian stages A–D; n=1588). A linear regression model, delineating the mean change in third molar angulation per year based on the third molar follicle's initial angle, showed a significant correlation ($p<0.0001$). The greater the initial angle of the third molar follicle, the higher the mean annual change in angulation (Figure 2.3). Third molar follicles with an initial angle of 27.0° [26.1°; 27.9°] were least likely to change their angulation over time. Third molar follicles with an initial angle greater than 27.0° had the tendency to enlarge their angulation over time, whereas third molar follicles with an initial angle smaller than 27.0° had the tendency to reduce their angulation over time.

At T1, 503 left mandibular third molar follicles and 498 right mandibular third molar follicles (1001/1588; 63.0%) showed an angulation larger than 27.0°, severely reducing the eruption chances of these teeth. Orthodontic treatment significantly affected the mean annual angulation change ($p=0.0001$). However, this effect was only observed between maxillary versus mandibular treatments, whereas no significant differences were observed between mandibular treatments (braces and/or activator) ($p=0.9495$).

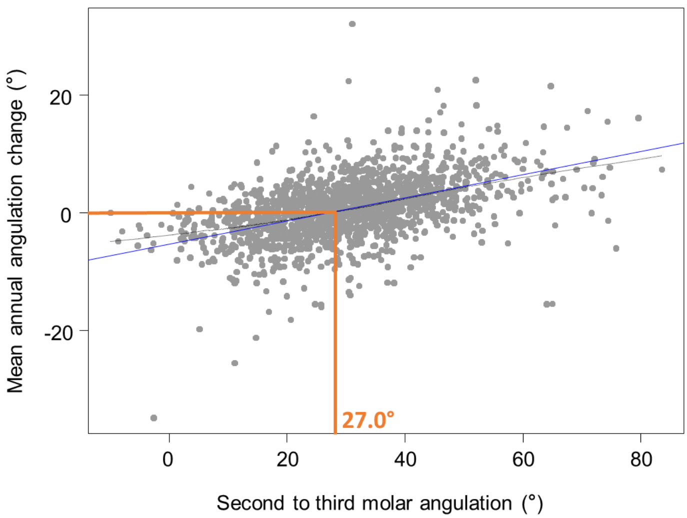

Figure 2.3. *Linear regression model showing the mean annual angulation change of mandibular third molars, based on the third molar follicle's initial angle (n=1588). Third molar follicles with an initial angle greater than 27.0° had the tendency to enlarge their angulation over time, whereas third molar follicles with an initial angle smaller than 27.0° had the tendency to reduce their angulation over time.*

Survival analysis for third molar eruption confirmed that severely angulated third molars have a significantly lower chance of eruption over time, compared with third molars with small angulations (Figure 2.4).

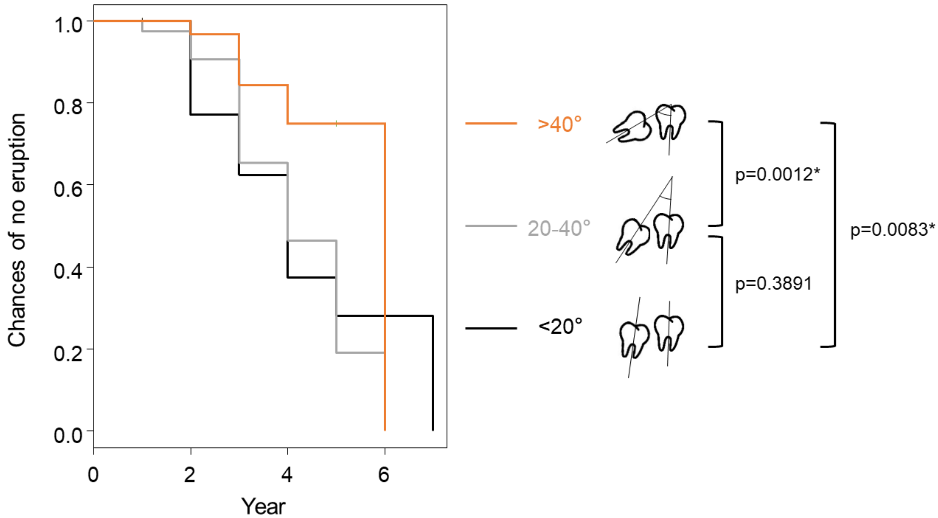

Figure 2.4. *Survival analysis for eruption of mandibular third molars in premature development stage. Severely angulated third molars (>40°) have a significantly lower chance of eruption over time (orange).*

2.2. Predictive value of mandibular molar angulations for third molar eruption

We attempted to draft a prediction model for eruption using a generalized linear mixed model (GLMM). As a result of strict inclusion criteria (three-year time-interval), the subsample contained too few fully erupted third molars so that a clinically applicable eruption model could not be obtained. Nevertheless, a strong correlation was observed between the mandibular molar angulations (α, β, γ) at T1 and the probability of third molar eruption at T2 (p<0.0001) (Table 2.2). Orthodontic treatment had no significant influence (p=0.1273).

Table 2.2. *Predictive value of mandibular molar angulations for third molar eruption and development of a relation with the mandibular canal.*

	Eruption potential	**Nerve relation**
Angle	*P-value*	*P-value*
α 7/8	*<.0001**	*0.3849*
β 6/8	*<.0001**	*0.4476*
γ 6/7	*<.0001**	*0.005**

*siginificant p-value

2.3. Predictive value of mandibular molar angulations for development of a relation with the mandibular canal

At T1, 299 third molars showed presence of Whaites' markers. By T2, this number had increased to 995. This meant that approximately half of the third molar sample (995/2022; 49.2%) showed an elevated risk of neurosensory complications to inferior alveolar nerve when being removed. Looking at third molars with advanced root formation only (n=681), it was shown that the risk of mandibular canal involvement decreased with full eruption status (Table 2.3).

Table 2.3. *Decreasing risk of nerve relation with increasing eruption status in subset of patients with third molars with advanced root formation (n=681).*

	No risk	**Risk of relation**
No eruption	20.4%	79.6%
Partial eruption	35.2%	64.8%
Full eruption	43.5%	56.5%

A similar prediction model based on the mandibular molar angulations was drafted to estimate the potential relation with the mandibular canal. This GLMM showed a significant correlation between angle γ and the future risk of a nerve relation (p=0.005) (Table 2.2). In other words, a large angle between the first and second mandibular third molar increased the probability of the third molar developing a relation with the mandibular canal.

Discussion

In 2012, Philips et al. reviewed the available literature on the predictability of the position of the third molars over time.[14] They concluded a lack of longitudinal data with respect to positional third molar changes during development. It is hard to perform prospective research on this matter, since one is dependent on the available radiographic data based on the clinical needs of patients, rather than radiographs acquired at fixed time points. Apart from that, Philips et al. (2012) confirmed the findings of Ricchardson et al. (1978) that static impactions are rare. Our results correspond to this former research. We observed an average third molar angulation change of 2.1° (± 13.8) from T1 to T2. The large standard deviation can partly be explained by the unfixed time-interval between the two evaluated panoramic radiographs.

According to the reviewed papers concerning longitudinal research on third molar positional changes, the present study comprised the biggest sample ever published on this topic. Many longitudinal studies struggle with incomplete data as a consequence of the removal of third molars during the follow-up period.[15,16] This drawback was overcome by retrospective inclusion of patients with full mandibular dentition at both time points. Moreover, our study sample was considered highly appropriate to extrapolate to the broader population, considering the constantly increasing dental care and preservation of 32 teeth.

The sample comprised relatively young patients, given the fact that they were recruited in the orthodontic department. Subsequently, it is possible that the reason for non-eruption at T2 was due to young age, so that the prevalence of final fully erupted third molars could have been underestimated. Nevertheless, daily clinical practice shows a critically low number of functional third molar eruptions in fully dentate jaws.[3,17] Moreover, orthodontically treated patients are more likely to end up with partially erupted third molars.[18] It would be of high clinical interest to iterate this research set-up to a sample of older age, preferably the age of third molar eruption.

In accordance with our findings that an angle exceeding 27° was unfavorable for eruption, a study of Nance et al. (2006) revealed a third molar angulation greater than 35° to be unfavorable.[20] Only 3% of the third molars exceeding 35° erupted to the occlusal plane during a follow-up period of 2.2 years. Since, orthodontic treatment of the lower jaw had a significant influence on the mean annual angulation change, only the subsample of patients with mandibular orthodontic treatment was used for linear regression analysis. The group of patients with maxillary treatment was too small to obtain reliable results. Accordingly, the transition angle of 27.0° only relates to patients with mandibular orthodontic treatment.

One must be aware of the geometric distortion of the dental arch on a panoramic image.[21] Additionally, positional errors when placing the patient in the panoramic X-ray machine may result in discrepancies between the molar angulation measurements at T1 and T2. In order to avoid these inconveniences, the FANC image quality guidelines were applied.[*] The question might raise if three-dimensional images would be better suited for research on angulation changes and nerve relation risk. However, panoramic radiography remains an undoubtedly useful tool and the method of choice for third molar diagnosis. Radiographic markers indicating a potentially elevated risk of relation with the mandibular canal have been identified in the past.[13,22] It should be noted that these markers are merely indicative and additional cone-beam computed tomography (CBCT) is essential to properly evaluate the exact relationship between the third molar and the mandibular canal. Nonetheless, it is not proven that CBCT reduces the prevalence of iatrogenic nerve damage.[23,24] In order to minimize neurosensory complications, early removal of the third molars may be advised if it is observed that the third molar roots are reaching out towards the mandibular canal without proper chances of functional eruption. According to this, and in line with the study of Monaco et al. (2012), we found that fully developed impacted third molars are at increased risk of being in a relationship with the mandibular canal, compared with erupted third molars.[25] In these cases, early removal may have been benefical, or other surgical procedures such as coronectomy are to be advocated.[25–27]

Major limitation of the present study was the lack of retromolar eruption space measurements, which is considered at least as important as the angulation of the third molar itself. The dimensions of the dental arch are largely predefined by ones

[*] fanc.fgov.be/nl/professionelen/medische-professionelen/tandheelkunde/aanbevelingen-voor-goede-praktijk

genetics. In case of a small mandible, eventual uprighting of the third molar teeth will not increase the eruption potential, since the lack of retromolar space will still impede eruption. Hattab et al. (1999) concluded that the most significant variable associated with third molar impaction is inadequate space.[28] Nonetheless, Hattab et al. (1997) also found that 17% of third molars with adequate retromolar space still failed functional eruption.[29]

Conclusions

Since prophylactic removal of wisdom teeth remains a matter of debate, prediction of third molar eruption at early age can help clinicians in their treatment decision and avoid retention of non-functional third molars and their associated pathologies. From the present sample of patients with mandibular orthodontic treatment, it is concluded that severely angulated third molars have critically low chance of eruption. The threshold angulation turned out to be 27.0°. Pre- and peri-eruptive rotational changes were insufficient to upright severely angulated third molars.

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CHAPTER 3
Artificial Intelligence (AI)-driven molar angulation measurements to predict third molar eruption on panoramic radiographs

Vranckx M.[1]
Van Gerven A.[2]
Willems H.[2]
Vandemeulebroucke A.[1]
Ferreira Leite A.[1,3]
Politis C.[1]
Jacobs R.[1,4]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]Relu, R&D, Leuven, Belgium.

[3]Department of Dentistry, Faculty of Health Sciences, University of Brasília, Brasília, Brazil.

[4]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: The present Artificial Intelligence (AI)-tool aimed to automatically segment the mandibular molars on panoramic radiographs and to extract the molar orientations in order to predict the third molars' eruption potential.

Methods: In total, 838 panoramic radiographs were used for training (n=588) and validation (n=250) of the network. A fully convolutional neural network with ResNet-101 backbone jointly predicted the molar segmentation maps and an estimate of the orientation lines, which was then iteratively refined by regression on the mesial and distal sides of the segmentation contours. Accuracy was quantified as the fraction of correct angulations (with predefined error intervals) compared to human reference measurements. Performance differences between the network and reference measurements were visually assessed using Bland-Altman plots.

Results: The quantitative analysis for automatic molar segmentation resulted in mean IoUs approximating 90%. Mean Hausdorff distances were lowest for first and second molars. The network angulation measurements reached accuracies of 79.7% [−2.5°; 2.5°] and 98.1% [−5°; 5°], combined with a clinically significant reduction in user-time of >53%.

Conclusion: This study validated a new and unique AI-driven tool for fast, accurate, and consistent automated measurement of molar angulations on panoramic radiographs. Complementing the dental practitioner with accurate AI tools will facilitate and optimize dental care and synergistically lead to ever-increasing diagnostic accuracies.

Key words: artificial intelligence, convolutional neural network, orientation, panoramic radiography, segmentation, third molar

Introduction

The digital revolution in dentistry has largely automated the conventional dental workflow and drastically reshaped the field. Digital innovations have smoothened and accelerated the daily practice and created an important ease-of-use in different areas, resulting in a significant reduction of work time and costs. The introduction of cone-beam computed tomography (CBCT) allowed cross-sectional imaging with limited radiation dose.[1] Consequently, the availability of three-dimensional (3D) imaging data has led to tremendous progress in terms of clinical accuracies and optimization of diagnosis and treatment planning. The use of intraoral scanners and computer-aided systems (computer-aided design/computer-aided manufacturing CAD/CAM) enabled digitized prosthodontics.[2,3] Moreover, 3D-printing is increasingly gaining ground, allowing patient-customized guided surgery.[4,5] Furthermore, recent innovations like virtual and augmented reality created new visualization systems for anatomic exploration.[6]

Last decade, also the use of artificial intelligence (AI) progressed remarkably. Deep learning algorithms or convolutional neural networks (CNN) are rapidly emerging in the field of dentomaxillofacial radiology.[7] CNNs are designed to learn patterns from large datasets, without the need for a supervisor labeling the data. The term “deep” refers to the number of (hidden) network layers to progressively extract information and features from the input data. The layers are interconnected via nodes or neurons. Each hidden layer uses the output of the previous layer as its input, thereby increases the complexity and detail of what it is learning from layer to layer.[8] By mimicking human cognition in terms of learning and problem solving, CNNs prove to be as accurate as human observers and enable highly time-efficient and precise calculations.[8] Newly developed AI tools can assist dentists and dentomaxillofacial radiologists in comprehensive and fast evaluation and documentation of dental radiographs.[9] By synergistically applying CNNs in routine care, we create an outstanding opportunity to optimize our diagnostic capacities and clinical accuracies. CNNs have shown excellent results in diagnosis and classification of diseases, such as caries staging[10], root fracture detection[11], cancer screening[12,13], and diagnosis of periodontal disease.[14] Moreover, AI applications are highly time-saving in preoperative treatment planning in implantology, orthodontics, and orthognathic surgery, by automated detection and segmentation of anatomical structures.[15,16] Furthermore, they allow efficient and precise evaluation of treatment outcomes and can help us towards highly accurate prediction of diseases.[17]

In the present study, we developed and validated the first AI-model for automated tooth angulation measurements on panoramic radiographs, in order to predict wisdom tooth eruption in adolescent patients. Evaluation of the third molars' eruption potential at the end of orthodontic treatment allows timely removal of third molars at the stage of lowest risk of mandibular nerve injury.[18] In 1997, Ventä et al. developed transparent device to overlay panoramic images to assess the probability of third molar eruption or impaction.[19] More recently, Begtrup et al. (2013) presented a method for eruption prediction based on cephalometric and panoramic radiographic measurements.[20] Accordingly, panoramic radiographs acquired to evaluate orthodontic alignment at the end of treatment can concomitantly be used to estimate the eruption chances of the third molars. Vranckx et al. (2019) identified a critical third molar angle of 27.0°, upward of which future functional eruption becomes unlikely.[21] Third molars with an angle greater than 27.0°, relative to the vertical axis of the second molar, tended to enlarge their angulation over time. The purpose of the presented deep learning tool was to automatically extract the orientations of the six molars in the mandible in order to predict the eruption chances of the third molars. The hypothesis was that the tool would be as accurate as human manual angulation measurements, but would be highly time-saving in routine workflow.

Materials and Methods

This study was approved by the Ethics Committee Research of the University Hospitals of Leuven (Belgium), and was conducted in compliance with the ICH-GCP principles and the Declaration of Helsinki (2013).

Panoramic radiographs

Panoramic radiographs were retrospectively selected from the Department of Orthodontics at University Hospital Leuven (Belgium) in accordance with the protocol of Vranckx et al. (2019) (Chapter 2).[21] Patients with fully erupted mandibular dentition, apart from the third molars, were included. In total, 838 panoramic radiographs were selected: 588 for training and technical validation and 250 for clinical validation of the network. Radiographs were acquired with the Cranex Tome (Soredex, Tuusula, Finland), Veraviewepocs 2D (Morita, Kyoto, Japan) and VistaPano S Ceph (Dürr Dental, Bientigheim-Bissingen, Germany). All image data were anonymized prior to analysis.

Deep Learning Network (CNN) construction and training

The segmentation model was a fully convolutional neural network with pretrained Resnet-101 backbone.[22,23] The network measurements were done in two stages: molar segmentation and orientation estimation (Figure 3.1). In the first stage, a deep learning algorithm segmented the 6 molars in the mandible. In the second stage, the segmentation maps were used to estimate the molar's orientation based on an iterative algorithm. These functionalities were integrated in a software tool based on the open source LabelMe project.[24]

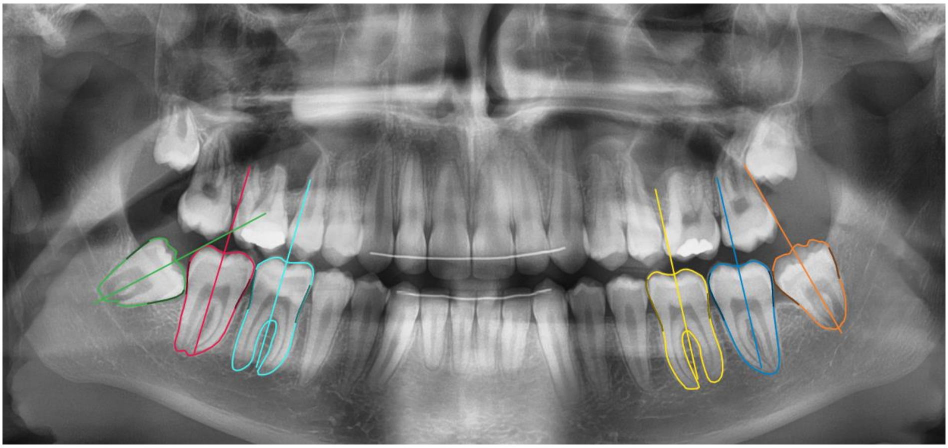


Figure 3.1. *The network calculations were two-fold: six mandibular molar segmentation maps and orientation lines.*

The **segmentation** model was trained and technically validated on a dataset of 550 panoramic images. A separate test set of 38 images was kept for final evaluation. The CNN jointly predicted the molar segmentation maps, and estimations of the middle point of the molars' occlusal surfaces and the pulp chamber floor. The latter estimated locations served as reference points for an initial estimate of the molar orientation. To reduce overfitting during training, following data augmentations were used: rotations, mirroring, random crops, and changes in illumination (brightness and contrast).

The **molar angulations** were calculated from the segmentation maps by iteratively refining the initial orientation as described in Figure 3.2. First, the molars were rotated to the initial (upright) orientation (1 and 2). Next, the roots and occlusal surfaces were censored, leaving a section of the crown and cervix of the tooth which was used to determine the updated orientation (3). Regression was performed on the mesial and distal surfaces of this part of the tooth (green lines in 4). The average of the orientations of the regression lines (blue line in 4) was added to the initial orientation (5) to form a new, better estimate of the orientation. This process was repeated 10 times to ensure the most accurate fit.

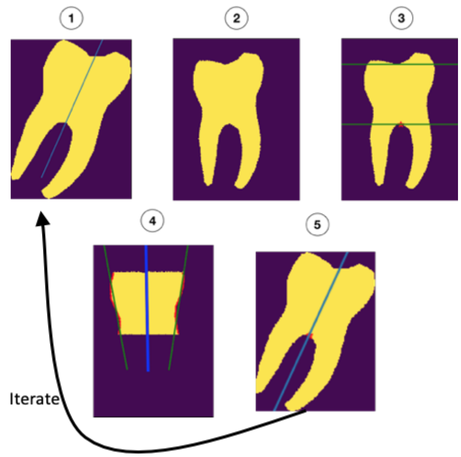
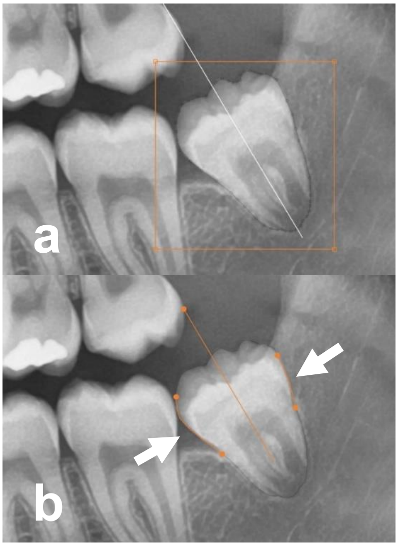


Figure 3.2. *Visual representation of the orientation estimation by the network (iterative algorithm).*



The software allowed for the user to evaluate and manually refine the final molar angulations by either: (1) editing the segmentation map as demonstrated in Figure 3.3a (drag, cut or re-create segmentation contours), and (2) manually dragging the start and end points of the regression lines on the mesial and distal side of the molars as illustrated in Figure 3.3b.

Figure 3.3. *Manual adaptations to the network: (a) editing the segmentation map and (b) manipulating the orientation line by manually dragging the mesial and distal regression lines.*

Technical validation

The deep learning architecture was evaluated based on four accuracy metrics:

- Intersection over Union (IoU): $\frac{TP}{TP+FP+FN}$
- Precision: $\frac{TP}{TP+FP}$
- Recall: $\frac{TP}{TP+FN}$
- Hausdorff distance: the maximal Euclidean distance in pixels between the ground truth and the prediction.

where *TP*, *FP*, *TN* and *FN* represent the number of pixel-wise True Positives, False Positives, True Negatives and False Negatives, respectively. An IoU of 1 represents perfect segmentation.

Clinical validation

To test the clinical validity of the methodology, 250 images with 1500 mandibular molars were measured, of which 500 were third molars. The visual inspection and corrections of the network segmentations and orientations were carried out by two independent observers, both trained to use the software tool at its full extent.

Diagnostic performance of the tool was evaluated based on four parameters. First, the network angulations were compared to the manual measurements from Vranckx et al. (2019) (GIMP 2.0 Ink software, University of California, Berkeley, CA, USA).[21] Both pre-correction angles (original network calculations) and post-correction angles (final network calculations) were compared to the human reference measurements or clinical reference. **Accuracy** was quantified as the fraction of correct angulations (with predefined error intervals) compared to the human reference measurements. Error intervals of [−1°; 1°], [−2.5°; 2.5°] and [−5°; 5°] were applied. Secondly, the extent of **manual refinements** or corrections executed on the network calculations was assessed. Both minor segmentation adjustments and total re-creation of the segmentation maps were categorized under manual manipulations. Other parameters considered were **tooth position** (first M1, second M2, third molar M3, respectively) and **development stage** of the third molars. This allowed for an intermolar comparison of the segmentation and orientation accuracy. Development stage was recorded based on a shortened version of Demirjian's classification (Appendix A): follicles without root formation (stages A–D), third molars with starting root bifurcation (stage E) and third molars with root length equal or greater than the crown height (stages F–H).[25] Lastly, the **time** consumed for execution of manual measurements versus automated network calculations, including manual refinements, was recorded for 10% of the sample.

Data analysis

Performance differences were visually assessed using Bland-Altman graphs, plotting the differences between the manual and AI measurements on the y-axis, against the averages of values on the x-axis. This statistical method allows evaluation of the agreement between the two methods of measurements (manual vs. AI). Moreover, a Mann–Whitney U test was performed to evaluate the differences between manual refinements to the network executed on M1, M2, and M3. Intraclass correlation coefficients (ICC) were calculated to determine the reliability of angulation measurements among and within observers. The intra-observer agreement also served as a measure of test-retest reliability or consistency of the network calculations. Statistical analyses were performed in MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd., Ostend, Belgium). The statistical level of significance was set at $p<0.05$.

Results

The validation of the sample was based on 250 orthodontic panoramic images of which 109 were males and 141 were females. Mean age was 15 (± 1.9) years (range 11–21 years). Third molars appeared in three stages of development: 117 early development stage (no roots), 174 starting root formation (bifurcation), and 209 third molars with developed roots.

Table 3.1 shows the accuracy metrics of the newly developed software tool. The quantitative analysis for automated segmentation of the molars resulted in mean IoUs approximating 90%, which is considered good performance. Considering the lowest mean Hausdorff distances (maximum number of pixels between the clinical reference and AI prediction), M1 and M2 showed the best performance.

Table 3.1. *Accuracy metrics of the new tool for automated molar segmentation and orientation calculation on panoramic radiographs. IoU = Intersection over Union; M1, M2, and M3 = first, second and third molar, respectively.*

Mandibular molar	IoU	Precision	Recall	Hausdorff
M1	0.875	0.939	0.928	18.8
M2	0.885	0.946	0.933	18.3
M3	0.884	0.941	0.938	20.47
Overall	0.880	0.940	0.930	19.2

3.1. Manual measurements

The average manual angle among 1500 measured molars was 27.0° ± 15.0 (range 3.4–75.5°). M1 angles were on average 16.7° ± 5.2, M2 angles 19.4° ± 6.8, and M3 angles 44.8° ± 11.2 (Table 3.2). When divided into angulation ranges, 1001 (66.7%) molars were angulated in between 0–30°, 459 (30.6%) between 30–60°, and 40 (2.7%) between 60–90°. The data showed 16.4% of the third molars orientated between [24.50°; 29.50°], the acceptable interval around the 27.0° critical angle for eruption, demonstrated by Vranckx et al. (2019) (Figure 3.4).[21]

3.2. Network measurements

The network results were twofold: the original network angulations and the final network angulations (including manual refinements). The average original angle was 28.3° ± 15.6 (range 0.6–88.5°). After minor manual adjustments, the average angle was 28.0° ± 14.7 (range 3.7–77.7°). Table 3.2 shows the final network angulations closely approximating the manual measurements (for all molars in total and divided per molar).

Table 3.2. *Average angulations among 1500 mandibular molars on 250 panoramic images: human reference measurements vs. final network results. M1, M2, and M3 = first, second and third molar, respectively.*

Molar	Manual measurements	Final network measurements
M1	16.7° ± 5.2 (range 3.4–32.2°)	17.9° ± 5.0 (range 4.1–31.0°)
M2	19.4° ± 6.8 (range 3.9–39.9°)	20.7° ± 6.5 (range 3.7–38.0°)
M3	44.8° ± 11.2 (range 5.2–75.5°)	45.4° ± 11.0 (range (7.8–77.7°)
All molars	27.0° ± 15.0 (range 3.4–75.5°)	28.0° ± 14.7 (range 3.7–77.7°)

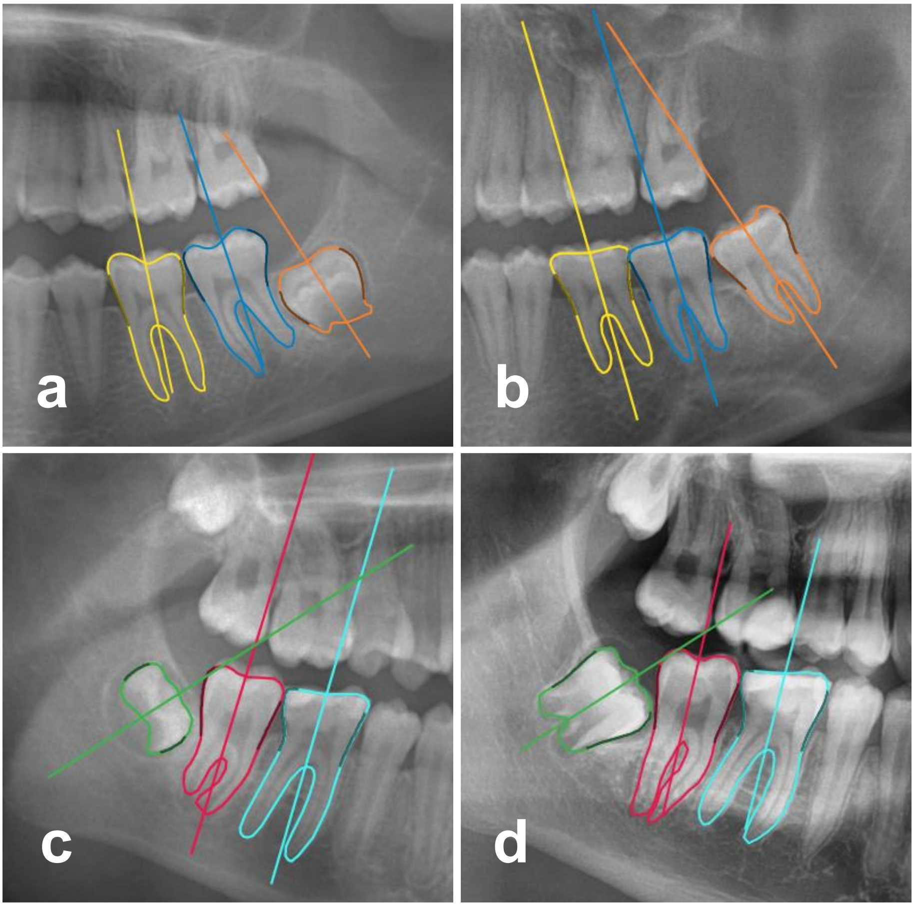


Figure 3.4. *Consecutive panoramic radiographs with a 4-year interval showing third molar eruption in (a) and (b); and third molar impaction in (c) and (d).*

<u>3.3. Network accuracy</u>

The accuracy of network measurements was calculated using the manual measurements as reference standard. Depending on the applied error intervals of [−1°; 1°], [−2.5°; 2.5°], and [−5°; 5°], the original accuracy of the network was 25.8%, 56.5%, and 83.9%, respectively (Table 3.3). After minimal manual adjustments to the segmentation maps and/or orientation lines, the final network accuracy increased to 36.6%, 79.7%, and 98.1%, respectively. The average difference between the manual measurements and the AI calculations was −1.1° ± 1.9 (range −14.1–13.7°). The [−5°; 5°] accuracy was higher in M1 and M2 (99.2%), compared to M3 (96.0%). Right [−5°; 5°] accuracy was slightly better than left (right 98.4% vs. left 97.9%). Excluding underdeveloped third molars (no roots, n=117) from the sample achieved similar network accuracies of 98.3% [−5°; 5°], 79.9% [−2.5°; 2.5°], and 37.3% [−1°; 1°].

Table 3.3. *Network accuracies, quantified as the fraction of correct angulation measurements (with predefined error intervals) compared to human reference measurements.*

Accuracy	Original network results	Final network results
[−1°; 1°]	25.8%	36.6%
[−2.5°; 2.5°]	56.5%	79.7%
[−5°; 5°]	83.9%	98.1%

3.4. Manual adjustments to the network measurements

In 782 molars, minor manual refinements to the network's segmentation maps and/or orientation lines were necessary. Within this subsample, 64 adjustments (8.2%) fell within the [−1°; 1°] range, 338 (43.2%) within the [−2.5°; 2.5°] range, and 605 (77.4%) within the [−5°; 5°] range. In total, 177 edits were >|5°| (22.6%), of which 72 were >|10°| (9.2%). The average manual refinement was 0.5° ± 6.3 (range −75.5–61.1°). This average refinement differed among molars as displayed in Table 3.4 and Figure 3.5. A Mann–Whitney U test showed significant differences in the size or extent of the manual refinements executed on M1 and M2, compared to M3 (p=0.0421).

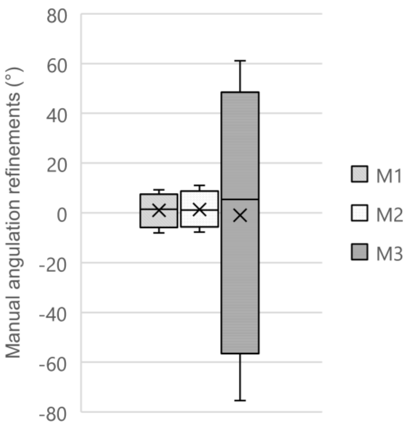


Figure 3.5. *The mean manual refinements on the network measurements displayed per molar. Manual edits to the first (M1) and second (M2) molar were small and limited. Manual edits to the third molar (M3) varied widely. These differences were statistically significant (p=0.0421).*

Table 3.4. *Average manual refinements to the network calculations. M1, M2, and M3 = first, second, and third molar, respectively. SD = standard deviation.*

	M1	M2	M3
Average	0.74	0.45	0.18
SD	2.20	1.75	10.59
Min.	−8.03	−7.70	−75.45
Max.	9.25	11.07	61.11

Almost half of the molars did not require any manual refinement (718/1500; 47.9%). These were mainly molars is the 0–30° range (501/718; 69.8%). Large edits (>|5°|) were mainly performed in molars categorized in the 30–60° range (128/177; 72.3%).

3.5. Time efficiency

On average, the AI tool was twice as fast as manual angulation measurements (Figure 3.6). The average time to manually measure the angulations of six mandibular molars on a panoramic radiograph was 63.9 sec, compared to 30.4 sec for the AI network (including manual refinements by the observer). This translated as a clinically significant time reduction of 53%. In cases where no manual refinements were needed, the AI network was up to four times faster (<15 sec) than the average manual measurements. The few cases in which the network measurements took longer than manual measurements were cases of major errors in the segmentation maps.

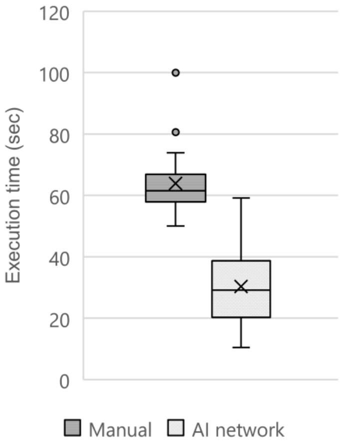


Figure 3.6. *Boxplots showing the time consumed for execution of manual measurements vs. the Artificial Intelligence (AI) network measurements. The network measurements were twice as fast as the manual measurements. The time dispersion for AI measurements was larger, due to some mis-segmentations that needed to be recreated manually.*

3.6. Precision and consistency

Figure 3.7 displays the Bland-Altman plots for evaluation of the agreement between the two methods of measurements (manual vs. AI). The angulation differences between the two methods were plotted on the y-axis, against the means of both methods on the x-axis. The plots show good, unbiased agreement between the manual measurements and the network. Limits of agreement (LOA) (mean ± 1.96 SD) were narrow. The final network measurements within the LOA showed an average of 27.4° (± 14.4) (range 3.7–77.7°). These observations were distributed as: 67.6% in range 0–30°, 29.4% in 30–60°, and 2.9% in 60–90°. The measurements outside of the LOA were angulations with an average of 40.5° (± 14.9) (range 11.2–65.1°), subdivided as 29.0% in range 0–30°, 63.8% in 30–60°, and 7.2% in 60–90°.

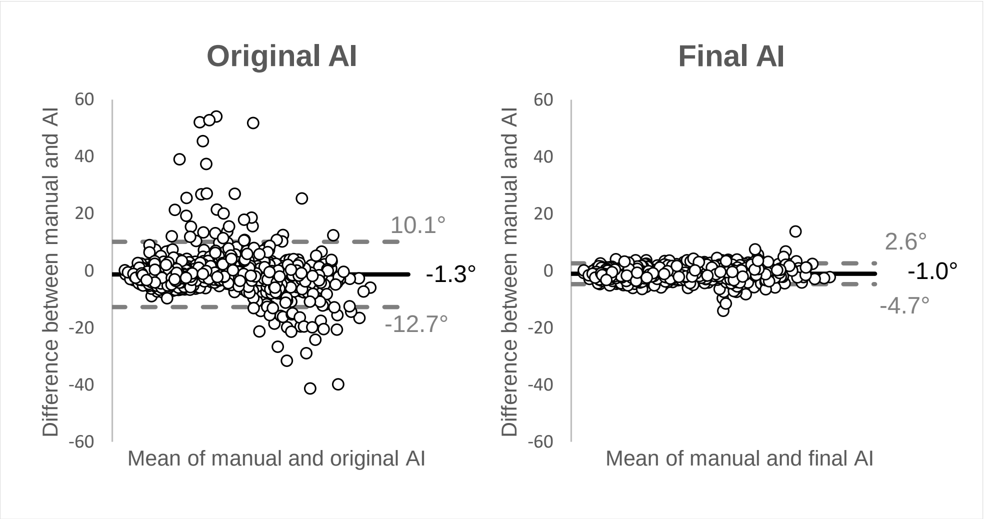


Figure 3.7. *Bland-Altman plots showing good, unbiased agreement between manual and AI molar angulation measurements. Solid line representing the mean, dashed lines representing the upper and lower levels of agreement (mean ± 1.96 SD). Limits of agreement were narrow, translating as high precision of the method of measurement.*

Overall, interobserver agreement was excellent with an ICC of 0.9799 (95% CI, 0.9778–0.9819). Similar excellent scores were recorded for intraobserver agreement, with an ICC of 0.9990 (95% CI, 0.9984–0.9993).

Discussion

The new AI-driven auto-angulation tool showed accurate and fast orientation estimations for third molar eruption prediction. The network automatically segmented the mandibular molars on panoramic radiographs, and measured their angulations in order to estimate the eruption chances of the third molars at adolescent age. The present study was a continuation of an earlier research project (Chapter 2), of which we automated the angulation measurements with 80% to 98% accuracy.[21]

Third molar eruption prediction relies on the fact that severely angulated third molar barely change angulation over time.[19,26] The minimal pre-eruptional angulation changes observed by Vranckx et al. (2019), in combination with the critical angle for (un)favorable direction of rotation (upright or inclined), resulted in reliable estimation of the eruption chances of the mandibular third molars during adolescence.[21] In addition, the available space between the distal side of the second molar and the anterior border of the ramus should be sufficient to accommodate the third molar.[20,26] Consequently, third molars that will fail to erupt in a functional position in the mouth can be timely removed, at early development stage (no roots) and stage of least risk of mandibular nerve injury.[18]

The network calculations were twofold: molar segmentation and orientation estimation. Segmentation of teeth (and other structures) in the context of treatment planning or surgery preparation is a time-consuming and operator-dependent process.[16] Automation of this treatment step facilitates the dental practitioner's daily practice. It is generally observed that multirooted teeth present a higher degree of difficulty in automated AI segmentation tools, compared to single-rooted teeth.[16] Since our application focused on mandibular molars only, we observed a relatively high need for manual segmentation refinement. Still, the time-efficiency of our tool was 2 to 4 times faster than the manual measurements. Besides, it is important to note that the network measurements came with automatic segmentation maps and orientation calculations, whereas manual angulation measurements were executed by merely visually drawing the vertical midline of the molars based on two predefined reference points, without performing manual segmentation of each tooth. This proves the network to be even more time-efficient than at first sight (>53%). Additionally, the test-retest reliability, represented by the excellent intraobserver agreement score (ICC 0.9990 with 95% CI 0.9984–0.9993), shows the outstanding consistency of the network measurements. This observation is substantiated by comparing our results with the inter- and intrareliability scores of the manual measurement in Vranckx et al. (2019), ranging from 0.7227 to 0.9604.[21] Altogether, the combination of automated segmentation and orientation estimation was considered unique, the first of its kind.

Regarding the tooth segmentation, the mean IoU approximated 90% for all molars. This performance was similar to other CNNs reported in literature.[16,27,28] Moreover, it is important to state that the CNNs in literature were designed to detect and segment all teeth on a panoramic radiograph, and were not limited to mandibular molars only.[15,16,27,28] Though, fully accurate tooth segmentation (e.g. for treatment planning purposes) was not the main scope of the presented study. The segmentation maps served as a first step in the orientation estimation process.

Therefore, the segmentation maps sufficed to be fully accurate on the mesial and distal sides of the molars to perform the regression. Lower segmentation performance, and thus higher need of manual refinements, on the molars' occlusal surfaces or root apices did not compromise the network's orientation estimation in any event. Manual adjustments to the estimated segmentation maps or orientation lines were mostly required in (underdeveloped) third molars and third molars with great angulations (>30°).

Panoramic radiographs do not reflect a true representation of the 3D dental arches. Subsequently, molar angulations were subject to distortions, because the X-ray beam in a panoramic device is not orthogonal to the mandibular arch.[29] Taking this into account, the [−5°; 5°] error interval was considered more than acceptable for third molar eruption prediction. The inherent 2D deformation of the 3D orofacial bone structures on panoramic radiographs makes the molars show wider and the front teeth more narrow.[30] It is only in the critical third molar angulation range of 25–30°, that a smaller error (<|5°|) would be desirable. Fortunately, only 16.4% of the third molars in our sample appeared in this region. In these selected cases, larger measurement errors could lead to false estimation of the future rotation direction (upright or inclined) of the third molar in development, which could result in less accurate eruption prediction and treatment decision.

It was initially hypothesized that the network would fail segmentation of third molars in early development stages, the stages mostly observed in adolescent patients ending their orthodontic treatment.[31] However, the accuracies were very similar among development stages. Moreover, various CNNs have shown to be accurate in all stages of development and are therefore increasingly applied in forensic age estimation.[32,33]

Figure 3.5 showed wide variability in third molar refinements compared with first and second molars. The latter showed very consistent calculations. High anatomical variability exists in third molar appearance with regard to crown morphology and size, aberrant orientations, multirooted versus fused roots, etc. Especially proper visualization and interpretation of buccolingual orientations pose a challenge in 2D panoramic radiography. CBCT is more suited to visualize aberrant orientations and the anatomical relation of structures. The ultimate goal is the development and implementation of similar AI-driven segmentation tools in 3D, as CBCT is the most commonly used imaging modality in the virtual preoperative treatment planning of various dental and maxillofacial procedures.

The Bland-Altman plots for evaluation of the agreement between the two methods of measurements showed excellent performance of the network compared to the manual measurements. The high precision of the network measurements is visually demonstrated by the narrow width of the limits of agreement that encompass more than 95% of the observations. Differences were observed in the distribution of measurements within the LOA (majority 0–30°) and the observations outside of the LOA (majority 30–60°). Altogether, the network performance was considered excellent.

Conclusions

In conclusion, this study presented and validated a new AI-driven tool for fast, accurate, and consistent automated measurement of molar angulations on dental panoramic radiographs. The network accurately predicted the molars' segmentation maps and orientation lines, and could be implemented in standard image viewing software to allow easy and fast prediction of third molar eruption at adolescent age. Complementing the dental practitioner with accurate AI tools will facilitate and optimize routine care and lead to synergistic ever-increasing diagnostic accuracies.

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THIRD MOLAR REMOVAL

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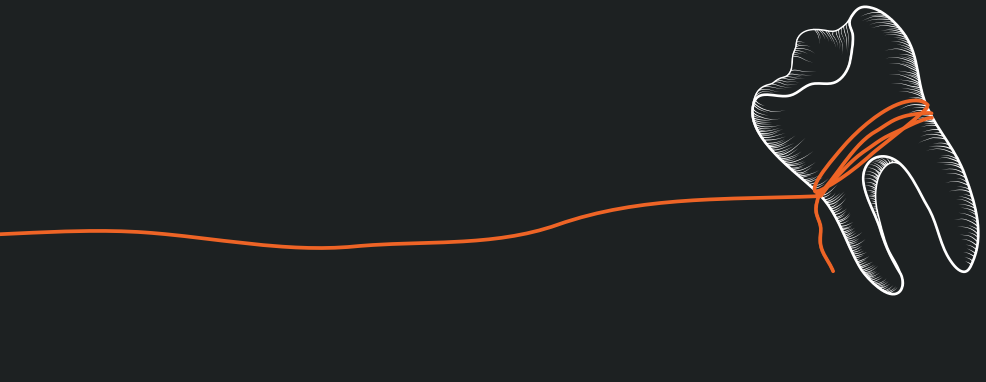
THIRD MOLAR REMOVAL



CHAPTER 4

Prophylactic vs. symptomatic third molar removal, and the effect of age on postoperative morbidity

Vranckx M.[1]

Fieuws S.[2]

M3BE research group

Jacobs R.[1,3]

Politis C.[1]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]L-BioStat, Leuven Biostatistics and Statistical Bioinformatics Centre, KU Leuven, Leuven, Belgium.

[3]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: The present study aimed to assess differences in postoperative morbidity between prophylactic and symptomatic third molar removals, and to assess the effect of age on the recovery of the patient.

Methods: Patients admitted for third molar removal were prospectively followed up four times during treatment in context of the M3BE study. Data were collected through pre-, peri- and postoperative surveys (days 3 and 10). Uni- and multivariable logistic regression was used to assess the probability of postoperative symptoms of discomfort on day 3 and day 10 according to several patient- and surgery-related predictive factors (age, gender, indication for removal, method of extraction, anesthesia and number of extracted maxillary and/or mandibular third molars).

Results: In total, 6010 patients with a mean age of 25.2 (± 11.2) underwent 6347 surgeries to have 15357 third molars removed. Frequently observed symptoms of postoperative discomfort were pain, trismus and swelling, all of which were transient in nature with steep decreases from postoperative days 3 to 10. Increasing age was associated with an enhanced risk of persistent pain, trismus and swelling, and a significantly higher risk of iatrogenic injury to the inferior alveolar nerve. Indications for removal were more likely to be symptomatic with increasing patient age (>25 years), but these symptomatic indications had no prolonging effect on patient recovery. Other factors related to postoperative morbidity were female gender, intraoperative osteotomy and the number of extractions.

Conclusion: The results of this study suggest that there are convincing patient- and surgery-related factors that favor timely third molar removal, preferably before the age of 25. A greater age at the time of surgery significantly increased the risk of persistent postoperative morbidity. Symptomatic indications for removal were more common in patients over age 25 years, but these pre-existing pathologies did not compromise the postoperative recovery process.

Key words: extraction, indications, complications, prophylactic, third molar, wisdom teeth

Introduction

Lack of space in the jawbones often leads to difficulties for the last teeth, the third molars or wisdom teeth, to erupt into their natural functional position. Compromised third molar eruption can result in impaction, a state in which the third molars are impeded from eruption by adjacent teeth, dense bone, or an overgrowth of soft tissue.[1] Impaction is frequently associated with complications such as pain, discomfort and pathology.[2] There is no debate about the removal of third molars with signs or symptoms of disease, but consensus is lacking about how to proceed in the absence of clear signs of pathology.[3] In the last two decades, several international treatment guidelines have advised a conservative approach for asymptomatic disease-free third molars through active clinical and radiological surveillance, rather than prophylactic removal.[4–6] Among these guidelines are the 2000 National Institute for Health and Care Excellence (NICE) guidelines[4] from the United Kingdom, the 2000 Scottish Intercollegiate Guidelines Network (SIGN) guidelines[5], and the 2012 Belgian Health Care Knowledge Centre (KCE) report.[6]

In the United Kingdom, the introduction of the NICE guidelines was initially followed by a reduction in third molar removals. However, studies have shown that the guidelines ultimately did not affect the management of asymptomatic third molars in daily practice.[7] In a 10-year period after implementation of the NICE guidelines, the first drop in surgery rates was counteracted by an increase in the mean age of patients admitted for third molar surgery, as well as an increase in diagnoses such as pericoronitis and caries on second and/or third molars.[7] Thus, increasing evidence suggests that conservative treatment guidelines might have a reversed effect in the long run, leading to increases in third molar removal under unfavorable conditions, at greater average age, with further development of the roots, and more pathological circumstances.[7,8]

Treatment guidelines should be based on the best available research, but the striking lack of high-quality prospective and/or longitudinal data makes drafting evidence-based treatment guidelines easier said than done. For this reason, the overarching aim of this epidemiological study was to gain insight into the current indications for third molar removal, the postoperative recovery process and the incidence of postoperative discomfort associated with this type of oral surgery, through a large-sample prospective cohort study. The hypotheses were that (1) removal of symptomatic third molars would be associated with more and/or longer postoperative discomfort, as compared with prophylactic third molar extractions; and that (2) postoperative discomfort and extraction-related morbidity would be increased and prolonged with increasing age of the patient at the time of surgery.

Patients and Methods

This prospective epidemiological study was carried out in compliance with the principles of the Declaration of Helsinki (2013) and the principles of ICH-GCP, and in accordance with all applicable regulatory requirements. The Ethics Committee Research of the University Hospitals of Leuven (Belgium) approved the M3BE study protocol on September 10, 2015 (B322201525552). The trial was registered in the clinicaltrials.gov registry with ID number NCT02481700. Data were collected from September 2015 until December 2019. Written informed consent was recorded from all eligible subjects prior to completion of any survey. Participation in the study was considered non-interventional, non-invasive and with minimal burden for the patients. Patient inclusion was carried out by independent research associates assisted by (bio)medical and dental students.

Five Belgian centers participated in this multicenter study: University Hospitals Leuven, Mariaziekenhuis Pelt, Ziekenhuis Oost-Limburg Genk, AZ Sint-Blasius Dendermonde and Centre Hospitalier Universitaire de Liège. Patients with a minimum age of 12 years consulting at the Oral and Maxillofacial Surgery (OMFS) department for advice on the management of their wisdom teeth were included in the study. No restriction for maximum age was applied. Exclusion criteria were limited: patients with supernumerary teeth and patients with additional coinciding oral interventions were excluded from the study.

Pre-, peri- and postoperative data were collected by the use of standardized surveys at four time points throughout each patient's treatment course (Figure 4.1). The first survey was completed at the time of consultation at the OMFS department to register demographic data of the patient as well as referral and reason for consultation. The third molar extraction procedure was registered through a standardized survey completed by the surgeon. Postoperatively, patients were asked to record their recovery status and ability to resume daily household and work activities at day 3 and day 10. Symptoms reported on day 3 after surgery are further referred to as immediate postoperative discomfort, whereas symptoms reported on day 10 are considered as late or persistent morbidity. The surveys inquired after (Appendix B):

- **Consultation:** age, gender, referral, reason for visit, (past) complaints, orthodontic treatment, smoking habits, BMI, and medical history;
- **Surgery:** indication for third molar removal, active infections at the time of surgery, method of extraction (need for osteotomy), number of extractions, anesthesia (local, procedural sedation, general), preoperative diagnostic imaging, and visualization of the inferior alveolar nerve during surgery;
- **Postoperative day 3:** pain (visual analogue scale VAS), painkiller use, trismus, swelling, altered sensations to lip/tongue, and the ability to resume household and work/studies;
- **Postoperative day 10:** pain (VAS), pain development from day 3 to day 10 after surgery, painkiller use, trismus, swelling, altered sensations to lip/tongue, the ability to resume household and work/studies, reconsultation with a doctor in 10 consecutive days after surgery (other than control appointment), and postoperative prescription of antibiotics.

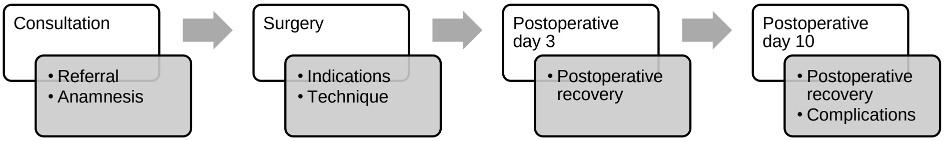


Figure 4.1. *Pre-, peri- and postoperative data were collected by the use of standardized surveys at four time points throughout the patient's treatment course.*

Indications for third molar removal were assessed according to the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 nomenclature Chapter K. Symptomatic indications included caries (K02), periapical pathology (K04), periodontal disease (K05.2), pericoronitis (K05.0), tooth fracture (K03.81), odontogenic cysts (K09.0) and resorption (K03.3). Asymptomatic indications included impaction because of lack of space in the dental arch (K01.1), impaction because of aberrant third molar orientation (K01.1), non-functional third molars (malocclusion), prophylactic removal because of difficulties in maintaining oral hygiene distally in the mouth, or extraction in context of another treatment (dental or medical). All types of third molar development stages, eruption classes and impaction statuses (soft tissue, bony) were included.

Descriptive analysis was performed on the entire population (n=6010). Univariate and multivariable logistic regression models were conducted to assess the probability of occurrence of immediate and late postoperative discomfort according to several patient- and surgery-related predictive factors. Generalized estimating equations were used for patients who underwent multiple surgeries. Statistical analysis was performed on surgery-level (not on tooth-level). The models were fitted on >3000 cases with postoperative data present (n=dependent on the variable). Predictive factors (consultation and surgery survey) were gender, age (≤16, 17–25, 26–35, 36–55, >55 years), BMI, indication for removal (symptomatic or asymptomatic), type of anesthesia (local or systemic), method of extraction (osteotomy or not) and a factor combining the number of extracted teeth and involved jaws. Outcome variables (postoperative surveys for day 3 and 10) were dichotomized: slight, moderate or extensive presence of symptoms (combined into one category) versus no symptoms. Odds ratios (OR) were reported.

The number of days before a patient could resume daily household activities, work or studies, and stopped using painkillers was visually assessed by means of cumulative incidence curves, constructed with the complements of the Kaplan-Meier estimates for each of these outcome variables. Univariate and multivariable Cox regression models were used, censoring the subjects for which the number of days exceeded 10. Hazard ratios (HR) were reported. A robust estimator was used to handle the presence of multiple surgeries for a single subject. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at $p<0.05$.

Results

In total, 6010 patients (2752 males (45.8%); 3258 females (54.2%)) were included in this study. Mean age was 25.2 (± 11.2) years (median 22; range 12–93). Tables 4.2.a and 4.2.b show an overview of all parameters recorded over the four time points in this study. More than half of the patients (57.4%) had current or a history of orthodontic treatment. The sample included 14.1% smokers.

4.1. Consultation

In total, 15.9% of the patients visited the department on their own initiative, 56.6% were referred by their dentist, 21.7% by their orthodontist and 4.4% by another clinician (e.g. general practitioner, dental specialist). Almost half of the patients (47.3%) had had complaints or experienced symptoms for which they consulted the OMFS department. One third (32.5%) of the patients were referred based on aberrations detected on a dental radiograph, and 20.1% consulted the OMFS department for third molar advice in the context of another medical or dental treatment. Patients with preoperative symptoms complained of episodes of pain without symptoms of inflammation (19.2%), 7.8% experienced symptoms of inflammation (dolor, calor, tumor, rubor, fever, trismus) and 0.5% experienced altered sensation in the lower lip and/or tongue. At the time of consultation 71.7% of the patients were symptom free.

4.2. Surgery

In total, 15357 third molars (49.2% maxilla; 50.8% mandible) were removed in 6347 surgical interventions. The average number of extractions was 2.9 (± 1.2) third molars. Almost half of the surgeries (49.2%) involved extraction of all four third molars, and 9.7% involved three third molars. One fourth of the surgeries (25.4%) were extractions of two third molars, and 15.7% were single third molar extractions. Indications for removal are tabulated in Table 4.2.a. In 1649 patients (32.6%; 2473 third molars), symptomatic indications for removal were diagnosed. Another 3409 patients (67.4%; 12147 third molars) underwent third molar removal for prophylactic asymptomatic indications (e.g. impaction). Indication for removal remained unknown in 465 surgeries (737 third molars).

The proportion of symptomatic indications increased with increasing age, whereas the share of surgeries for impaction reasons declined drastically with increasing age (Figure 4.2). Symptomatic indications such as pericoronitis, caries, periapical pathology and periodontitis increasingly gained ground in the older age categories. The five indications for removal displayed in Figure 4.2 encompassed 96.5% of all diagnoses in the sample. Moreover, in 14.2% of the patients an active infection was diagnosed at the time of intervention. In 76.3% of the surgeries, osteotomy was performed (in one or more teeth). No coronectomies were performed in the context of this study.

Most patients were diagnosed and treated based on a preoperative panoramic radiograph (86.7%), and 10.8% had an additional cone-beam computed tomography (CBCT) image. One in five (19.3%) mandibular third molars evaluated with CBCT were diagnosed as being in close relation with the inferior alveolar nerve (IAN). In 4.9% of the surgeries involving mandibular third molar extraction, the IAN was visualized during the procedure. Overall, 39.7% of surgeries were performed under local anesthesia (LA), 57.5% under procedural sedation (SED) and 2.9% under general anesthesia (GA).

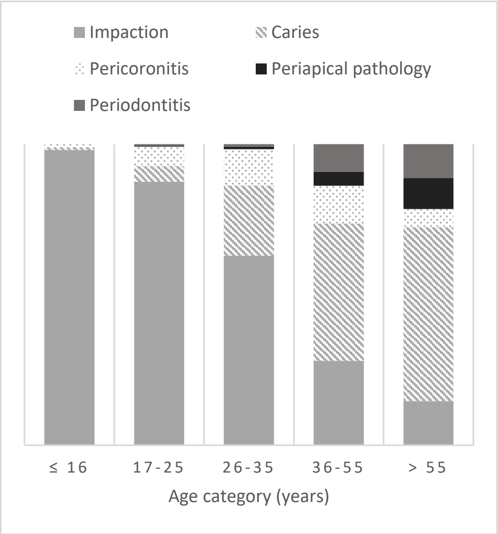


Figure 4.2. *Distribution of the five most common indications for third molar extraction within each age category. These 5 diagnoses encompassed 96.5% of all diagnoses in the sample (n=12354). Symptomatic indications drastically gained ground with increasing patient age.*

4.3. Postoperative day 3

In total, 3757 (59.2%) patients filed a postoperative report on day 3 after surgery, and 3628 (57.2%) did so on day 10. On day 3 after surgery, 43.9% of patients reported minor pain (VAS 1–3), 35.9% experienced moderate to severe pain (VAS 4–7) and 8.7% reported unbearable pain levels (VAS 8–10) (Table 4.2.b). One in ten patients (11.5%) reported being pain free on day 3. Moreover, 85.5% of patients reported presence of trismus, and 79.1% reported swelling of the cheeks on the extraction side(s). Three out of four patients (75.6%) were still on painkillers, 64.0% were able to resume daily household activities, and 57.8% resumed work or studies.

Table 4.1 shows an overview of neurosensory disturbances of the IAN or the lingual nerve (LN) reported on day 3 and day 10 after surgery. On day 3, a total of 343 patients (9.2%) reported altered sensation in the lower lip, of whom 85 reported numbness, 17 tingling, 16 stabbing pain or pain upon touch, 38 a combination of these symptoms, and 201 reports were not further specified. An additional 304 patients reported altered feeling in the tongue, of whom 96 reported altered taste perception. These symptoms were attributed to the extensive use of mouth rinse. The remaining 208 patients (5.6%) reported sensory dysfunctions such as numbness (n=97), tingling (n=44) or a combination of symptoms (n=41), and 44 reports were not further specified.

Table 4.1. *An overview of neurosensory disturbances of the IAN or LN reported on day 3 and day 10 after surgery.*

Postoperative altered sensation	**Lower lip**		**Tongue**	
	D3	**D10**	**D3**	**D10**
Numbness	85	21	97	39
Tingling	17	8	44	18
Stabbing pain/pain upon touch	16	3	0	0
Combination	38	11	41	21
Other	8	2	10	3
Not specified	193	92	34	66
Total	**343 (9.2%)**	**110 (3.1%)**	**208 (5.6%)**	**88 (2.5%)**

<u>4.4. Postoperative day 10</u>

On day 10 after surgery, 44.8% of patients reported being pain free, another 43.2% reported minor pain, 10.3% reported moderate pain and 1.7% were experiencing unbearable pain. Among the patients who were still experiencing pain, 85.9% reported a decrease from day 3 to day 10 after surgery. On the other hand, 14.1% reported increased pain, which could suggest postoperative infection or complications. More than half of the patients (54.8%) reported being free from any trismus symptoms, and 75.8% of patients were free from swelling.

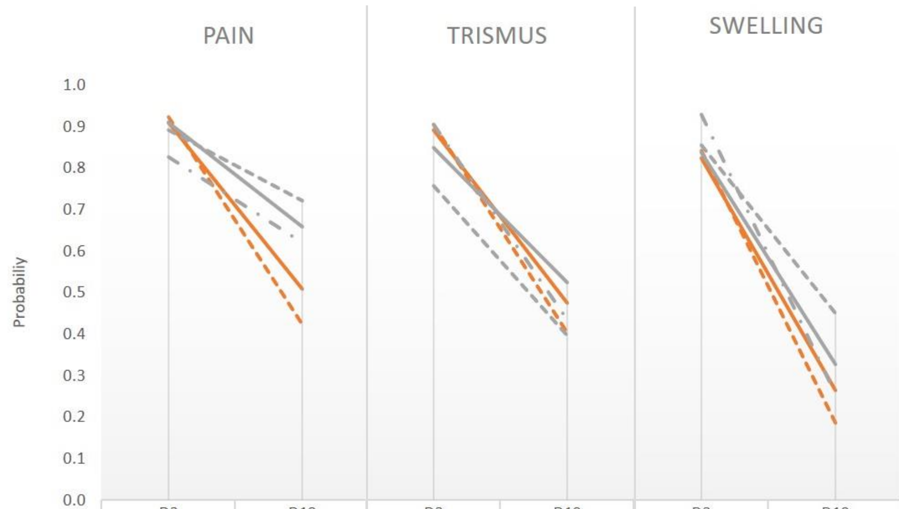
One in five patients (20.7%) revisited a doctor during the 10 consecutive days after surgery (other than a control visit): 38.5% for persistent discomfort such as pain or bleeding, 39.6% with signs of inflammation (pain, fever, swelling, trismus), 6.1% for altered sensation in the lower lip or tongue, and another 13.0% for a combination of these symptoms.

At 10 days, the number of patients reporting altered sensation in the lower lip had decreased to 110 cases (3.1%) (Table 4.1): 21 patients reported numbness of the lower lip and chin area, 8 reported tingling, 3 suffered from stabbing pain and pain upon touch, and 13 reported a combination of these symptoms (92 unknown). In total, 145 patients reported altered feeling in the tongue, with 57 of them citing altered taste perception. The other 88 cases (2.5%) were sensory dysfunctions of the LN: 39 reports of numbness, 18 of tingling, 24 of combinations of symptoms, and 66 that remained unspecified.

Of all of these patients, 152 suspected cases of iatrogenic nerve injury (64 IAN; 68 LN; 20 both) operated in University Hospitals Leuven were followed up until 6 months after surgery (total postoperative reports n=2510). Within this subsample, it was concluded that 69 patients (41 IAN; 23 LN; 5 both; 69/2510; 2.7%) suffered temporary neurosensory disturbances (resolved within 6 months after third molar removal). Seven patients (5 IAN; 2 LN; 7/2510; 0.3%) were diagnosed as having permanent trigeminal nerve injury (6-month cut-off). Another 53 patients reporting altered sensation in the lower lip or tongue appeared to have suffered from complications other than iatrogenic nerve injury (e.g. extensive swelling, infection, dry socket) that caused subjective altered sensation in the respective area. For another 23 cases, the outcome remained unknown (drop-out in follow-up period).

The associations between patient- and surgery-related predictor variables and the probability of immediate (day 3) and late (day 10) postoperative discomfort are reported below, from both univariate (Tables 4.3.a, 4.4.a, 4.5.a) and multivariable (Tables 4.3.b, 4.4.b, 4.5.b) models.

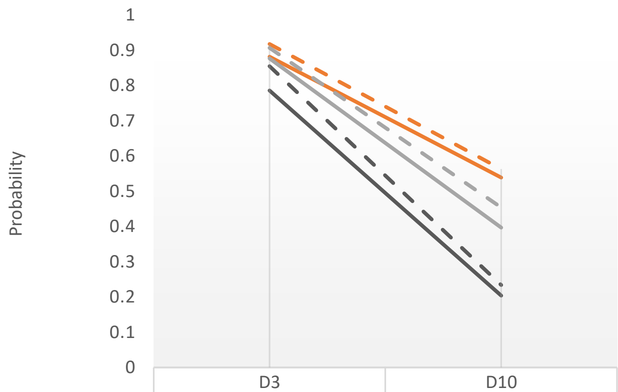
The effect of **age** on postoperative morbidity varied depending on the immediate or late nature of symptoms. The reference age category was 17–25 years, the most common age for third molar removal. In general, patients younger than 16 were more likely to suffer immediate and persistent swelling and trismus, as compared to the reference age (Tables 4.4 and 4.5; OR>1; $p<0.05$). On the other hand, older patients (age >25 years) were less likely to suffer immediate symptoms of pain, trismus and swelling (Tables 4.3, 4.4 and 4.5; OR<1; $p<0.05$). Yet, older age significantly increased the odds of suffering persistent postoperative morbidity (pain, trismus and swelling until day 10) (OR>1; $p<0.05$). Figure 4.3 shows the differences in probabilities of immediate and late postoperative morbidity according to age. The decreases in morbidity from day 3 to day 10 were the steepest in the youngest age categories (age <25 years).



	PAIN D3	PAIN D10	TRISMUS D3	TRISMUS D10	SWELLING D3	SWELLING D10
≤ 16	0.923	0.423	0.909	0.405	0.824	0.183
17-25	0.910	0.508	0.895	0.476	0.807	0.259
26-35	0.910	0.658	0.851	0.526	0.819	0.320
36-55	0.892	0.721	0.760	0.398	0.838	0.441
> 55	0.826	0.621	0.908	0.437	0.910	0.250

Figure 4.3. *Probability of postoperative pain, trismus and swelling on day 3 and day 10 after surgery according to age. An evident decrease is observed for all postoperative symptoms from day 3 to day 10 postoperatively. These decreases were the steepest for young patients (age <25 years).*

Further, the **indication** for removal was associated with both immediate and late symptoms of discomfort (Tables 4.3, 4.4 and 4.5). The univariate model revealed that symptomatic indications for removal were associated with less self-reported postoperative morbidity (Tables 4.3.a, 4.4.a, 4.5.a; OR<1; p<0.05). However, in the multivariable model, this effect was observed only on day 3 after surgery (Tables 4.3.b, 4.4.b, 4.5.b). Patients undergoing prophylactic removal of asymptomatic third molars had higher probability of suffering postoperative symptoms, compared with patients undergoing removal of symptomatic third molars (Figure 4.4; dashed lines above solid lines).



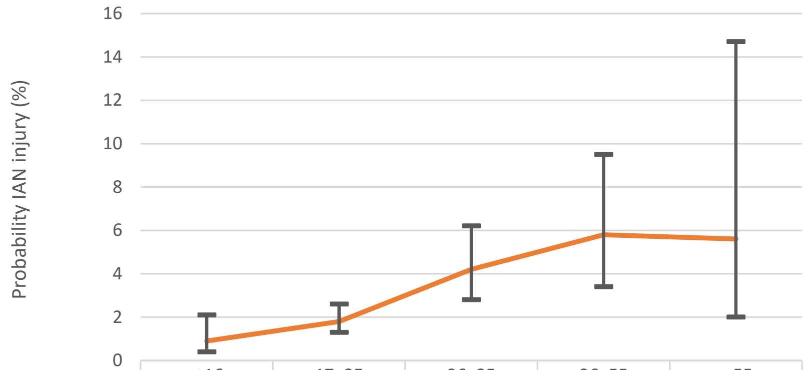
	D3	D10
Pain - symptomatic removal	0.882	0.539
Pain - prophylactic removal	0.918	0.563
Trismus - symptomatic removal	0.877	0.397
Trismus - prophylactic removal	0.907	0.454
Swelling - symptomatic removal	0.786	0.204
Swelling - prophylactic removal	0.855	0.234

Figure 4.4. *Probability of postoperative pain, trismus, and swelling on day 3 and day 10 after surgery according to the preoperative indication for removal. An evident decrease is observed for all postoperative symptoms from day 3 to day 10 postoperatively. Patients undergoing prophylactic removal (dashed lines) had higher chances of suffering from the assessed symptoms, compared with patients undergoing therapeutic removal of symptomatic third molars. This effect of indication on the occurrence of postoperative symptoms was significant for all symptoms on day 3 but remained significant on day 10 for trismus only (Table 4.4.b).*

In addition, both models showed significant associations of **gender**, **method of extraction and number of extracted teeth and involved jaws** with the occurrence of postoperative pain, trismus and swelling (Tables 4.3, 4.4 and 4.5). In particular, female gender, intraoperative osteotomy and multiple extractions in both maxilla and mandible were factors associated with higher occurrence of immediate and late discomfort (pain, trismus and swelling). The univariate model also showed significant associations between the type of anesthesia and immediate and late occurrence of postoperative pain, trismus and swelling (Tables 4.3.a, 4.4.a, 4.5.a). However, after adjusting for covariates, these effects did not remain in the multivariable model (Tables 4.3.b, 4.4.b, 4.5.b).

The univariate analysis also included **BMI and severity of symptomatic indication** as potential predictive variables. Effects of BMI varied according to the immediate vs. late nature of the postoperative discomfort (Tables 4.3.a, 4.4.a, 4.5.a). In general, higher BMI (>25 kg/m^2) resulted in lower odds of immediate pain, trismus and swelling, as compared with patients who had normal BMI (18–25 kg/m^2). Within the category of symptomatic indications for removal, preoperative presence of pericoronitis, tooth resorption and cysts/tumors resulted in significantly higher odds of pain, trismus and swelling, as compared with carious third molars. The multivariable effects of these two parameters could not be modelled because they remained unknown in too many cases. With their exclusion, the multivariable regression analysis could be modelled on >3000 cases for all parameters.

The multivariable logistic regression model revealed significant effects of age and method of extraction on the occurrence of temporary or permanent IAN injury, as reported 3 and 10 days after surgery (Table 4.6.a). Older patients (age >25 years) had significantly higher odds of suffering iatrogenic IAN injury, as compared with the reference category of those aged 17–25 years (p-values for day 3 ranged from 0.0045 to 0.0474; p-values for day 10 ranged from 0.0007 to 0.0464). The probability of suffering temporary or permanent IAN injury was 0.9% when ≤16 years, 1.8% when 17–25, 4.2% when 26–35, 5.8% when 36–55 years, and 5.6% for patients over 55 years (Figure 4.5). Additionally, intraoperative osteotomy was significantly related to IAN neurosensory disturbances as well (Table 4.6.a; day 3 $p<0.0001$; day 10 $p=0.0003$). Interventions requiring osteotomy resulted in a 3.1% chance of IAN injury, compared with 0.8% in the non-osteotomy group. The model revealed no clear associations between the assessed patient- and surgery-related factors and (temporary or permanent) LN injury, as reported on day 3 after surgery, except for intraoperative osteotomy and age category 26–35 years (Table 4.6.b). Day 10 reports contained too few cases of LN sensory dysfunction to construct a meaningful multivariable model.



	≤ 16	17–25	26–35	36–55	> 55
Probability	0.9	1.8	4.2	5.8	5.6
Lower limit (95% CI)	0.4	1.3	2.8	3.4	2
Upper limit (95% CI)	2.1	2.6	6.2	9.5	14.7

Figure 4.5. *Probability of suffering iatrogenic IAN injury following third molar removal according to the patient's age. Results obtained from the multivariable model (for a population having the same distribution for the other variables involved in the model as the distribution observed in the sample).*

The ability to resume daily household activities and work or studies over 10 consecutive days after surgery, according the indication for removal, is plotted in Figure 4.6. On average, patients reported being unable to perform their daily household activities for 3 (± 2.4) days after surgery, and skipped work or studies for 4 (± 2.5) days after surgery. Sick leaves longer than 10 days or other circumstances (e.g. retirement, holidays) were omitted from this calculation. Patients undergoing removal of symptomatic third molars reported resuming their daily lives and work/studies sooner than patients undergoing prophylactic removal of asymptomatic third molars (HR 1.282 $p<0.0001$ and HR 1.284 $p<0.0001$ respectively). These effects, however, did not stand in the multivariable model (HR 0.997 $p=0.9507$ and HR 0.988 $p=0.7906$ respectively). In addition, Figure 4.6 illustrates the need for painkillers during 10 consecutive days after surgery, according to the indication for removal. On average, patients reported taking painkillers for 6 (± 3.0) days. Patients undergoing removal of symptomatic third molars stopped painkillers sooner than patients undergoing removal of asymptomatic third molars (HR 1.123 $p=0.0016$). When considering confounding by covariates, the effect disappeared (HR 1.004 $p=0.9226$).

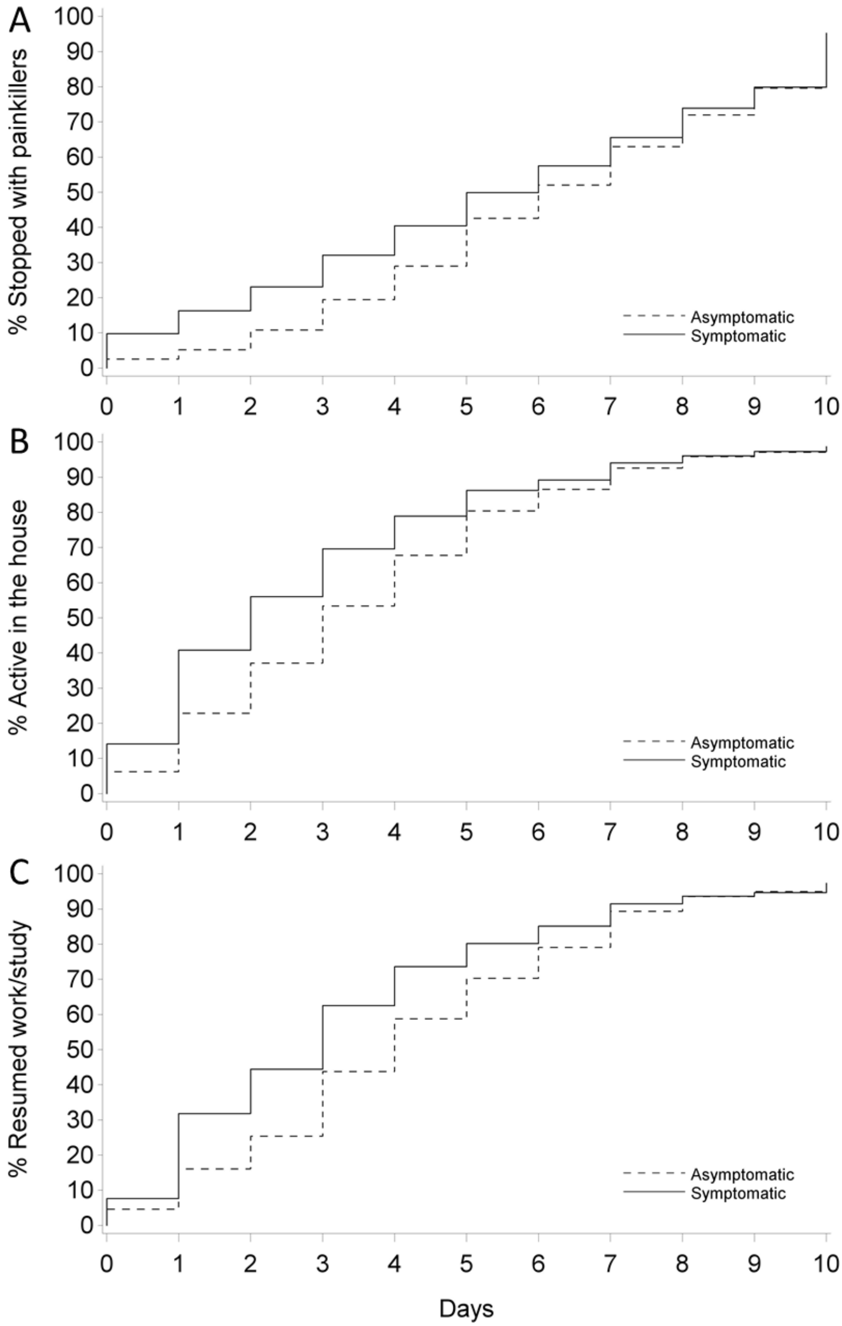


Figure 4.6. *Visual assessment of the number of days before a patient (A) stopped using painkillers, and (B) was able to resume daily household activities and (C) work or studies, according to the indication for removal. Patients with symptomatic indications reported resuming their daily activities sooner, as well as stopping painkillers sooner, as compared with patients undergoing prophylactic third molar removal.*

Table 4.2.a. *Overview of all parameters recorded over the four time points throughout the patients' treatment course.*

Consultation	**N = 6010**	**Surgery (N teeth = 15357)**			**N = 6347**
Referral		**Symptomatic indication (ICD-10 code)** 1649 patients; 2473 teeth			*N in teeth*
Own initiative	15.9	Caries K02			50.9
Dentist	56.6	Periapical pathology K04			3.2
Orthodontist	21.7	Periodontal disease K05.2			5.5
Other	5.8	Pericoronitis K05.0			33.6
Reason for visit		Tooth fracture K03.81			1.3
Complaints	47.3	Odontogenic cysts K09.0			1.7
Radiographs	32.5	Resorption K03.3			3.9
Other treatment	20.2	**Asymptomatic indication (ICD-10 code)** 3409 patients; 12147 teeth			*N in teeth*
Current complaints		Impaction lack of space K01.1			23.6
None	71.7	Impaction orientation K01.1			62.2
Pain & discomfort	19.5	Non-functional third molars			6.4
Inflammation	8.1	Prophylaxis (oral hygiene)			4.3
Altered sensation	0.7	Other treatment (dental or medical)			3.6
BMI		**Method of extraction: no osteotomy**			26.4
< 18	6.2	**Method of extraction: osteotomy**			73.6
18–25	71.3	**Number of third molar extractions**			*N in patients*
26–30	16.6	(1) 15.7	(2) 25.4	(3) 9.7	(4) 49.2
> 30	5.9	**Anesthesia**			
Orthodontics		Local anesthesia			39.7
Yes	57.4	Procedural sedation			57.5
No	42.6	General anesthesia			2.9
Smoking		**Infection at time of surgery**			14.2
Yes	14.1	Mandibular third molar in relation with IAN			19.3
No	85.9	IAN exposure during surgery			4.9

Numbers are percentages of the total. Parameters in bold were included in the univariate and multivariable logistic regression models.

Table 4.2.b. Overview of all parameters recorded over the four time points throughout the patients' treatment course.

Postoperative day 3	**N = 3757**	**Postoperative day 10**	**N = 3628**
Pain		**Pain**	
No pain VAS 0	11.5	No pain VAS 0	44.8
Minor pain VAS 1–3	43.9	Minor pain VAS 1–3	43.2
Moderate pain VAS 4–7	35.9	Moderate pain VAS 4–7	10.3
Unbearable pain VAS 8–10	8.7	Unbearable pain VAS 8–10	1.7
		Pain development (if pain)	
		Decrease ↓	85.9
		Increase ↑	14.1
Trismus		**Trismus**	
No	14.5	No	54.8
Slight	34.9	Slight	33.9
Moderate	35.1	Moderate	9.1
Extensive	15.5	Extensive	2.2
Swelling		**Swelling**	
No	20.9	No	75.8
Slight	36.8	Slight	20.7
Moderate	26.4	Moderate	2.6
Extensive	16.0	Extensive	0.8
Altered sensation lip	9.2	**Altered sensation lip**	3.1
Altered sensation tongue	5.6	**Altered sensation tongue**	2.5
Active in house	64.0	**Active in house (average days)**	3 ± 2.4
Resumed work/studies	57.8	**Resume work/studies (average)**	4 ± 2.5
Painkiller use	75.6	**Painkiller intake (average)**	6 ± 3.0
		Revisit doctor (≠ control)	20.7
		Postoperative antibiotics	8.0

Numbers are percentages of the total. Parameters in bold were included in the univariate and multivariable logistic regression models.

Table 4.3.a. *Results from univariate logistic regression using generalized estimating equations modeling the probability of suffering from postoperative pain immediately after surgery (day 3) and late (day 10).*

Univariate	PAIN			
	D3		D10	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Gender				
Female	#		#	
Male	0.476 (0.387;0.586)	<.0001	0.649 (0.567;0.743)	<.0001
Age				
≤ 16	1.429 (0.962;2.123)	0.0767	0.847 (0.693;1.034)	0.1021
17–25	#		#	
26–35	0.637 (0.487;0.834)	0.0011	1.298 (1.081;1.559)	0.0052
36–55	0.318 (0.238;0.425)	<.0001	1.045 (0.834;1.308)	0.7026
56–75	0.151 (0.099;0.230)	<.0001	0.551 (0.365;0.831)	0.0045
> 75	0.220 (0.065;0.745)	0.0150	0.655 (0.175;2.448)	0.5296
BMI				
< 18	0.846 (0.454;1.580)	0.6005	0.627 (0.421;0.932)	0.0211
18–25	#		#	
26–30	0.647 (0.436;0.959)	0.0303	0.986 (0.752;1.292)	0.9163
> 30	0.397 (0.234;0.673)	0.0006	0.662 (0.434;1.009)	0.0550
Indication				
Asymptomatic	#		#	
Symptomatic	0.388 (0.313;0.481)	<.0001	0.831 (0.717;0.964)	0.0036
Caries	#		#	
Pericoronitis	2.512 (1.657;3.810)	<.0001	1.635 (1.219;2.194)	0.0010
Periodontitis	1.105 (0.551;2.214)	0.7788	1.263 (0.657;2.429)	0.4837
Tooth resorption	1.314 (0.624;2.766)	0.4725	1.470 (0.766;2.823)	0.2466
Periapical pathology	0.610 (0.313;1.189)	0.1468	0.732 (0.368;1.459)	0.3757
Cysts/tumors	6.569 (0.972;44.406)	0.0535	3.369 (1.193;9.513)	0.0219
Method of extraction				
No osteotomy	#		#	
Osteotomy	3.829 (3.089;4.745)	<.0001	2.405 (2.040;2.836)	<.0001
Anesthesia				
Local anesthesia	#		#	
Sedation	2.303 (1.863;2.847)	<.0001	1.516 (1.314;1.750)	<.0001
General anesthesia	3.776 (1.171;12.177)	0.0261	1.217 (0.711;2.083)	0.4733
Number of teeth + jaw				
1 upper	#		#	
1 lower	3.263 (2.187;4.867)	<.0001	3.748 (2.510;5.596)	<.0001
2 upper	1.883 (1.164;3.046)	0.0099	2.080 (1.283;3.374)	0.0030
2 right or left	5.559 (3.745;8.253)	<.0001	3.666 (2.503;5.369)	<.0001
2 lower	7.246 (3.745;14.020)	<.0001	4.828 (2.975;7.837)	<.0001
3 teeth	8.673 (5.214;14.426)	<.0001	5.792 (3.842;8.730)	<.0001
4 teeth	8.585 (6.092;12.098)	<.0001	4.305 (3.023;6.129)	<.0001

The modelled response was presence of pain (slight, moderate or extensive presence). OR = Odds Ratio. Values in orange represent significant p-values.

Table 4.3.b. *Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from postoperative pain immediately after surgery (day 3) and late (day 10).*

Multivariate	PAIN			
	D3		**D10**	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Gender				
Female	#		#	
Male	0.453 (0.359;0.573)	<.0001	0.601 (0.518;0.699)	<.0001
Age				
≤ 16	1.193 (0.763;1.867)	0.4391	0.708 (0.566;0.885)	0.0024
17–25	#		#	
26–35	0.996 (0.725;1.369)	0.9805	1.860 (1.500;2.307)	<.0001
36–55	0.815 (0.555;1.199)	0.3000	2.501 (1.849;3.381)	<.0001
56–75	0.470 (0.272;0.815)	0.0071	1.584 (0.985;2.545)	0.0576
Indication				
Asymptomatic	#		#	
Symptomatic	0.670 (0.507;0.885)	0.0049	0.907 (0.752;1.093)	0.3041
Method of extraction				
No osteotomy	#		#	
Osteotomy	2.017 (1.531;2.658)	<.0001	2.296 (1.873;2.814)	<.0001
Anesthesia				
Local anesthesia	#		#	
Sedation or GA	0.780 (0.520;1.169)	0.2290	1.199 (0.932;1.542)	0.1577
Number of teeth + jaw				
1 upper	#		#	
1 lower	3.114 (1.989;4.877)	<.0001	3.313 (2.157;5.087)	<.0001
2 upper	1.464 (0.859;2.494)	0.1609	2.373 (1.392;4.046)	0.0015
2 right or left	3.572 (2.292;5.566)	<.0001	3.612 (2.339;5.578)	<.0001
2 lower	5.229 (2.361;11.580)	<.0001	4.360 (2.455;7.743)	<.0001
3 teeth	5.593 (2.964;10.554)	<.0001	4.765 (2.902;7.826)	<.0001
4 teeth	4.552 (2.621;7.907)	<.0001	3.814 (2.384;6.102)	<.0001

The modelled response was presence of pain (slight, moderate or extensive presence). OR = Odds Ratio. Values in orange represent significant p-values.

Table 4.4.a. *Results from univariate logistic regression using generalized estimating equations modeling the probability of suffering from postoperative **trismus** immediately after surgery (day 3) and late (day 10).*

Univariate	TRISMUS			
	D3		D10	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Gender				
Female	#		#	
Male	0.486 (0.403;0.586)	<.0001	0.566 (0.495;0.649)	<.0001
Age				
≤ 16	1.710 (1.142;2.561)	0.0092	1.266 (1.036;1.548)	0.0209
17–25	#		#	
26–35	0.491 (0.383;0.628)	<.0001	0.855 (0.716;1.022)	0.0845
36–55	0.201 (0.154;0.261)	<.0001	0.648 (0.515;0.816)	0.0002
56–75	0.077 (0.050;0.117)	<.0001	0.282 (0.171;0.465)	<.0001
> 75	0.104 (0.034;0.318)	<.0001	0.903 (0.242;3.372)	0.8791
BMI				
< 18	0.722 (0.404;1.292)	0.2726	0.916 (0.620;1.352)	0.6576
18–25	#		#	
26–30	0.438 (0.308;0.622)	<.0001	0.762 (0.583;0.997)	0.0473
> 30	0.259 (0.159;0.421)	<.0001	0.624 (0.405;0.960)	0.0321
Indication				
Asymptomatic	#		#	
Symptomatic	0.290 (0.239;0.353)	<.0001	0.553 (0.475;0.644)	<.0001
Caries	#		#	
Pericoronitis	4.047 (2.770;5.913)	<.0001	1.913 (1.409;2.598)	<.0001
Periodontitis	1.099 (0.594;2.033)	0.7631	1.256 (0.622;2.536)	0.5250
Tooth resorption	6.028 (2.175;16.707)	0.0006	1.675 (0.859;3.265)	0.1301
Periapical pathology	0.816 (0.430;1.545)	0.5318	0.930 (0.438;1.978)	0.8512
Cysts/tumors	12.056 (1.776;81.842)	0.0108	4.306 (1.657;11.191)	0.0027
Method of extraction				
No osteotomy	#		#	
Osteotomy	7.361 (6.033;8.980)	<.0001	4.464 (3.688;5.404)	<.0001
Anesthesia				
Local anesthesia	#		#	
Sedation	3.739 (3.061;4.566)	<.0001	1.681 (1.454;1.943)	<.0001
General anesthesia	6.157 (1.914;19.801)	0.0023	2.112 (1.231;3.621)	0.0066
Number of teeth + jaw				
1 upper	#		#	
1 lower	2.547 (1.777;3.650)	<.0001	2.827 (1.822;4.387)	<.0001
2 upper	2.759 (1.732;4.394)	<.0001	1.573 (0.912;2.712)	0.1032
2 right or left	5.699 (3.950;8.224)	<.0001	3.546 (2.335;5.386)	<.0001
2 lower	10.488 (5.545;19.838)	<.0001	3.432 (2.050;5.745)	<.0001
3 teeth	9.130 (5.835;14.286)	<.0001	4.520 (2.911;7.017)	<.0001
4 teeth	13.327 (9.540;18.618)	<.0001	4.841 (3.265;7.178)	<.0001

The modelled response was presence of trismus (slight, moderate or extensive presence). OR = Odds Ratio. Values in orange represent significant p-values.

Table 4.4.b. *Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from postoperative* ***trismus*** *immediately after surgery (day 3) and late (day 10).*

Multivariate		TRISMUS			
		D3		D10	
		OR (95%CI)	P-value	OR (95%CI)	P-value
Gender					
	Female	#		#	
	Male	0.445 (0.355;0.556)	<.0001	0.518 (0.445;0.604)	<.0001
Age					
	≤ 16	0.994 (0.635;1.554)	0.9777	1.142 (0.911;1.431)	0.2489
	17–25	#		#	
	26–35	0.856 (0.635;1.153)	0.3063	1.335 (1.080;1.652)	0.0076
	36–55	0.574 (0.405;0.814)	0.0019	1.627 (1.198;2.209)	0.0018
	56–75	0.318 (0.187;0.541)	<.0001	0.970 (0.547;1.720)	0.9170
Indication					
	Asymptomatic	#		#	
	Symptomatic	0.734 (0.572;0.943)	0.0156	0.793 (0.657;0.956)	0.0153
Method of extraction					
	No osteotomy	#		#	
	Osteotomy	4.306 (3.379;5.488)	<.0001	3.867 (3.090;4.839)	<.0001
Anesthesia					
	Local anesthesia	#		#	
	Sedation or GA	1.217 (0.841;1.760)	0.2971	0.932 (0.725;1.198)	0.5825
Number of teeth + jaw					
	1 upper	#		#	
	1 lower	1.873 (1.240;2.829)	0.0028	2.046 (1.283;3.263)	0.0026
	2 upper	1.788 (1.063;3.006)	0.0285	1.445 (0.794;2.629)	0.2285
	2 right or left	2.435 (1.599;3.707)	<.0001	2.259 (1.424;3.584)	0.0005
	2 lower	3.636 (1.675;7.891)	0.0011	1.942 (1.065;3.542)	0.0304
	3 teeth	2.558 (1.459;4.486)	0.0010	2.467 (1.463;4.158)	0.0007
	4 teeth	2.708 (1.616;4.537)	0.0002	2.512 (1.524;4.139)	0.0003

The modelled response was presence of trismus (slight, moderate or extensive presence). OR = Odds Ratio. Values in orange represent significant p-values.

Table 4.5.a. *Results from univariate logistic regression using generalized estimating equations modeling the probability of suffering from postoperative* ***swelling*** *immediately after surgery (day 3) and late (day 10).*

Univariate	SWELLING			
	D3		**D10**	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Gender				
Female	#		#	
Male	0.691 (0.589;0.811)	<.0001	0.878 (0.751;1.026)	0.1024
Age				
≤ 16	2.789 (1.935;4.020)	<.0001	1.670 (1.340;2.082)	<.0001
17–25	#		#	
26–35	0.508 (0.415;0.622)	<.0001	1.133 (0.921;1.394)	0.2382
36–55	0.315 (0.248;0.401)	<.0001	0.981 (0.751;1.281)	0.8861
56–75	0.209 (0.139;0.313)	<.0001	1.287 (0.808;2.050)	0.2886
> 75	0.805 (0.164;3.957)	0.7897	1.740 (0.433;6.984)	0.4350
BMI				
< 18	1.186 (0.700;2.011)	0.5260	0.933 (0.585;1.488)	0.7705
18–25	#		#	
26–30	0.604 (0.445;0.818)	0.0012	1.133 (0.840;1.530)	0.4129
> 30	0.622 (0.381;1.014)	0.0571	0.676 (0.394;1.161)	0.1562
Indication				
Asymptomatic	#		#	
Symptomatic	0.306 (0.258;0.363)	<.0001	0.748 (0.626;0.894)	0.0014
Caries	#		#	
Pericoronitis	2.776 (2.014;3.826)	<.0001	1.176 (0.811;1.703)	0.3924
Periodontitis	0.854 (0.460;1.586)	0.6177	1.075 (0.488;2.369)	0.8572
Tooth resorption	6.321 (2.449;16.315)	0.0001	1.958 (0.955;4.016)	0.0666
Periapical pathology	0.769 (0.396;1.492)	0.4371	1.692 (0.788;3.636)	0.1774
Cysts/tumors	15.377 (2.035;116.16)	0.0081	2.109 (0.778;5.718)	0.1425
Method of extraction				
No osteotomy	#		#	
Osteotomy	8.423 (7.027;10.097)	<.0001	3.616 (2.819;4.639)	<.0001
Anesthesia				
Local anesthesia	#		#	
Sedation	2.438 (2.062;2.882)	<.0001	1.214 (1.028;1.434)	0.0221
General anesthesia	3.842 (1.638;9.010)	0.0020	1.292 (0.705;2.370)	0.4069
Number of teeth + jaw				
1 upper	#		#	
1 lower	4.123 (2.840;5.985)	<.0001	3.789 (2.112;6.799)	<.0001
2 upper	2.697 (1.718;4.235)	<.0001	1.285 (0.598;2.762)	0.5203
2 right or left	6.848 (4.774;9.823)	<.0001	3.742 (2.134;6.561)	<.0001
2 lower	7.984 (4.760;13.391)	<.0001	4.272 (2.230;8.183)	<.0001
3 teeth	10.382 (6.815;15.818)	<.0001	4.111 (2.294;7.367)	<.0001
4 teeth	12.384 (8.897;17.238)	<.0001	3.853 (2.246;6.610)	<.0001

The modelled response was presence of swelling (slight, moderate or extensive presence). OR = Odds Ratio. Values in orange represent significant p-values.

Table 4.5.b. *Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from postoperative* ***swelling*** *immediately after surgery (day 3) and late (day 10).*

Multivariate		SWELLING			
		D3		D10	
		OR (95%CI)	P-value	OR (95%CI)	P-value
Gender					
	Female	#		#	
	Male	0.665 (0.548;0.806)	<.0001	0.827 (0.697;0.982)	0.0299
Age					
	≤ 16	2.162 (1.409;3.316)	0.0004	1.494 (1.163;1.918)	0.0017
	17–25	#		#	
	26–35	0.893 (0.691;1.153)	0.3843	1.567 (1.242;1.976)	0.0002
	36–55	0.967 (0.688;1.357)	0.8442	2.110 (1.498;2.972)	<.0001
	56–75	1.106 (0.662;1.847)	0.6998	3.529 (2.002;6.223)	<.0001
Indication					
	Asymptomatic	#		#	
	Symptomatic	0.624 (0.498;0.782)	<.0001	0.835 (0.671;1.039)	0.1056
Method of extraction					
	No osteotomy	#		#	
	Osteotomy	5.426 (4.379;6.722)	<.0001	3.681 (2.758;4.913)	<.0001
Anesthesia					
	Local anesthesia	#		#	
	Sedation or GA	0.739 (0.537;1.017)	0.0631	0.869 (0.657;1.150)	0.3269
Number of teeth + jaw					
	1 upper	#		#	
	1 lower	2.724 (1.810;4.100)	<.0001	2.549 (1.388;4.681)	0.0026
	2 upper	2.401 (1.454;3.964)	0.0006	1.386 (0.613;3.134)	0.4327
	2 right or left	3.543 (2.338;5.370)	<.0001	2.808 (1.519;5.188)	0.0010
	2 lower	3.176 (1.670;6.040)	0.0004	3.050 (1.466;6.348)	0.0029
	3 teeth	5.087 (2.947;8.780)	<.0001	2.944 (1.507;5.751)	0.0016
	4 teeth	4.324 (2.653;7.046)	<.0001	2.749 (1.436;5.261)	0.0023

The modelled response was presence of swelling (slight, moderate or extensive presence). OR = Odds Ratio. Values in orange represent significant p-values.

Table 4.6.a. *Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from neurosensory disturbances in the* ***lower lip*** *immediately after surgery (D3) and late (D10).*

Multivariate		ALTERED FEELING LOWER LIP			
		D3		**D10**	
		OR (95%CI)	P-value	OR (95%CI)	P-value
Gender					
	Female	#		#	
	Male	0.941 (0.737;1.202)	0.6257	0.573 (0.369;0.890)	0.0133
Age					
	≤ 16	1.460 (1.018;2.093)	0.0398	0.473 (0.195;1.147)	0.0975
	17–25	#		#	
	26–35	1.612 (1.157;2.247)	0.0048	2.383 (1.389;4.091)	0.0016
	36–55	1.622 (1.006;2.617)	0.0474	3.311 (1.655;6.622)	0.0007
	56–75	2.691 (1.360;5.324)	0.0045	3.199 (1.019;10.044)	0.0464
Indication					
	Asymptomatic	#		#	
	Symptomatic	0.954 (0.695;1.310)	0.7709	0.603 (0.350;1.039)	0.0686
Method of extraction					
	No osteotomy	#		#	
	Osteotomy	2.381 (1.588;3.570)	<.0001	3.888 (1.870;8.083)	0.0003
Anesthesia					
	Local anesthesia	#		#	
	Sedation or GA	1.039 (0.711;1.518)	0.8428	1.240 (0.605;2.545)	0.5569
Number of teeth + jaw					
	1 upper	#		#	
	1 lower	1.639 (0.801;3.355)	0.1765	1.303 (0.451;3.763)	0.6249
	2 upper	0.901 (0.323;2.512)	0.8413	0.246 (0.027;2.234)	0.2131
	2 right or left	1.255 (0.597;2.638)	0.5495	0.664 (0.225;1.959)	0.4585
	2 lower	0.844 (0.307;2.321)	0.7424	0.555 (0.119;2.592)	0.4542
	3 teeth	1.370 (0.587;3.198)	0.4663	0.529 (0.153;1.828)	0.3143
	4 teeth	1.159 (0.520;2.586)	0.7181	0.690 (0.207;2.303)	0.5462

The modelled response was presence of altered sensation in the lower lip. OR = Odds Ratio. Values in orange represent significant p-values, indicating a significant predictive value of this particular parameter on the occurrence of neurosensory disturbances in the lower lip.

Table 4.6.b. *Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from neurosensory disturbances in the* ***tongue*** *immediately after surgery (D3). Day 10 reports contained too few cases of lingual nerve sensory dysfunction to construct a meaningful model.*

Multivariate		ALTERED FEELING TONGUE			
		D3		**D10**	
		OR (95%CI)	P-value	OR (95%CI)	P-value
Gender					
	Female	#		#	
	Male	0.955 (0.692;1.319)	0.7812	-	-
Age					
	≤ 16	0.958 (0.583;1.575)	0.8667	-	-
	17–25	#		#	
	26–35	2.145 (1.453;3.167)	0.0001	-	-
	36–55	1.761 (0.933;3.323)	0.0807	-	-
	56–75	2.497 (0.919;6.781)	0.0727	-	-
Indication					
	Asymptomatic	#		#	
	Symptomatic	0.708 (0.476;1.053)	0.0884	-	-
Method of extraction					
	No osteotomy	#		#	
	Osteotomy	1.631 (1.018;2.613)	0.0418	-	-
Anesthesia					
	Local anesthesia	#		#	
	Sedation or GA	0.716 (0.439;1.167)	0.1802	-	-
Number of teeth + jaw					
	1 upper	#		#	
	1 lower	2.837 (0.959;8.395)	0.0596	-	-
	2 upper	0.363 (0.039;3.392)	0.3740	-	-
	2 right or left	2.673 (0.884;8.082)	0.0815	-	-
	2 lower	3.434 (0.907;12.993)	0.0693	-	-
	3 teeth	2.366 (0.683;8.195)	0.1743	-	-
	4 teeth	3.464 (1.040;11.534)	0.0429	-	-

The modelled response was presence of altered sensation in the tongue. OR = Odds Ratio. Values in orange represent significant p-values, indicating a significant predictive value of this particular parameter on the occurrence of neurosensory disturbances in the tongue.

Discussion

In light of the ongoing discussion about prophylactic third molar removal, the overarching aim of this prospective epidemiological study was to gain insight into the current indications for third molar removal and the postoperative recovery process associated with this type of oral surgery. To the best of the authors' knowledge, the present sample represents the largest prospective cohort study on third molar removal in the recent literature (6010 patients and 15357 third molars). The results of this multicenter study showed that postoperative discomfort after third molar removal is associated with different patient- and surgery-related predictive factors, including gender, age, indication for removal, method of extraction and the number of extractions and involved jaws.

The present study demonstrated significant associations between patient age and the occurrence of immediate and persistent postoperative morbidity. Younger patients suffered more immediate discomfort such as trismus and swelling, probably because of the removal of unerupted third molars at age ≤16 years (Tables 4.4 and 4.5).[9] On the other hand, young patients were less likely to suffer persistent pain (Table 4.3). Instead, the odds of suffering persistent pain were higher in patients aged 25 years and older. In line with Yuasa et al. (2004) and Bello et al. (2011), persistent swelling was shown to be related with increasing patient age as well (Table 4.5.b).[9,10] Pérez-Gonzàlez et al. (2018), however, showed an inverse relationship of age and postoperative swelling.[11] Moreover, the present results showed that, with increasing patient age, the odds of suffering immediate trismus were lower, whereas the odds of suffering persistent trismus were higher (Table 4.4.b). The ability to recover from a surgical intervention diminishes as we grow older, and the risk of postoperative complications increases.[12–20] Complication rates climb because of changes in bone physiology, deteriorated systemic physiologic conditions and potential extended operation time and increased difficulty of the procedure.[20,21] Moreover, the incidence of symptomatic indications for third molar removal increases with age (Figure 4.2). Patients admitted to the OMFS department for symptomatic reasons were generally over the age of 25. A recent systematic review from Vandeplas et al. (2020) showed that retention of third molars rarely occurs disease-free.[8] Retention of (once) asymptomatic third molars eventually leads to pathological changes, such as dental caries, severe periodontitis (inflammation and loss of connective tissues distal to the second molar), pulpal or periapical pathology, root resorption and the development of a odontogenic cysts or tumors.[8] Nevertheless, symptomatic indications for removal did not seem to have a prolonging effect on the recovery of the patient, in contrast to what was hypothesized (Tables 4.3.a, 4.4.a and 4.5.a). Our results showed that shortly after surgery (day 3), symptomatic indications for removal were associated with less (self-reported) postoperative morbidity. On day 10 after surgery, this effect remained only for trismus. Patients who underwent therapeutic removal of symptomatic third molars were probably relieved that the potential cause of preoperative pain and discomfort was removed. It is likely that for this reason, they subjectively reported a lower level of pain, as compared with patients who underwent removal of asymptomatic third molars (prophylactic extractions). However, as displayed in Figure 4.4, the observed difference in the probability of suffering postoperative discomfort between these two groups was small.

Although no prolonging effect of symptomatic indications on postoperative morbidity (pain and swelling) was observed, it has been shown that diseased third molar extraction sites are prone to postoperative complications.[22,23] For example, a postoperative infection can result from a previous unresolved pericoronitis.[22,23] Within the category of symptomatic indications for removal, slight differences in recovery were observed (Tables 4.3.a, 4.4.a, 4.5.a). Pericoronitis, tooth resorption and cysts/tumors were associated with a higher occurrence of pain, trismus and swelling, as compared with carious third molars. Yet, clear-cut comparison of results in terms of pre-existing pathology affecting recovery is difficult because measured outcomes among study records are diverse. Many mainly involve the effect of preoperative symptoms or disease on the occurrence of complications such as alveolar osteitis or dry socket, hemorrhage or infection.[13,19,24] The present study, however, focused primarily on the anticipated transient symptoms of postoperative discomfort, rather than on the aforementioned complications.

Significant gender differences were observed in postoperative pain reporting (Tables 4.3.a and 4.3.b). Females reported higher levels of immediate and persistent pain. In agreement, Phillips et al. (2010) and Benediktsdottir et al. (2004) reported significantly longer pain recovery in female patients.[20,25] Smaller jaw sizes, different bone physiology, and hormonal status might be contributing factors.[26] The gender effect on pain sensitivity has been widely studied in pain research.[26,27] Moreover, gender differences in pain reporting are shown to be affected by age and preoperative/existing pain.[28] Female gender was also related to immediate and persistent trismus and swelling. Likewise, intraoperative osteotomy and multiple extractions in both jaws was associated with a higher occurrence of trismus and swelling (Tables 4.4 and 4.5). Symptoms like trismus and swelling are related to the invasiveness, surgical difficulty, and accordingly, also the duration of the surgical procedure.[29,30]

The type of anesthesia did not play a significant role in the occurrence of postoperative morbidity. Tables 4.3.a, 4.4.a and 4.5.a show the univariate effects of anesthesia on pain, trismus and swelling, all of which disappeared in the multivariable model (Tables 4.3.b, 4.4.b and 4.5.b). It is likely that the observed univariate effect was confounded by the number of extractions, rather than being an intrinsic effect of the type of anesthesia (1 or 2 extractions mostly under LA; 3 or 4 extractions mostly under SED or GA).

Our results also showed that a higher BMI (>25 kg/m^2) resulted in lower odds of suffering trismus. No straightforward effect on swelling was observed. The predictive value of BMI in terms of trismus and swelling has been studied in several papers, but the reported results are diverse and contradictory.[11,31,32]

The most severe complication associated with third molar surgery is iatrogenic nerve injury to the IAN or LN. Injury to these mandibular nerve branches can cause temporary or lifelong paresthesia of the ipsilateral skin of the chin and lower lip or tongue, respectively. Although these injuries are relatively uncommon and mostly transient in nature, they severely affect the patient's quality of life. Immediate action is always required.[33] The observed incidences of iatrogenic trigeminal nerve injury after third molar removal in this study were in line with earlier findings (Table 4.1).[23,34] Loescher et al. (2003) reported incidences of iatrogenic nerve damage after third molar removal ranging from 1.3% to 7.8% for IAN injury and 0.2% to 22% for LN injury.[35] The numbers in our study lie within the lower parts of these ranges, with the incidence of permanent nerve injury (within one center) being 0.3% (0.2% IAN, 0.1% LN) and 2.7% (1.7% IAN, 1.0% LN) for temporary nerve injury. Data on the temporary or permanent nature of neurosensory disturbances inflicted in other centers were not available. The present study reported the odds of suffering from (temporary or permanent) IAN injury being significantly higher in older patients (age >25 years). These results were obtained from a multivariable model, considering potential confounding by other variables (Table 4.6.a). For the lingual nerve, no clear association between age and neurosensory dysfunction was observed, except for age 26–35 years (day 3; Table 4.6.b). Preoperative assessment of the difficulty of extraction is crucial to ensure an optimal treatment plan and minimize the risk of nerve complications. CBCT may guide the careful consideration of the course of the IAN and its relation to the third molar.[36] Nevertheless, studies have shown that preoperative CBCT imaging does not reduce the incidence of temporary or permanent IAN injuries.[37,38] The combination of radiographic information and a thorough clinical evaluation remains key to identifying risk indicators for postoperative complications.[20]

The socioeconomic costs associated with third molar removal are also important to consider in the treatment decision process. In the current work, the number of days a patient was absent from work was longer (4 ± 2.5 days) than in previous reports. One study showed that 81% of patients undergoing third molar removal took time off work, with an average of 3 days off (range 0–10 days).[39] Another study showed an average of 1.26 (± 1.49) work days missed and 1.23 (± 2.98) days of inability to perform daily activities.[40] Differences may also depend on the number of days of sick leave prescribed by the treating surgeon. Ultimately, a trade-off or risk–benefit analysis must be made between prophylactic removal and retention of third molars. It remains difficult to convert the cost of prophylactic removal versus lifelong “active surveillance” into hard numbers. It seems that retention of third molars until they become symptomatic or diseased might cost society more because of dental control visits and potential absence from work, as compared with prophylactic removal in adolescence or early adulthood. A few days of school leave are considered economically less costly than work leave. Additionally, when surgery is performed at a later age, the higher risk of complications can result in multiple postoperative hospital visits. All in all, the socioeconomic cost associated with prophylactic third molar removal might, in the end, be lower than the costs of lifelong active surveillance and eventual extraction at a later age.[41] A recent Health

Technology Assessment (HTA 2020) from the UK has indicated as much.[42] Furthermore, well-informed patients seem to prefer third molar removal in adolescence to avoid problems later in life.[43] All things considered, guidelines advocating conservative treatment over prophylactic removal might lead to a reversed and adverse effect of saving some patients from surgery at younger age, but causing a shift of interventions performed in unfavorable conditions at later age.[7]

Although it was not the principal aim to study progressive changes in recovery over 10 consecutive days after surgery, the study set-up did allow for comparison of differences of postoperative recovery at two points in time (day 3 and day 10). This way, distinction could be made between immediate and late occurrence of postoperative discomfort. Earlier studies mostly included only one postoperative follow-up moment (whether or not fixed in time), or adhered to retrospective study designs. The prospective nature of our data collection at multiple pre-set time points was considered preferential to study the research question. Records describing similar study designs include Malkawi et al. (2011), de Santana-Santos et al. (2013) and Yuasa et al. (2004), although their sample sizes and number of assessed parameters were limited compared to those of the M3BE study.[9,30,31]

Research on the topic is generally prone to limitations inherent to the nature of the procedure. It remains difficult to obtain a total picture of the need for third molar removal in the entire population. Most studies are performed on a patient population selected in the OMFS department. Hence, patients who undergo third molar extraction in first-line dental care are missed. Moreover, proper follow-up studies are hard to perform because many retained third molars are eventually removed for pathologies associated with these retained teeth.[2,41,44] Additionally, one might question the validity of surveying data with regard to the proper assessment of postoperative recovery and complications. Surveys remain highly subjective. Yet, to perform epidemiological research at this level, surveys are the method of choice and pose a minimal burden for the patient. Fixed control appointments at two points in time would mean a very high socioeconomic cost for the patient, OMFS department, and society. Study designs relying on patient self-reports depend on good communication between patient and the medical professional. To minimize subjectivity, proper and elaborate explanation was provided to every patient prior to inclusion. Moreover, the VAS scale was used to minimize subjectivity in pain reporting, although gender and ethnicity seem to inevitably introduce some level of bias in pain reporting.[26,27] In addition, missing data is unavoidable when using patient surveys. All analyses were therefore based on the assumption that missingness was complete at random. In other words, that the non-included cases were well-represented by the included cases. The present study did not include anatomical features or surgical difficulty as potential risk factors for prolonged recovery; however, the inclusion criteria did not distinguish based on any type of eruption or impaction status or on surgical difficulty of the third molars to be removed. Finally, postoperative outcome can also depend on the surgeon's level of experience, which has been analyzed in Chapter 5.[45,46]

Conclusions

The results of this study broaden our knowledge about the ongoing but debated practice of prophylactic third molar removal. The current findings address the gap in large-scale prospective data on the topic and potentially form a basis or directive for updated treatment guidelines on the management of third molars. There are convincing patient- and surgery-related factors that favor timely third molar removal, preferably before the age of 25. Increasing age at the time of surgery significantly increased the risk of persistent postoperative morbidity (higher incidence of IAN injury and persistent postoperative pain, trismus and swelling). Symptomatic indications for removal were more common in patients over age 25 years, but these pre-existing pathologies did not compromise the postoperative recovery process.

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CHAPTER 5

Surgeon's inexperience has limited effect on postoperative morbidity following third molar removal

Vranckx M.[1]
Fieuws S.[2]
Jacobs R.[1,3]
Politis C.[1]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]L-BioStat, Leuven Biostatistics and Statistical Bioinformatics Centre, KU Leuven, Leuven, Belgium.

[3]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: This study aimed to assess differences in postoperative morbidity when third molar removal was performed by a (supervised) surgical resident versus a senior surgeon in oral and maxillofacial surgery, and this at two fixed time points after surgery.

Methods: Patients admitted for removal of asymptomatic third molars were prospectively followed up on day 3 and 10 after surgery in the context of the M3BE study. Uni- and multivariable logistic regression was performed to assess the associations between surgeon's inexperience and postoperative discomfort.

Results: In total, 7 senior surgeons and 28 surgical residents operated 2560 patients (8672 third molars). Differences in postoperative morbidity on day 3 and 10 after surgery were small. The results showed no significant associations between surgeon's inexperience and postoperative symptoms of discomfort (pain, trismus, swelling), except for the occurrence of persistent pain (day 10; OR 1.468; p=0.0016). No effect was observed on the occurrence of nerve complications either. It was shown that postoperative morbidity was more dependent on factors like age, gender, number of extractions and intraoperative osteotomy, than the inexperience of the surgeon.

Conclusion: Based on the results of this study, it was concluded that the recovery of patients undergoing third molar removal is limitedly affected by the level of experience of the surgeon. Only when pain symptoms persisted, it was more likely that the patient was operated by a surgical resident.

Key words: extraction, recovery, surgeon experience, third molar, wisdom teeth

Introduction

Third molar removal is one of the most common interventions in oral and maxillofacial surgery (OMFS) and is often one of the first procedures performed by surgical residents in the field. The removal of third molars involves traumatic manipulation of bone, connective tissue and muscle tissues, followed by postoperative symptoms of discomfort, including pain, trismus and swelling. These symptoms are generally transient in nature, but in infrequent cases these symptoms persist longer than expected.[1]

Patient-related factors known to be compromising postoperative recovery are older age, positive medical history, medication use, anatomical position of the third molars, etc. Other and more prevailing factors contributing to patient morbidity are intraoperative variables like the number of extractions, extraction time, need for osteotomy, type of flap, presence of pericoronitis etc.[2–4] Besides these aforementioned and frequently studied demographic and intraoperative variables, surgery outcome can also be dependent on the skills and experience of the operator. Many studies have shown a relation between surgeon's experience and the incidence of postoperative complications like dry socket, infection and hemorrhage.[5–7] In general, it is expected that less experienced surgeons have longer and more traumatic surgeries and, consequently, higher complication rates. Other studies, however, have failed to reveal any correlation between the experience of the surgeon and postoperative complications.[8]

It is evident that complications severely compromise the patient's quality of life. Yet, also transient postoperative symptoms of discomfort like pain, trismus, swelling and inability to work are important to consider. The effect of surgical (in)experience on the transient occurrence of postoperative discomfort is little studied. Therefore, the aim of this study was to assess differences in patients' postoperative recovery when third molar removal is performed by an OMFS surgical resident (in a supervised setting) versus a senior surgeon (with several years of experience), and this at two fixed time points after surgery.

Patients and Methods

As part of an epidemiological multicenter study on the surgical removal of third molars (M3BE study; Chapter 4) carried out by the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven (Belgium), patients undergoing prophylactic third molar removal between September 2015 and December 2019 were prospectively monitored from the time of surgery until ten days after. The study was approved by the Ethics Committee Research of the University Hospitals of Leuven (Belgium) (B322201525552), and was carried out according to the ICH-GCP principles and the Declaration of Helsinki (2013). Written informed consent was obtained prior to inclusion of every patient.

Patients were admitted for prophylactic removal of asymptomatic third molars in four hospitals: University Hospitals Leuven (UZL), Mariaziekenhuis Pelt (MZP), Ziekenhuis Oost-Limburg Genk (ZOL) and AZ Sint-Blasius Dendermonde (SBD). In total, 28 OMFS resident surgeons operated (in a supervised setting) in University Hospitals Leuven and 7 senior surgeons (with experience) operated in three local hospitals (MZP, ZOL, SBD).

Intraoperative variables assessed were: experience of the surgeon (resident level, <10 years, 10–30 years and >30 years), number of third molar extractions and involved jaws, extraction method (need for osteotomy) and anesthetic technique (local anesthesia, procedural sedation, general anesthesia).

Postoperative recovery variables, inquired after through a standardized survey on day 3 (D3) and day 10 (D10) after surgery, were: pain (visual analogue scale VAS), pain development (from D3 to D10), painkiller intake, symptoms of trismus, swelling, altered sensation in lower lip or tongue, and the ability to resume daily activities and work or studies within ten days after surgery. Symptoms reported on day 3 after surgery are further referred to as immediate postoperative discomfort, whereas symptoms on day 10 postoperatively are considered late or persistent morbidity.

The relationship between the surgeon's level of experience (resident or senior surgeon) and the occurrence of immediate (D3) and late (D10) postoperative discomfort was analyzed using uni- and multivariable logistic regression. Odds ratios (OR) were reported. Generalized estimating equations were used to take into account the correlation between multiple surgeries of the same patient. The multivariable model contained surgeon's experience (resident vs. senior surgeon), gender, age (≤16, 17–25, 26–35, >35 years), method of extraction (osteotomy or not) and a factor defined by the number of extracted teeth and involved jaws. Outcome variables were dichotomized: slight, moderate and extensive presence of symptoms (combined into one category) versus no symptoms.

For the assessment of the number of days until resuming daily activities, until resuming work/studies and until last intake of pain medication, Cox regression was used, using the same predictors as the multivariable logistic regression model. Subjects for which the number of days exceeded 10 were censored (since for those patients the exact number of days was not known). Hazard ratios (HR) were reported. A robust estimator was used to handle the presence of multiple surgeries for a single subject. Moreover, the number of days before a patient could resume daily household activities, work or studies, and stopped using painkillers was visually assessed by means of cumulative incidence curves, constructed with the complements of the Kaplan-Meier estimates for both levels of surgeon's experience. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at $p<0.05$.

Results

The sample consisted of 2560 patients (1448 females; 1112 males) undergoing 2646 surgeries. One in ten patients (12.0%) visited the department on their own initiative, all others were referred through first line dental or medical caregivers. In total, 8672 third molars were extracted for prophylactic reasons, implicating that at the time of extraction the third molars showed no signs or symptoms of disease. Indications for removal included: impaction because of lack of space in the dental arch (64.1%), impaction because of aberrant orientation (21.5%), no function in the occlusion (5.1%), hygienic prophylaxis (5.4%), and extraction in the context of another (dental) treatment (3.9%) (Table 5.1).

Mean age of the patients was 21.3 (± 6.9) years (median 19; range 12-83). Patients treated by residents were on average two years older than patients treated by senior surgeons: 21.9 (± 7.4) vs. 19.8 (± 5.6) years, respectively.

In total, 1854 surgeries (70.1%) were performed by 28 surgical residents and 792 surgeries (29.9%) by 7 senior surgeons. Surgical experience of the senior surgeons varied from less than 10 years of experience (0.15% of surgeries), 10 to 30 years of experience (26.6%) and more than 30 years of surgical experience (3.2%) (Table 5.1). The senior surgeons' levels of experience were merged for further analysis.

Table 5.1. *Detailed overview of the procedures: 2561 patients, 2646 surgical interventions, 8672 third molars extracted.*

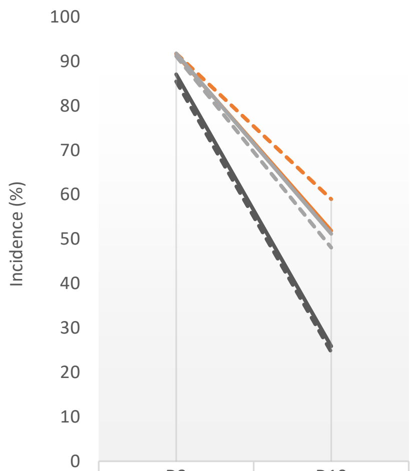
Surgical details	**N**	**%**
Asymptomatic indication	*N in teeth (n=8672)*	
Impaction lack of space	4754	64.1
Impaction orientation	1595	21.5
Non-functional third molars	380	5.1
Prophylaxis (oral hygiene)	397	5.4
Other (dental) treatment	290	3.9
Number of third molar extractions per surgery	*N in surgeries (n=2646)*	
4	1651	62.4
3	252	9.5
2	569	21.5
1	174	6.6
Surgeon's experience		
Resident	1854	70.1
Senior surgeon <10 years	4	0.15
Senior surgeon 10–30 years	704	26.6
Senior >30 years	84	3.2
Method of extraction: no osteotomy	368	14.2
Method of extraction: osteotomy	2230	85.8
Anesthesia		
Local	720	27.4
Sedation	1818	69.1
General anesthesia	92	3.5

The majority of surgeries were total third molar extractions (4 teeth; n=1651), 252 surgeries included three third molar extractions, 569 two and 174 were single third molar extractions (Table 5.1). The average number of extractions per surgery was 3.1 (± 1.1) for residents and 3.6 (± 0.8) for senior surgeons. In 85.8% of surgeries, osteotomy was required to facilitate the extraction. Senior surgeons performed osteotomy in 91.9% of their surgeries, compared with 83.4% in the resident group. More than two thirds of surgeries (69.1%) were performed under procedural sedation, 27.4% under local anesthesia and 3.5% under general anesthesia (Table 5.1).

Table 5.2. *Differences in immediate and late postoperative discomfort according to the treating surgeon's experience level. Percentages represent presence of postoperative symptoms of discomfort on day 3 and day 10 after surgery.*

	Immediate discomfort		Late discomfort	
	Residents	**Senior surgeons**	**Residents**	**Senior surgeons**
Pain				
No pain VAS 0	7.6	6.9	40.8	47.9
Minor pain VAS 1–3	46.3	37.9	48.2	39.4
Moderate pain VAS 4–7	38.5	42.5	9.8	10.3
Unbearable pain VAS 8–10	7.6	12.7	1.2	2.4
Pain development D3 → D10				
Decrease ↓	-	-	49.4	47.0
Increase ↑	-	-	8.2	6.0
Painkiller use	78.5	83.1	-	-
Average number of days	-	-	6 ± 2.8	6 ± 2.6
Trismus				
No	8.8	7.6	51.7	48.5
Slight	36.2	31.6	37.0	34.4
Moderate	37.3	41.7	9.2	12.9
Extensive	17.8	19.2	2.2	4.2
Swelling				
No	14.2	12.0	75.3	74.0
Slight	36.8	34.9	21.6	19.9
Moderate	30.6	30.6	2.4	4.0
Extensive	18.5	22.5	0.8	2.1
Altered sensation lower lip	10.1	8.0	3.5	2.6
Altered sensation tongue	5.2	6.4	1.9	2.9
Resumed daily activities	59.9	53.6	-	-
Average number of days	-	-	3 ± 2.3	4 ± 2.4
Resumed work/studies	55.4	42.1	-	-
Average number of days	-	-	4 ± 2.4	5 ± 2.1

Almost 70% of the patients filed postoperative recovery reports: 1836 reports on day 3 after surgery and 1772 on day 10. Table 5.2 demonstrates the differences in immediate (D3) and late (D10) postoperative discomfort according to the surgeon's level of experience. Frequently occurring postoperative symptoms were pain, trismus and swelling (Table 5.2). Differences in postoperative recovery among patients operated by residents or senior surgeons were small (Figure 5.1). In general, patients operated by residents reported slightly less immediate and late discomfort (pain, trismus and swelling) than patients operated by senior surgeons (Table 5.2), but these differences were not significant (Table 5.3). However, patients operated by resident surgeons were more likely to suffer persistent

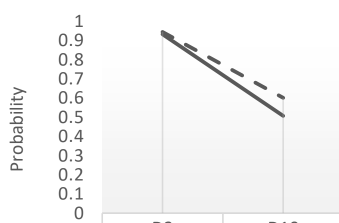


	D3	D10
Pain - R	91.8	59.0
Pain - S	91.6	51.9
Trismus - R	91.2	48.1
Trismus - S	91.8	51.2
Swelling - R	85.5	24.6
Swelling - S	87.1	25.9

Figure 5.1. *Incidences of pain, trismus and swelling were very similar among treatment groups, except for late pain. Incidence of late pain was higher in resident treated group (dashed orange line). The solid orange line lies almost entirely along the solid light grey line. R = resident; S = senior surgeon.*

postoperative pain until 10 days after surgery (OR 1.332; p=0.0109), even when considering potential confounding by other variables (OR 1.468; p=0.0016) (Table 5.3). Accordingly, the probability of suffering persistent pain was significantly lower for patients operated by senior surgeons, as compared with resident surgeons (0.507 vs. 0.601, respectively) (Figure 5.2).

The data showed a slightly higher incidence of altered sensation in the lower lip, indicating neurosensory disturbances of the inferior alveolar nerve (IAN), for patients treated by the resident group (3.5% vs. 2.6%), and conversely for altered sensation in the tongue, indicating neurosensory disturbances of the lingual nerve (LN) (1.9% vs. 2.9%) (Table 5.2). These differences were not significant either (Table 5.3). Yet, it must be noted that no meaningful multivariable model could be constructed, because the data contained too few cases of neurosensory disturbances on day 10 postoperatively.



	D3	D10
Senior surgeon	0.932	0.507
Resident	0.944	0.601

Figure 5.2. *Probability of suffering pain (obtained from the multivariable model) until three and ten days after surgery as a function of the surgeon's experience (p=0.3710 and p=0.0016 at D3 and D10, respectively).*

The number of days to resume daily activities and work/studies was on average one day longer in patients treated by senior surgeons compared with the resident-treated group (Table

5.2). The results showed a significant univariate effect of surgeon's inexperience on the ability to resume daily activities and work/studies 3 and 10 days after surgery (Table 5.3). These effects did not stand in the multivariable analysis, except for the ability to resume work as recorded on day 10 after surgery. The need for painkillers was on average 6 days in both patient groups. Figure 5.3 illustrates the need for painkillers and the ability to resume daily life and work/studies over 10 consecutive days after surgery according to the level of experience of the treating surgeon. Patients operated by resident surgeons stopped painkillers sooner and resumed daily activities and work/studies sooner than senior surgeon patients.

The associations between the considered confounders in the multivariable model and symptoms of postoperative discomfort can be accessed in Supplementary Tables 5.4 to 5.10. On day 3 after surgery, female gender and intraoperative osteotomy were associated with higher occurrence of postoperative pain, trismus and swelling ($p<0.05$) (Supplementary Tables 5.4, 5.5 and 5.6). Moreover, multiple extractions involving both mandible and maxilla were associated with higher occurrence of pain and swelling shortly after surgery (D3). Age was not related to immediate symptoms of discomfort (pain, swelling trismus), except for lower odds of trismus in the patient group age >35 years. Self-reported altered sensation in the lower lip (D3) was linked to increased age (age ≥26 years) and intraoperative osteotomy (Supplementary Table 5.7).

On day 10 after surgery, female gender, increased age (age ≥26 years), intraoperative osteotomy and multiple extractions in both mandible and maxilla were significantly associated with persistent pain ($p<0.05$) (Supplementary Table 5.4). Persistent trismus was related to female gender and intraoperative osteotomy (Supplementary Table 5.5), whereas persistent swelling was related to age and intraoperative osteotomy (Supplementary Table 5.6). Gender and method of extraction were significantly related to the ability to resume daily activities and work/studies, and to stop painkillers over ten days after surgery (Supplementary Tables 5.8, 5.9 and 5.10). Day 10 reports contained too few cases of neurosensory disturbances in the lower lip and/or tongue to construct a meaningful multivariable model (Supplementary Table 5.7).

Table 5.3. *The effect of surgeon's inexperience on the occurrence of postoperative discomfort and complications, modelled by uni- and multivariable logistic regression and Cox regression. The odds ratio/hazard ratio and 95% confidence interval (CI) for each symptom of postoperative discomfort was calculated to compare the likelihood of a patient suffering that outcome according to the surgeon's level of experience (resident vs. senior).*

Resident vs. senior surgeon		**Univariate associations**		**Multivariable associations**	
		Ratio° (95% CI)	P-value	Ratio° (95% CI)	P-value
Pain					
	D3	0.909 (0.596;1.385)	0.6570	1.236 (0.777;1.969)	0.3710
	D10	1.332 (1.068;1.661)	0.0109*	1.468 (1.157;1.862)	0.0016*
Trismus					
	D3	0.853 (0.571;1.272)	0.4346	1.412 (0.901;2.217)	0.1320
	D10	0.879 (0.706;1.094)	0.2478	1.086 (0.856;1.377)	0.4972
Swelling					
	D3	0.823 (0.593;1.140)	0.2420	1.295 (0.903;1.859)	0.1594
	D10	0.938 (0.731;1.205)	0.6184	1.080 (0.824;1.416)	0.5754
Altered sensation lower lip					
	D3	1.304 (0.886;1.919)	0.1784	1.462 (0.969;2.208)	0.0704
	D10	1.350 (0.693;2.632)	0.3787	-	-
Altered sensation tongue					
	D3	0.812 (0.17;1.277)	0.3685	0.855 (0.526;1.387)	0.5244
	D10	0.646 (0.322;1.299)	0.2200	-	-
Resume daily activities					
	D3	1.297 (1.044;1.610)	0.0189*	1.009 (0.801;1.271)	0.9397
	D10	1.188 (1.081;1.304)	0.0003*	1.027 (0.933;1.129)	0.5963
Work/studies					
	D3	1.709 (1.337;2.188)	<.0001*	1.258 (0.967;1.637)	0.0871
	D10	1.309 (1.179;1.453)	<.0001*	1.160 (1.042;1.292)	0.0069*
Stop painkillers					
	D3	0.745 (0.562;0.987)	0.0404*	1.028 (0.760;1.391)	0.8581
	D10	1.222 (1.094;1.364)	0.0004*	1.115 (0.991;1.255)	0.0701

*Significant p-value; °Ratio was Odds Ratio for first five outcome parameters (logistic regression) and Hazard Ratio for last three outcome parameters (Cox regression); CI = Confidence Interval; D10 reports contained too few cases of neurosensory disturbances to draft a relevant model.

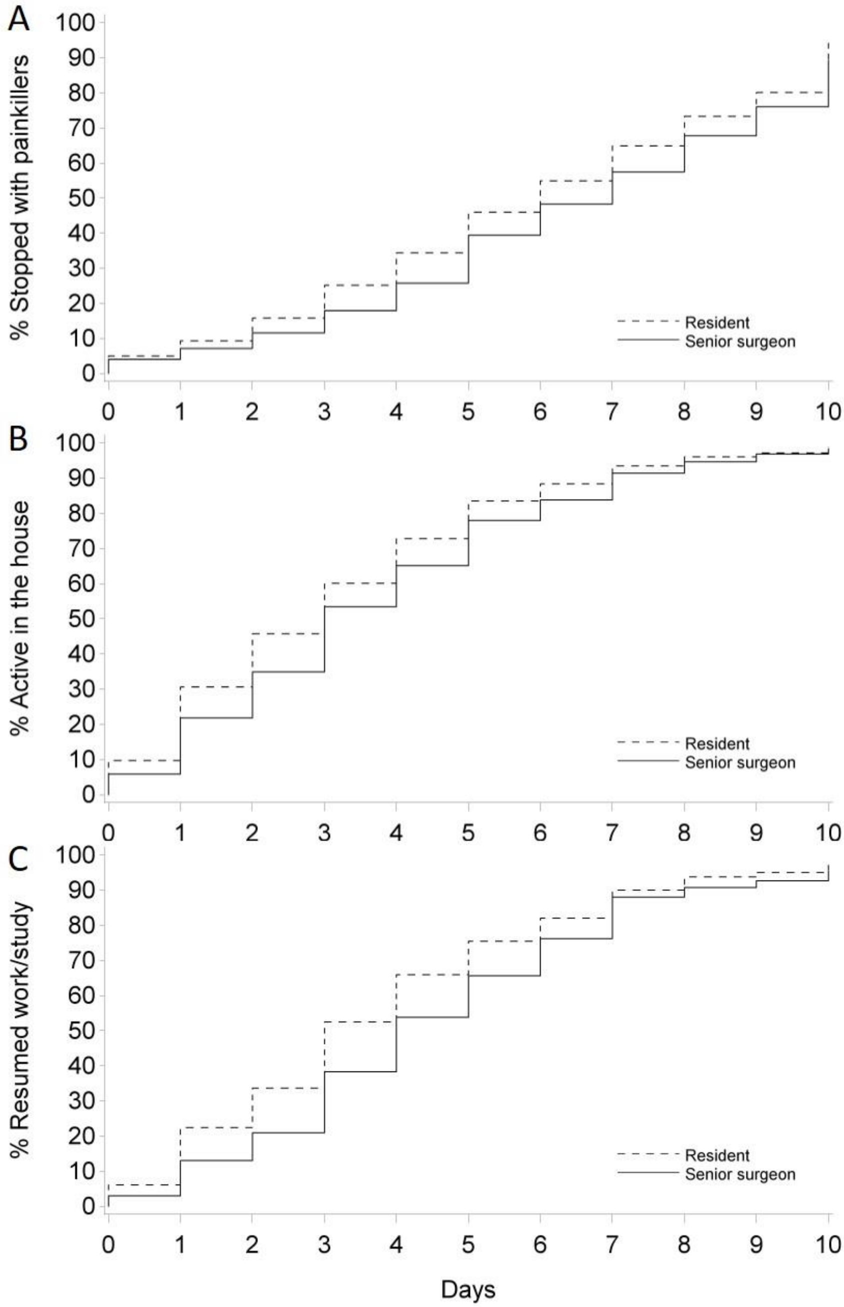


Figure 5.3. *Visual assessment of the number of days before a patient (A) stopped using painkillers; (B) could resume daily household activities and (C) work or studies, according to the level of experience of the treating surgeon. Patients operated by (supervised) resident surgeons reported stopping painkillers sooner and resume their lives sooner, as compared with patients treated by senior surgeons.*

Discussion

Within the field of oral and maxillofacial surgery, third molar removal is one of the first and most commonly performed interventions by OMFS residents during their surgical training. It is therefore of utmost importance that patient morbidity after treatment by a resident surgeon is within acceptable limits and proportional to the invasiveness of the procedure. Irrespective of the slight descriptive differences in recovery between the treatment groups, the multivariable analyses showed only few significant effects of surgeon's inexperience on the patients' postoperative outcome.

Back in 1986, Sisk et al. already demonstrated significantly higher incidences of complications following third molar removal by a surgical resident, with a triple incidence for dry socket (19.5% vs. 6.4%) and a quadruple incidence for nerve dysesthesia (2.5% vs. 0.6%).[7] Jerjes et al. (2006 and 2010) showed significantly higher incidences of trismus, alveolar osteitis and infection in a resident-treated patient group.[5,8] Patients treated by senior surgeons reported more postoperative bleeding.[5,8] Another study, by de Boer et al. (1995), found higher complication rates in resident-treated patients in terms of swelling, alveolar osteitis and postoperative bleeding.[4] Our study did not show any association between surgical inexperience and the presence of immediate and late postoperative morbidity (Table 5.3), except for the occurrence persistent postoperative pain. The odds of suffering persistent postoperative pain were significantly higher in the resident-treated group, as compared with patients treated by senior surgeons. Our study focused primarily on the expected transient symptoms of postoperative discomfort after third molar removal. As a result, the assessed postoperative parameters were not fully in compliance with former studies on the topic. A surgical extraction procedure implies the risk of complications, such as hemorrhage, infection and alveolar osteitis or dry socket. These complications have been the topic of many studies comparing postoperative morbidity among patients treated by residents and senior surgeons.[4,5,7–9] Differences in postoperative outcome parameters complicated proper and clear-cut comparison of results.

The average number of extractions per surgery was slightly higher for senior surgeons as compared to residents, which could have contributed to slightly higher subjective reporting of discomfort (Table 5.2 and Figure 5.1). Accordingly, the fact that patients operated by residents reported being slightly sooner back on their feet (Figure 5.3), could be attributable to the lower number of extractions (3.1 vs. 3.6) and less surgeries requiring osteotomy (83.4% vs. 91.9%) in the resident group, rather than to an intrinsic effect of the level of experience of the treating surgeon.

The results showed a higher incidence of IAN neurosensory disturbances in patients treated by resident surgeons (3.5% vs. 2.6%), however, no significant effect of surgical inexperience was observed in the uni- and multivariable logistic regression models (Table 5.3). This is in contrast with the studies of Jerjes et al. (2006 and 2010) showing significant differences in occurrence of IAN and LN injuries in resident vs. senior surgeon treated patient groups (p=0.048 and p<0.001).[5,8] On the other hand, de Boer et al. (1995) reported higher incidences of paresthesia in the surgeon-treated group.[4] Loescher et al. (2003) reported incidences of iatrogenic nerve damage following third molar removal ranging between 1.3–7.8% for IAN injury and 0.2–22% for LN injury.[10] Irrespective of surgeon's level of experience, the incidences in the present study lie within these reported ranges.

Especially for complex extractions, experience and practice contribute to meticulous and proper execution of the surgical procedure. Also preoperative planning and difficulty estimation was shown to improve with increasing surgical experience, which indirectly influences the patients' postoperative recovery.[11] Moreover, Susarla et al. (2013) demonstrated that surgical experience influences extraction time.[12] Unfortunately, the duration of the surgeries was not recorded is this study. Though, specific risk factors for extended operation time are older age of the patient and several radiographic risk indicators, such as horizontally positioned teeth, third molars in close relation to the IAN and third molars with aberrant root curvature or morphology.[2] The current work did not assess the preoperative anatomical position, degree of impaction or root morphology of the extracted third molars. However, the extent of the present sample (n=8672) and the all-inclusive protocol of the M3BE data collection may imply that all kinds of impaction states and surgical difficulties were included. Furthermore, to avoid potential selection bias in surgical difficulty of cases operated by (supervised) residents versus senior surgeons, we compared surgery outcomes from a university training center (UZL) versus three local hospitals (MZP, ZOL, SBD). Otherwise, within one and the same training center, potential selection bias could have occurred of senior surgeons (supervising the residents) operating the more difficult cases.

A systematic review on surgical experience, work load and patient morbidity, conducted by Jerjes et al. (2018) concluded that most records on the topic have retrospective study designs.[9] The present study collected prospective data at fixed time points throughout the patient's treatment course. This allowed for comparison of postoperative recovery at two points in time (D3 and D10). Accordingly, differences in occurrence of immediate and late morbidity could be observed. It was demonstrated that for immediate discomfort (pain, trismus, swelling), no effect of surgical inexperience was observed. Yet, when postoperative pain persisted until day 10, it was more likely that the patient was operated by a resident. Despite the fact that experience might matter to some extent, many factors affect the outcome of the surgery. Immediate and late postoperative morbidity was shown to be more dependent on factors like gender, age, number of extractions and need for intraoperative osteotomy (Supplementary Tables 5.4 and 5.5). These results were in line with risk factors reported in the literature for many decades.[1,13–15]

The validity of surveying data can be called into question when it comes to the proper assessment of postoperative morbidity. Self-reports are highly subjective. Therefore, studies dependent on surveying data rely mainly on good and clear communication between the researcher or medical professional and the patient. Clear instructions were given prior to inclusion of every patient. Bias in pain measures were attempted to be minimized by use of the VAS scale. Nevertheless, gender, ethnicity and other factors are repeatedly shown to introduce limited but inevitable bias in pain reporting.[16–18] Same can be expected for subjective description of swelling and trismus complaints. Fixed postoperative control appointments to objectively assess patients' postoperative morbidity would be preferred, but pose a high burden on the patient, OMFS department and society, especially when considered relative to the invasiveness of the surgical intervention. Accordingly, such study set-up was considered infeasible on present extensive sample size.

Interesting to consider in future research would be the potential improvement in surgical outcome throughout the resident's training, as well as comparing surgical residents to different levels of experience among senior surgeons. It might be hypothesized that senior surgeons, spending most of their professional time on maxillofacial surgery, end up less skilled in "simple" dentoalveolar procedures.[9] This would sign off as a potential peak in the surgical learning curve and career. Momin et al. (2018) demonstrated a direct correlation between the level of resident training and the complication rate.[6] Surgical residency knows a gradient course, starting with observation of as many procedures as possible during early training, followed by a progressive but steady increase in involvement in surgical procedures. Therefore, combining all resident levels into one category could have masked differences in patient morbidity among patients treated by first year residents, compared with senior year residents and experienced surgeons.

All in all, surgical experience and its effect on patients' postoperative morbidity is a delicate topic of research. Evidence suggesting higher complications rates in the hands of resident surgeons might lead to changes in guidelines or training programs that highly affect the daily practice of training hospitals. It also raises ethical arguments to leave patients in resident hands (although in a supervised setting), when knowing inexperience could lead to higher complication rates.[6,9] The patient should always be the center of care. Nevertheless, surgeons of today have the moral task to properly train the surgeons of tomorrow. This can only be achieved by hours of direct observation and assisting senior surgeons, and through thorough and well-supervised hands-on training.[9]

Conclusions

Based on the results of this study, we can conclude that the recovery of patients undergoing prophylactic third molar removal is limitedly affected by the level of experience of the surgeon. Only when pain symptoms persisted, it was more likely that the patient was operated by a resident surgeon. It was shown that postoperative morbidity was more dependent on factors like gender, age, number of extractions and need for intraoperative osteotomy, than the (in)experience of the surgeon. These results are substantial to an intervention that is frequently performed by resident surgeons in oral and maxillofacial surgery.

Supplementary Material

Supplementary Table 5.4. *Multivariable logistic regression model assessing the relationship between patient- and surgery related factors and immediate (D3) and late (D10) postoperative pain. The modelled response was presence of the particular symptom (varying from slight, moderate to extensive presence).*

	PAIN	
	D3	**D10**
	OR (95%CI)	OR (95%CI)
Gender		
Female	#	#
Male	0.380 (0.260;0.555)**	0.522 (0.426;0.640)**
Age		
≤ 16	0.921 (0.527;1.612)	0.637 (0.491;0.826)*
17–25	#	#
26–35	0.806 (0.483;1.344)	1.662 (1.206;2.290)*
> 35	0.539 (0.271;1.069)	2.550 (1.413;4.603)*
Surgeon's experience		
Asymptomatic	#	#
Symptomatic	1.236 (0.777;1.969)	1.468 (1.157;1.862)*
Method of extraction		
No osteotomy	#	#
Osteotomy	2.225 (1.358;3.646)*	2.633 (1.893;3.661)**
Number of teeth + jaw		
1 upper	#	#
1 lower	2.332 (0.767;7.093)	1.637 (0.722;3.713)
2 upper	0.845 (0.351;2.034)	1.593 (0.702;3.617)
2 right or left	2.126 (0.891;5.074)	2.128 (1.016;4.457)*
2 lower	6.296 (1.277;31.045)*	2.514 (1.055;5.994)*
3 teeth	4.027 (1.419;11.430)*	3.398 (1.597;7.230)*
4 teeth	2.987 (1.322;6.749)*	2.713 (1.349;5.456)*

*p<0.05; ** p<0.0001; # is the reference category; OR = Odds Ratio.

Supplementary Table 5.5. *Multivariable logistic regression model assessing the relationship between patient- and surgery related factors and immediate (D3) and late (D10) postoperative trismus. The modelled response was presence of the particular symptom (varying from slight, moderate to extensive presence).*

		TRISMUS	
		D3	**D10**
		OR (95%CI)	OR (95%CI)
Gender			
	Female	#	#
	Male	0.400 (0.278;0.575)**	0.488 (0.398;0.598)**
Age			
	≤ 16	1.144 (0.644;2.032)	1.137 (0.878;1.473)
	17–25	#	#
	26–35	0.838 (0.519;1.354)	1.183 (0.867;1.614)
	> 35	0.495 (0.257;0.953)*	1.516 (0.880;2.610)
Surgeon's experience			
	Asymptomatic	#	#
	Symptomatic	1.412 (0.901;2.217)	1.086 (0.856;1.377)
Method of extraction			
	No osteotomy	#	#
	Osteotomy	5.636 (3.767;8.433)**	3.982 (2.776;5.712)**
Number of teeth + jaw			
	1 upper	#	#
	1 lower	0.839 (0.323;2.182)	0.838 (0.359;1.959)
	2 upper	(1.405 (0.589;3.352)	0.706 (0.299;1.666)
	2 right or left	1.469 (0.655;3.297)	1.120 (0.545;2.301)
	2 lower	3.125 (0.788;12.385)	1.171 (0.505;2.714)
	3 teeth	2.056 (0.806;5.248)	1.301 (0.626;2.701)
	4 teeth	1.896 (0.883;4.071)	1.274 (0.644;2.519)

*p<0.05; ** p<0.0001; # is the reference category; OR = Odds Ratio.

Supplementary Table 5.6. *Multivariable logistic regression model assessing the relationship between patient- and surgery related factors and immediate (D3) and late (D10) postoperative swelling. The modelled response was presence of the particular symptom (varying from slight, moderate to extensive presence).*

	SWELLING	
	D3	**D10**
	OR (95%CI)	OR (95%CI)
Gender		
Female	#	#
Male	0.519 (0.386;0.697)**	0.903 (0.719;1.134)
Age		
≤ 16	1.911 (1.160; 3.148)*	1.404 (1.052;1.873)*
17–25	#	#
26–35	0.805 (0.539;1.201)	1.497 (1.069;2.096)*
> 35	0.561 (0.299;1.052)	1.934 (1.080;3.464)*
Surgeon's experience		
Asymptomatic	#	#
Symptomatic	1.295 (0.903;1.859)	1.080 (0.824;1.416)
Method of extraction		
No osteotomy	#	#
Osteotomy	5.577 (3.916;7.942)**	3.970 (2.386;6.604)**
Number of teeth + jaw		
1 upper	#	#
1 lower	3.479 (1.379;8.777)*	1.368 (0.509;3.678)
2 upper	2.722 (1.200;6.174)*	0.459 (0.150;1.404)
2 right or left	2.980 (1.425;6.320)*	0.925 (0.383;2.234)
2 lower	1.640 (0.674;3.990)	1.088 (0.405;2.920)
3 teeth	4.886 (2.122;11.249)*	1.179 (0.487;2.849)
4 teeth	3.254 (1.651;6.415)*	0.968 (0.421;2.229)

*p<0.05; ** p<0.0001; # is the reference category; OR = Odds Ratio.

Supplementary Table 5.7. *Multivariable logistic regression model assessing the relationship between patient- and surgery related factors and immediate (D3) postoperative altered sensation in the lower lip or tongue. The modelled response was presence of the particular symptom (varying from slight, moderate to extensive presence).*

	ALTERED SENSATION	
	LOWER LIP	**TONGUE**
	D3	**D3**
	OR (95%CI)	OR (95%CI)
Gender		
Female	#	#
Male	1.018 (0.739;1.402)	1.246 (0.820;1.894)
Age		
≤ 16	1.387 (0.921;2.088)	0.731 (0.408;1.310)
17–25	#	#
26–35	1.790 (1.140;2.809)*	1.229 (0.659;2.290)
> 35	2.574 (1.315;5.038)*	2.295 (0.900;5.849)
Surgeon's experience		
Asymptomatic	#	#
Symptomatic	1.462 (0.969;2.208)	0.855 (0.526;1.387)
Method of extraction		
No osteotomy	#	#
Osteotomy	2.482 (1.201;5.131)*	1.252 (0.608;2.576)
Number of teeth + jaw		
1 upper	#	#
1 lower	0.788 (0.260;2.392)	2.023 (0.395;10.354)
2 upper	0.412 (0.110;1.541)	0.333 (0.028;3.933)
2 right or left	0.434 (0.150;1.252)	0.860 (0.151;4.884)
2 lower	0.364 (0.092;1.448)	1.197 (0.174;8.222)
3 teeth	0.836 (0.296;2.362)	1.507 (0.283;8.034)
4 teeth	0.635 (0.242;1.670)	1.698 (0.343;8.419)

*p<0.05; ** p<0.0001; # is the reference category; OR = Odds Ratio.
Day 10 reports contained too few cases of neurosensory disturbances in the lower lip and/or tongue to construct a meaningful model.

Supplementary Table 5.8. *Multivariable Cox regression model assessing the relationship between patient- and surgery related factors and the ability to resume daily activities immediately after surgery (D3) and late (D10).*

	RESUME DAILY ACTIVITIES	
	D3	**D10**
	HR (95%CI)	HR (95%CI)
Gender		
Female	#	#
Male	1.979 (1.617;2.422)**	1.275 (1.162;1.398)**
Age		
≤ 16	0.721 (0.560;0.929)*	0.862 (0.775;0.958)*
17–25	#	#
26–35	1.076 (0.784;1.475)	1.027 (0.885;1.192)
> 35	0.819 (0.448;1.498)	0.928 (0.692;1.245)
Surgeon's experience		
Asymptomatic	#	#
Symptomatic	1.009 (0.801;1.271)	1.027 (0.933;1.129)
Method of extraction		
No osteotomy	#	#
Osteotomy	0.326 (0.227;0.469)**	0.624 (0.534;0.730)**
Number of teeth + jaw		
1 upper	#	#
1 lower	0.871 (0.330;2.300)	1.283 (0.757;2.173)
2 upper	1.042 (0.371;2.931)	1.228 (0.695;2.170)
2 right or left	0.558 (0.231;1.345)	1.104 (0.690;1.766)
2 lower	0.701 (0.263;1.866)	1.080 (0.652;1.790)
3 teeth	0.416 (0.172;1.010)	0.924 (0.576;1.480)
4 teeth	0.390 (0.167;0.908)*	0.850 (0.536;1.349)

*p<0.05; ** p<0.0001; # is the reference category; HR = Hazard Ratio.

Supplementary Table 5.9. *Multivariable Cox regression model assessing the relationship between patient- and surgery related factors and the ability to resume work/studies immediately after surgery (D3) and late (D10).*

		RESUME WORK/STUDIES	
		D3	**D10**
		HR (95%CI)	HR (95%CI)
Gender			
	Female	#	#
	Male	1.798 (1.444;2.239)**	1.213 (1.100;1.338)**
Age			
	≤ 16	0.621 (0.461;0.836)*	0.876 (0.783;0.980)*
	17–25	#	#
	26–35	0.805 (0.581;1.116)	0.899 (0.776;1.041)
	> 35	0.886 (0.441;1.779)	0.683 (0.493;0.945)*
Surgeon's experience			
	Asymptomatic	#	#
	Symptomatic	1.258 (0.967;1.637)	1.160 (1.042;1.292)*
Method of extraction			
	No osteotomy	#	#
	Osteotomy	0.406 (0.283;0.581)**	0.620 (0.516;0.745)**
Number of teeth + jaw			
	1 upper	#	#
	1 lower	0.764 (0.254;2.293)	0.969 (0.569;1.650)
	2 upper	0.924 (0.329;2.599)	0.978 (0.601;1.591)
	2 right or left	0.545 (0.220;1.351)	0.821 (0.528;1.278)
	2 lower	0.558 (0.202;1.543)	0.770 (0.486;1.221)
	3 teeth	0.318 (0.128;0.793)*	0.559 (0.360;0.869)*
	4 teeth	0.259 (0.108;0.620)*	0.517 (0.339;0.787)*

*p<0.05; ** p<0.0001; # is the reference category; HR = Hazard Ratio.

Supplementary Table 5.10. *Multivariable Cox regression model assessing the relationship between patient- and surgery related factors and the need for painkillers immediately after surgery (D3) and late (D10). The modelled response was stopping painkiller intake.*

		STOP PAINKILLERS	
		D3	**D10**
		HR (95%CI)	HR (95%CI)
Gender			
	Female	#	#
	Male	0.436 (0.340;0.557)**	1.172 (1.064;1.291)*
Age			
	≤ 16	0.980 (0.694;1.382)	1.160 (1.024;1.314)*
	17–25	#	#
	26–35	0.907 (0.644;1.277)	0.830 (0.718;0.959)*
	> 35	1.105 (0.593;2.059)	0.712 (0.545;0.931)*
Surgeon's experience			
	Asymptomatic	#	#
	Symptomatic	1.028 (0.760;1.391)	1.115 (0.991;1.255)
Method of extraction			
	No osteotomy	#	#
	Osteotomy	2.546 (1.822;3.559)**	0.605 (0.506;0.722)**
Number of teeth + jaw			
	1 upper	#	#
	1 lower	1.230 (0.533;2.843)	0.409 (0.265;0.630)**
	2 upper	0.850 (0.393;1.841)	0.660 (0.423;1.032)
	2 right or left	1.495 (0.737;3.030)	0.457 (0.316;0.663)**
	2 lower	2.995 (1.171;7.659)*	0.461 (0.303;0.701)*
	3 teeth	2.319 (1.100;4.893)*	0.489 (0.334;0.717)*
	4 teeth	2.695 (1.374;5.286)*	0.418 (0.289;0.605)**

*p<0.05; ** p<0.0001; # is the reference category; HR = Hazard Ratio.

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CHAPTER 6

Radiological risk indicators for persistent postoperative morbidity after third molar removal

Vranckx M.[1]
Lauwens L.[1]
Moreno Rabie C.[1]
Politis C.[1]
Jacobs R.[1,2]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: Although panoramic radiographs are extensively studied for diagnosis and preoperative planning in third molar surgery, research on the predictive value of this radiographic information regarding the postoperative recovery of patients remains underexploited. This study aimed to assess the potential relationship between radiologic risk indicators and persistent postoperative morbidity, in 1009 patients undergoing 2825 third molar extractions in context of the M3BE study.

Methods: Two observers evaluated ten radiographic parameters: vertical and horizontal eruption status, third molar orientation, surgical difficulty, nerve relation, maxillary sinus relation, presence of periapical and pericoronal radiolucencies, caries and third or second molar resorption. Patients' postoperative recovery was recorded three and ten days after surgery. Univariate logistic regression was performed to assess potential associations between radiographic risk indicators and persistent postoperative morbidity.

Results: Deep impactions were significantly associated with the persistence of postoperative pain, trismus and swelling until ten days after surgery, prolonged need for pain medication, and the inability to resume daily activities and work/studies. Pericoronal radiolucencies and resorption were significantly associated with persistent morbidity and a longer recovery time, whereas caries and periapical lesions were linked to a shorter recovery time.

Conclusion: Based on the results of this study, clinicians may better inform patients at risk for persistent postoperative discomfort according to what was preoperatively diagnosed on the panoramic radiograph.

Key words: extraction, impaction, panoramic radiograph, pathology, third molar, wisdom teeth

Introduction

Third molar removal is a routine procedure in oral surgery, involving surgical manipulation of the bone and soft tissues in the third molar area.[1] Expected postoperative symptoms are pain, swelling and trismus. These are generally transient in nature.[2-4] However, when symptoms linger, the postoperative impact of wisdom tooth removal on the patient’s quality of life is reported being threefold greater in patients who experience persistent pain, swelling and trismus (either alone or in combination), in comparison with asymptomatic patients.[5,6]

Besides patient- and surgery-related factors such as age, oral hygiene, surgery time and surgical technique, tooth-related factors have an important influence on the postoperative recovery of patients and the incidence of complications after wisdom tooth removal.[7] Tooth-related factors include number of wisdom teeth extracted, type of impaction (orientation), eruption level, relation to second molar or inferior alveolar nerve (IAN), proximity to the maxillary sinus, presence of pericoronitis and other pathological conditions.[3,8] Tooth-related factors are preoperatively evaluated using radiographs.

Panoramic radiography remains the most commonly used method for diagnosis and preoperative planning of third molar surgery.[9] The use of this imaging technique in relation to third molar removal has been studied extensively in a large number of research papers.[10,11] Yet, hardly any of these deal with the predictive value of radiographic information in relation to postoperative recovery. Therefore, current study aimed to assess the potential relation between radiologic risk indicators and persistent postoperative morbidity in a large prospectively studied sample, for both mandibular and maxillary third molars.

Materials and Methods

As part of a large-scale prospective study on surgical removal of wisdom teeth (M3BE study; Chapter 4) carried out by the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven (Belgium), 1009 patients were recruited in the period from October 2016 to May 2018. The M3BE study set-up allowed for prospective follow-up of patients undergoing surgical removal of the third molars, and this at two fixed time points after surgery (day 3 and day 10). The study was approved by the Ethics Committee Research of the University Hospitals of Leuven (Belgium) (B322201525552), and was carried out according to the ICH-GCP principles and the Declaration of Helsinki (2013). Written informed consent was obtained prior to inclusion of every patient. Patients consulted the department for third molar evaluation. As part of the diagnostic process, a preoperative panoramic radiograph was acquired using the VistaPano S Ceph panoramic device (Dürr Dental SE, Bietigheim-Bissingen, Germany). Exclusion criteria were: 1. panoramic radiographs acquired on another machine; 2. panoramic radiographs with major positioning errors; 3. concomitant oral procedures other than third molar removal; and 4. presence of supernumerary teeth.

Each patient's postoperative recovery was recorded three (D3) and ten (D10) days after surgery by means of standardized surveys. Recorded parameters were pain level (visual analogue scale), location of pain, painkiller intake, trismus, swelling of the cheeks, self-reported altered sensation in the lower lip and the ability to resume daily household activities and work or studies. While day 3 surveys represented expected and transient morbidity after third molar removal, day 10 surveys recorded persistent symptoms of postoperative morbidity, symptoms that last longer than expected. The present study focused on morbidity persisting until day 10 after surgery in relation to radiological findings.

Figure 6.1. *Radiographic variables assessed on 1009 panoramic radiographs and 2825 third molars. (a) vertical and horizontal eruption status; (b) orientation; (c) nerve relation IAN; (d) sinus relation; (e) tooth resorption; (f) periapical radiolucency; (g) pericoronal radiolucency; and (h) caries. The Pederson's surgical difficulty index was not displayed, but was calculated based on (a) and (b).*

Ten anatomical and pathological parameters were evaluated on the preoperative panoramic radiographs (Figure 6.1): vertical and horizontal eruption level, third molar orientation, surgical difficulty index, nerve relation, maxillary sinus relation, **periapical** and **pericoronal radiolucencies**, **caries** and **resorption** of the third or second molar.

Third molars' vertical eruption level (A, B, C) and horizontal eruption class (I, II, III) were assessed according to the **Pell & Gregory classification** (P&G) (Appendix A).[12] Vertical eruption levels were classified as eruption (A) if the occlusal plane of the third molar was at the same level as the occlusal plane of the second molar; partial eruption (B) if the third molar was between the occlusal plane and the cervical line of the second molar; and unerupted (C) if the third molar was below the cervical line of the second molar. Horizontal eruption classes were classified as sufficient distal space (I) if the mesiodistal diameter of the third molar would fit the available space; reduced space (II) if the available space was less than the mesiodistal diameter of the third molar; and total lack of eruption space (III). Third molar orientation was evaluated by **Winter's classification** (mesial, vertical, horizontal, distal) (Appendix A).[13] **Pederson's surgical difficulty index** for mandibular third molars was calculated from aforementioned parameters, resulting in three levels of surgical difficulty: slightly difficult to remove, moderately difficult to remove and very difficult to remove (Table 6.1).[14]

Table 6.1. *Pederson surgical difficulty index for the removal of impacted mandibular third molars (n=1419) as the sum of Winter's orientation and Pell & Gregory classification.*

Winter's orientation		P&G Vertical		P&G Horizontal		Pederson difficulty index		N
Mesioangular	*1*	A	*1*	I	*1*	Slightly difficult	*3–4*	181
Horizontal	*2*	B	*2*	II	*2*	Moderately difficult	*5–6*	888
Vertical	*3*	C	*3*	III	*3*	Very difficult	*7–10*	350
Distoangular	*4*							

The relation of the third molar with the mandibular canal was classified in three categories: (0) no contact; (1) radiographic superimposition of third molar and mandibular canal without presence of **Rood & Shehab markers** (R&S); and (2) if R&S markers were present (darkening, deviation or convergence of the roots; bifid apex; interruption, deviation or narrowing of the canal) (Appendix A).[15]

The relationship between the roots of the maxillary third molars and the **maxillary sinus** was assessed based on the available space between the roots and the sinus floor. We defined five categories: (1) sinus floor located above the roots of the third molar; (2) roots touch the sinus floor; (3) one third of the roots superimposed on the sinus floor; (4) two thirds of the roots superimposed on the sinus floor; and (5) cervix of the third molar extends into the sinus.[16]

Radiographic assessment was done by two calibrated observers in a dimmed observation room using a medical display system for diagnostic observations (Nio Color 3MP Dental, Barco, Kortrijk, Belgium). Prior to the observations, two training and calibration sessions were organized in which the observers jointly evaluated panoramic radiographs of third molar patients. Disagreements were resolved by discussion and by consultation of a third observer.

Data were statistically analyzed using S-plus for Linux 8.0 (Tibco, Palo Alto, CA). Inter- and intraobserver reliability was calculated based on 10% of the sample using Cohen's kappa. A three-month time-interval was applied between the original observations and repetitional observations. Univariate logistic regression was performed to describe the associations between radiologic features and postoperative recovery parameters on day 3 and 10 after extraction. Odds ratios (OR) were reported. Outcome variables were dichotomized: slight, moderate and extensive presence of symptoms (combined into one category) versus no symptoms. The number of days before a patient could resume daily activities and work/studies and the number of days patients needed painkillers was visually assessed by means of Kaplan Meier plots. Hazard ratios (HR) were reported. The statistical significance level was set at $p<0.05$.

Results

In total, 2825 third molars were removed in 1009 patients (481 males; 528 females; mean age 27.8 (± 12.4) years; median 24 years; range 11–88 years; 25 to 75st percentile 19–32 years). The sample consisted of 1406 maxillary (688 upper right and 718 upper left) and 1419 mandibular (718 lower left and 701 lower right) third molars. Table 6.2 gives an overview of the assessed anatomical and pathological parameters. Inter- and intraobserver reliability ranged from 0.60 to 0.74 for anatomical parameters and 0.59 to 0.66 for pathological parameters.

Table 6.2. *Results of the anatomical and pathological third molar parameters evaluated on the preoperative panoramic radiographs of 1009 patients, counting for 2825 removed third molars. Numbers are percentages of total (maxilla n=1406; mandible n=1419). M3 and M2 = third and second molar, respectively.*

Anatomical parameters (n=2825)								
Vertical eruption			**Horizontal eruption**			**Orientation**		
	Maxilla	Mandible		Maxilla	Mandible		Maxilla	Mandible
A	38.6	36.9	I	71.4	30.8	Vertical	60.9	36.4
B	19.6	34.5	II	18.2	48.6	Mesio	15.9	54.0
C	41.7	28.5	III	10.4	20.6	Disto	22.6	1.6
						Horizontal	0.6	7.9

Sinus relation (n=1406)	**Mesial**	**Distal**	**Nerve relation (n=1419)**	
Sinus floor above roots	15.4	16.6	No contact	32.3
Sinus floor touches root tips	31.5	33.9	Superimposition	19.8
Sinus floor superimposition 1/3	33.4	30.6	Rood & Shehab	47.9
Sinus floor superimposition 2/3	15.9	14.8		
Sinus floor extends to tooth cervix	3.8	4.1		

Pathological parameters (n=2825)	**N**	**%**
Resorption of the third or second molar	51	1.8
Periapical radiolucency	60	2.1
Pericoronal radiolucency	61	2.2
Caries lesion M3 and/or distal surface M2	356	12.6

Table 6.3 gives an overview of the associations between the assessed radiological features and persistent postoperative morbidity (until ten days after surgery). In general, anatomical parameters shown to be associated with persistent postoperative pain, trismus and/or swelling were: deep impactions (P&G classification), difficult extractions (Pederson's index) and third molars in close relationship with the IAN (R&S markers).

In the vertical plane, deep impactions (P&G level C; 35.1%) were associated with significantly higher odds of persistent postoperative pain, trismus and swelling, as compared with level A (and B) impactions. In the horizontal plane, deep impactions (P&G class III; 15.5%) were related with more pain, trismus and swelling, as compared with classes I (and II). Accordingly, patients with deeply impacted third molars (levels B and C; classes II and III) had a significantly higher chance of taking painkillers up till 10 consecutive days after surgery, as compared with other patients (Figure 6.2A; p=0.0001). In addition, Figure 6.2 visually assesses the time until patients could resume daily activities and work or studies. Deep impactions, in both vertical and horizontal planes, caused longer inability to do household chores and longer absence from work/studies (Figure 6.2BC; p=0.0001).

The Pederson's surgical difficulty levels were significantly associated with persistent postoperative pain, trismus and swelling as well. Patients scored with very difficult (24.7%) wisdom teeth to remove were more likely to suffer persistent pain, compared with moderately (62.6%) and slightly (12.8%) difficult teeth to remove (Table 6.3). Accordingly, difficult extractions caused longer need for painkillers, as compared with moderately (HR 1.1116 p=0.0062) and slightly (HR 1.4161 p=0.003) difficult extractions. Additionally, very difficult extractions were associated with persistent trismus (Table 6.3), longer inability to do household work (HR 1.0786 p=0.0127) and longer time to resume work/studies (HR 1.4874 p=0.0002), compared with slightly difficult extractions.

For maxillary third molars (n=1406), present data revealed an association between deep maxillary sinus relation (2/3 of roots extend into maxillary sinus) and persistent pain after third molar removal (Table 6.3). No significant associations with postoperative trismus or swelling were observed. For mandibular third molars (n=1419), present data showed an association between radiographic signs of nerve relation (R&S markers) and persistent pain and swelling (Table 6.3). Patients with third molars in close relationship with the IAN reported significantly more often suffer from pain and swelling until ten days after surgery, compared with patients without root-nerve relation.

Table 6.3. *Results from univariate logistic regression modeling the probability of suffering persistent postoperative symptoms of pain, trismus, and swelling until ten days after surgery.*

Associations post-op day 10	PAIN		TRISMUS		SWELLING	
P&G Vertical	OR	p-value	OR	p-value	OR	p-value
A	#		#		#	
B	1.7159	0.0087*	1.7307	0.2825	1.6067	0.1079
C	2.4826	0.0001*	2.9931	0.0008*	2.3725	0.0001*
P&G Horizontal						
I	#		#		#	
II	1.6920	0.0024*	1.2783	0.7021	1.5263	0.0978
III	2.6589	0.0001*	3.0130	0.0007*	2.8547	0.0001*
Orientation						
Vertical	#		#		#	
Mesioangular	1.3521	0.4924	1.5215	0.5661	1.7311	0.0890
Horizontal	1.8441	0.5013	1.9167	0.6580	1.8186	0.5238
Distoangular	1.3604	0.2789	0.9749	0.9998	1.1259	0.9399
Pederson's surgical difficulty						
Slight	#		#		#	
Moderate	1.5149	0.2669	4.5228	0.1695	0.9276	0.9931
Very difficult teeth	2.3998	0.0038*	8.0128	0.0266*	1.5605	0.4318
Nerve relation						
No contact	#		#		#	
Radiological superimposition	1.2250	0.6244	0.7903	0.8524	0.8755	0.8871
Rood & Shehab markers	1.9908	0.0002*	1.6861	0.1609	1.6234	0.0398*
Sinus relation						
Sinus floor above roots	#		#		#	
Sinus floor touches root tips	1.6085	0.3148	0.7807	0.9808	0.8259	0.9730
Sinus floor superimposition 1/3	1.5818	0.3379	0.9211	0.9997	0.9860	0.9999
Sinus floor superimposition 2/3°	2.8289	0.0011*	1.6725	0.7330	1.2674	0.9421
Pathology						
Absence of pathology	#		#		#	
Resorption	1.7578	0.0986	1.6734	0.2609	2.0991	0.0264*
Pericoronal radiolucency	2.1915	0.0231*	0.9481	0.9211	1.1827	0.6388
Periapical radiolucency	1.1208	0.7032	0.6076	0.4126	0.9006	0.7735
Caries	0.6459	0.0032*	0.6585	0.1261	0.9265	0.6704

is reference category; *significant p-value.
°There were too few cases of level 5 sinus relation to draft a relevant model.

More than half of the patients (n=528) had third molars with radiographic signs of pathology (Table 6.2). Pathological parameters shown to be associated with persistent postoperative morbidity were pericoronal pathology and tooth resorption (Table 6.3). Preoperative diagnosis of a pericoronal radiolucency (n=61) was shown to be significantly associated with persistent postoperative pain. Accordingly, these patients were significantly more likely to continue taking painkillers up till 10 days after surgery (HR 1.985 p=0.0002). Resorption of the third or second molar was related to persistent symptoms of swelling (Table 6.3). Moreover, patients with resorption showed significantly higher odds of not being able to resume daily household or work/studies over 10 consecutive days after surgery (HR 1.1502 p=0.0283; and HR 1.0967 p=0.0446, respectively).

On the other hand, two pathological parameters were associated with lower odds of persistent postoperative morbidity after third molar removal: caries and periapical radiolucencies. Patients with caries lesions were less likely to suffer pain until ten days after surgery (Table 6.3), compared with patients without caries. Moreover, they showed significantly lower odds of not being able to resume household and work/studies than patients without caries (HR 0.8056 p=0.0001; and HR 0.8279 p=0.0001, respectively). Same was observed for the presence of a periapical radiolucency and the time to resume household activities (HR 0.8054 p=0.0318). Moreover, patients with periapical pathology stopped painkillers sooner than patients without periapical lesions (HR 0.499 p=0.0389).

No associations were found for the radiographic assessment of third molar orientation and any of the postoperative recovery parameters (Table 6.3). Moreover, none of the assessed radiological variables was related to the occurrence of neurosensory disturbances of the lower lip, as reported ten days after surgery.

The associations between the assessed radiological parameters and immediate symptoms of discomfort, recorded three days after surgery, can be accessed in Supplementary Table 6.4. Deep impactions, in both vertical and horizontal plane, difficult extractions, radiographic signs of root-nerve relation and deep maxillary sinus relation (2/3 of roots into sinus) were significantly associated with immediate postoperative morbidity (pain, trismus and swelling). Presence of pericoronal pathology was associated with significantly higher odds of immediate postoperative pain. Periapical radiolucencies and caries were associated with less postoperative morbidity, as reported three days after surgery.

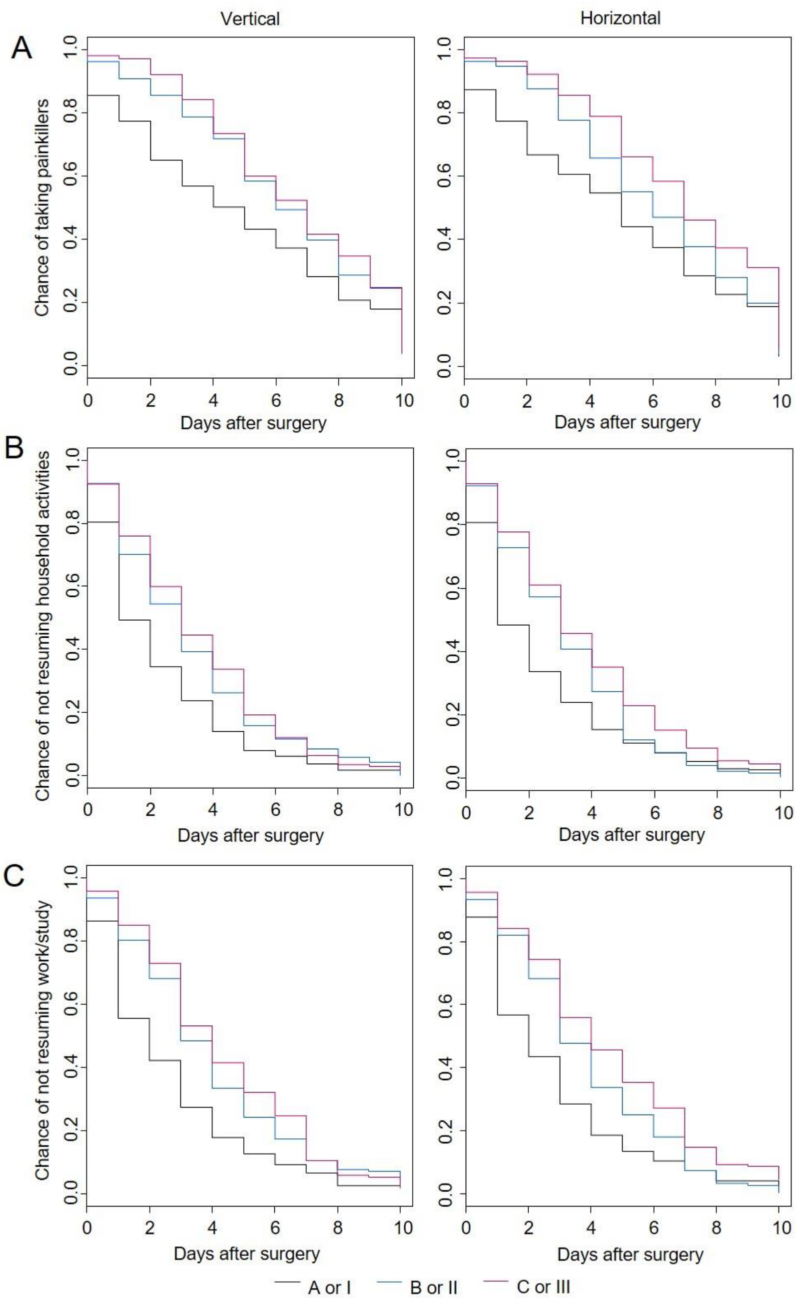

Figure 6.2. *The associations between the Pell & Gregory impaction classification (vertical and horizontal) and (A) the usage of painkillers during 10 days after surgery; (B) the time until resuming household activities; and (C) the time until resuming work/studies. Red and blue lines, representing deep impactions (level C and B; and class III and II), are continuously above the black line (level A and class I). These associations were significant with p-values of p<0.0001.*

Discussion

Panoramic radiographs are widely used in the preoperative evaluation of patients undergoing wisdom tooth removal.[9] The present study attempted to identify radiological risk indicators that can be predictive for persistent postoperative morbidity after third molar removal.

The P&G impaction classification was associated with persistent pain and painkiller intake. Deeply impacted wisdom teeth need more tissue manipulation and bone removal, leading to extensive traumatization of the tissues and consequently, more and longer postoperative pain and discomfort.[17] Besides pain, P&G vertical and horizontal impaction levels were significantly related to persistent trismus and swelling. Likewise, Yuasa et al. (2004) found an association between facial swelling and the relationship of the third molar to the available space between the distal side of the second molar and the anterior border of the mandibular ramus.[18] Other factors contributing to postoperative swelling are age and gender, according to Pérez-Gonzalez et al. (2018).[4,18] The majority of patients in the present study sample were between 19 and 32 years (25 to 75st percentile; with mean 27.8 and median 24 years), ranging up till 88 years old. It is generally known that increasing age may contribute to postoperative morbidity after oral interventions because of reduced bone resilience, presence of ankylosed elements and a potentially compromising medical history.[7] Moreover, smoking habits, oral hygiene and medication use can affect the postoperative recovery process of patients undergoing third molar removal.[7]

Furthermore, Pederson's surgical difficulty levels, derived from P&G and Winter's classifications, were associated with persistent postoperative morbidity. Patients with very difficult teeth to remove were more likely to suffer persistent symptoms of pain and trismus, as compared with patients with more easy extractions. Moreover, R&S markers, indicative for root-nerve relation, were related to persistent postoperative pain and swelling. Removal of deeply impacted, aberrantly orientated and other difficultly positioned third molars, whether or not in close relationship with the IAN, has to be executed meticulously and therefore might take longer, resulting in longer postoperative discomfort such as persistent pain and swelling of soft tissues. In order to minimize postoperative complications like neurosensory disturbances of the IAN, preoperative evaluation of the third molar's relation with the mandibular canal is crucial. Nevertheless, in the current work, the presence of R&S markers was not predictive for postoperative altered sensation in the lower lip. In line with these findings, Matzen et al. (2019) showed earlier that these markers may be useful in estimating (or ruling out) close relationship with the mandibular canal, however, they are not reliable in predicting neurosensory disturbances of the IAN.[19]

For maxillary third molars in particular, present data showed a significant association between maxillary sinus relation and persistent postoperative pain. Pain symptoms persisted when the third molar roots extended up to two thirds into the maxillary sinus. Preoperative evaluation of the third molars' maxillary sinus relation can help in reducing postoperative occurrence of oroantral communications (OAC).[20] A study by Santamaria et al. (2006) evaluating 553 maxillary third molar extractions, showed an OAC incidence of 5.1%.[21]

In contrast to other studies, no associations between third molar orientation and postoperative morbidity were observed. Earlier findings demonstrated significant associations between distoangular and horizontal third molar orientations and increased postoperative pain, trismus and swelling.[2] Vertical orientation is generally associated with least postoperative morbidity and complications.[22]

Important intraoperative factors that could have contributed to postoperative patient outcome are, amongst others, method and duration of the surgical procedure, number of extractions, development stage of the third molars, and third molar root morphology.[23] Although assessment of these intraoperative parameters did not fall within the scope of this paper, they should be carefully considered when estimating postoperative recovery of patients. Intraoperative variables, such as extraction method and duration, might exert a bigger effect on postoperative recovery, than a preoperative risk indicator in itself. However, intraoperative variables are directly related to the assessed preoperative risk indicators, such as deep impactions (P&G) requiring more osteotomy, and third molars in close relationship with the IAN (R&S) extending the duration of the surgical procedure. In this regard, the results of the present study can help in translating tooth-related factors, preoperatively diagnosable on panoramic radiographs, in postoperative morbidity of the patient, but should ideally be supplemented with intraoperative information for the most accurate estimation of the recovery process. Under no condition it was aimed that the radiologic findings in the current work would stand alone with regard to prediction of postoperative recovery.

Besides anatomical parameters, the present study also assessed the predictive value of pathological radiologic markers on the postoperative recovery process of the patient. Pre-existing radiological signs of resorption and the presence of pericoronal radiolucencies were related to a longer recovery time. On the other hand, our results showed that patients with caries lesions diagnosed on the panoramic radiograph, reported being significantly more often free of pain on day 10 after surgery, than patients without. This finding might be attributable to feelings of relief after removal of a potential cause of preoperative pain. Furthermore, our data suggests that patients diagnosed with a periapical lesion stopped their painkiller intake sooner and resumed their daily life sooner. One might question possible influence of prior antibiotic treatment in case of preoperative diagnosis of a periapical lesion. Potential preoperative antibiotic treatment was not recorded, but such patients might recover sooner because inflammatory responses could be controlled at an early stage. This was also suggested in a meta-analysis by Ren et al. (2007), concluding that early administration of antibiotics might reduce the rate of postoperative infections and complications.[24] However, it is important to state that systemic antibiotics should not be used routinely as pre- or postoperative care in third molar surgery.[25]

The large sample size, the extensive number of features scored on the panoramic radiographs and the use of fixed postoperative time points to assess patient recovery were clear advantages of this study. Moreover, earlier studies often cover only radiographic analysis of mandibular third molars, while this study also included maxillary third molars. The inter- and intraobserver agreement was considered moderate to substantial and varied depending on the anatomical or pathological nature of the observations (range 0.59–0.74). Pathological parameters were scored in slightly less agreement (0.59–0.66) than anatomical parameters (0.60–0.74), probably attributable to the variability of the assessed pathologies in their radiological appearance. The mean age of the included patients was relatively low, which accordingly could have resulted in relatively low pathology rates (except for caries) (Table 6.2). Nevertheless, third molar retention is a common cause of symptoms and disease.[26–29] Incidence of third molar pathology increases with age and retention time. Especially caries and periodontal pathology are commonly observed events.[29,30]

Although this study focused on the predictive value of panoramic data, in certain cases additional cone-beam computed tomography (CBCT) is recommended for proper diagnosis and treatment planning. Parameters that might demand three-dimensional visualization in order to realistically estimate their extent are signs of nerve relation, sinus relation, resorption and periapical radiolucencies. However, guidelines prescribe that CBCT should preferably be preceded by a two-dimensional radiographic examination.[31,32] This study can help to extract the maximum of information from panoramic radiographs, before proceeding to CBCT.

Conclusions

Based on the results of this prospective study, clinicians may better inform patients at risk for persistent postoperative discomfort after third molar removal. It was found that deep impactions and difficult extractions are related to persistent postoperative morbidity (pain, trismus and swelling). Moreover, pre-existing radiological signs of resorption and presence of pericoronal radiolucencies were significantly related to persistent postoperative pain, painkiller intake, swelling, and longer time to be able to resume daily household and work/studies. In contrast, caries and periapical lesions were linked to a shorter recovery period. The demonstrated associations between certain radiological risk indicators and persistent postoperative morbidity confirms the importance of panoramic radiographs in diagnosis, treatment planning, risk assessment and prediction of postoperative recovery after third molar removal.

Supplementary Material

Supplementary Table 6.4. *Results from univariate logistic regression modeling the probability of suffering immediate postoperative symptoms of pain, trismus, and swelling three days after surgery.*

Associations post-op day 3	PAIN		TRISMUS		SWELLING	
P&G Vertical	OR	p-value	OR	p-value	OR	p-value
A	#		#		#	
B	1.8822	0.0262*	2.3844	0.0001*	3.1566	0.0001*
C	3.7175	0.0001*	4.0016	0.0001*	10.2249	0.0001*
P&G Horizontal						
I	#		#		#	
II	2.2457	0.0003*	2.3283	0.0001*	4.5620	0.0001*
III	6.2539	0.0001*	3.1240	0.0001*	6.6489	0.0001*
Orientation						
Vertical	#		#		#	
Mesioangular	1.2977	0.7951	1.3263	0.4561	1.2354	0.7839
Horizontal	1.4707	0.9268	1.3665	0.8648	4.4619	0.1837
Distoangular	1.8322	0.0946	1.4883	0.0660	1.6303	0.0707
Pederson's surgical difficulty						
Slight	#		#		#	
Moderate	2.2198	0.0275*	2.0239	0.0170*	2.2427	0.0045*
Very difficult teeth	5.0201	0.0002*	2.7488	0.0005*	5.1335	0.0001*
Nerve relation						
No contact	#		#		#	
Radiological superimposition	1.6303	0.2805	1.0941	0.9026	1.3822	0.3751
Rood & Shehab markers	2.1834	0.0048*	1.9402	0.0001*	2.5138	0.0001*
Sinus relation						
Sinus floor above roots	#		#		#	
Sinus floor touches root tips	1.6003	0.4726	1.1147	0.9911	0.9381	0.9991
Sinus floor superimposition 1/3	1.6584	0.3826	1.5020	0.4099	1.5088	0.4811
Sinus floor superimposition 2/3°	3.6657	0.0029*	2.2036	0.0127*	3.5411	0.0006*
Pathology						
Absence of pathology	#		#		#	
Resorption	1.0367	0.9363	1.7646	0.0708	1.7188	0.1972
Pericoronal radiolucency	7.9051	0.0422*	1.5035	0.1759	1.5828	0.2466
Periapical radiolucency	0.0006	0.1929	0.2891	0.0007*	0.4015	0.0024*
Caries	0.4945	0.0003*	0.4288	0.0001*	0.3638	0.0001*

is reference category; *significant p-value.
°There were too few cases of level 5 sinus relation to draft a relevant model.

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NERVE COMPLICATIONS

3 NERVE COMPLICATIONS

CHAPTER 7
The anatomic relation of third molars and the retromolar canal

Moreno Rabie C.[1,2]
Vranckx M.[1]
Ignacia Rusque M.[1,2]
Deambrosi C.[1]
Ockerman A.[1]
Politis C.[1]
Jacobs R.[1,3]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]Department of Oral and Maxillofacial Radiology, Universidad de los Andes, Santiago, Chile.

[3]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: This study was designed to assess the prevalence of the retromolar canal and foramen in relation to the mandibular third molars in dry human mandibles by direct anatomical observations and cone-beam computed tomography (CBCT).

Methods: Caucasian dry mandibles (n=89) were macroscopically evaluated and by use of CBCT (Newtom VGI evo). The following parameters were assessed: presence of a retromolar foramen and retromolar canal, presence of the third molars, and orientation of the third molars.

Results: From a total of 89 mandibles, 73 showed a retromolar foramen, 49 of which were bilateral). A retromolar canal was identified in 64 mandibles, with a total of 101 canals (74 of which were bilateral). In addition, 112 hemimandibles contained a third molar. Orientation of the third molars did not seem to indicate the presence of retromolar foramina or canals. A similar prevalence of retromolar canals was found for both vertically (41/79; 52%) and mesially (17/33; 52%) orientated third molars.

Conclusion: Retromolar canals and foramina were present in most mandibles, with more than half being bilateral. We were unable to confirm a potential relation between the retromolar canal on the one hand, and the orientation of the third molar on the other.

Key words: CBCT, retromolar canal, retromolar foramen, third molar, wisdom teeth

Introduction

The retromolar area is a triangular area distal to the third mandibular molar, delimited laterally by the buccinator muscle, mesially and posteriorly by the tendon of the temporal muscle, and anteriorly by the alveolar process of the third molar. Some anatomical variations can be seen in this triangular shaped zone, such as the presence of a foramen which can be the output of a canal containing a neurovascular bundle.[1]

The presence of the retromolar canal was first described by Schejtman et al. in 1967 and by Ossenberg in 1987.[1,2] It can be defined as a branch of the inferior alveolar neurovascular bundle that runs along a bony path from the mandibular canal to its exit through the retromolar foramen.[1,2] The canal has been reported to contain a portion of nerves and at least one artery and vein, in which its clinical importance lies.[1] It has been associated with complications during third molar extractions or other procedures in the retromolar area, such as anesthetic block failure, hemorrhage and iatrogenic nerve damage.[2–5] Surgeons operating in this area should consider the presence and width of the retromolar canal preoperatively.

The retromolar canal can be identified radiographically. Unfortunately, most of the time conventional two-dimensional (2D) images like panoramic radiographs are not able to identify variants of these anatomical structures due to inherent technical characteristics, such as superimposition of anatomical structures, image distortion and magnification, and low spatial resolution.[5,6] Cone-beam computed tomography (CBCT) can more accurately identify the retromolar canal, considering its three-dimensional (3D) nature.[7,8]

Various studies have reported considerable differences in the prevalence of retromolar canals and foramina, with numbers ranging from 12% to 75% for canals and 0% to 52% for foramina.[1,5,7,9–16] These results can be explained by differences in the study samples, study designs (in vivo or ex vivo), radiographic techniques (2D vs. 3D), CBCT vs. medical CT (better trabecular delineation), inclusion and exclusion criteria, and anatomical definitions used.

To the best of our knowledge, the relation of the retromolar canal to the third molar has not been described, except for complications with the neurovascular bundle during third molar extraction or other procedures in the retromolar area.[2–5] There is no information regarding third molar orientation and the presence of a retromolar canal, or the association between the appearance of a retromolar canal and the gubernacular cord of the third molar. Therefore, the aim of the present study was to assess the prevalence of retromolar canals and foramina in relation to the mandibular third molar in dry human mandibles (ex vivo) by direct anatomical observations and CBCT imaging.

Materials and Methods

The sample consisted of 89 dry human mandibles of Caucasian origin, age and gender unknown. Ethical approval was obtained from the Ethics Committee Research of the University Hospitals of Leuven (Belgium).

Macroscopic evaluation

The mandibles were classified macroscopically according to the uni- or bilateral presence and eruption status of the third molars (eruption, impaction, agenesis or missing third molars (either from extraction or post-mortem loss)), and according to the uni- or bilateral presence or absence of a retromolar foramen. To consider a perforation in the retromolar area as a foramen, it was measured empirically and reported as present or not present in each hemimandible (Figure 7.1).

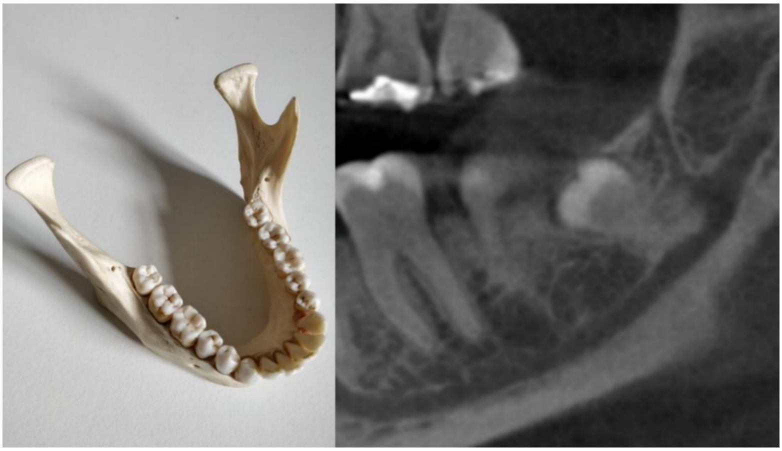

Figure 7.1. *Macroscopic observation of the retromolar foramen (left) and sagittal view of a retromolar canal on CBCT (right).*

Radiographic evaluation on CBCT

Mandibles were scanned in the Newtom VGI evo CBCT machine (QR Verona, Italy) with soft tissue substitution (Cu filter). The field of view was 10cm x 5cm and pixel value 0.125mm. Separately from, and independently of, the direct anatomical observations (macroscopic evaluation), each mandible was radiographically assessed for the uni- or bilateral presence of a retromolar canal by viewing the continuous sectional CBCT slices using MeVisLab software (Bremen, Germany). To consider presence or absence of the retromolar canal, the radiographic definition given by Capote et al. (2015) was used: *"The identification of a radiolucent image bounded by radiopaque lines present in the retromolar triangle, associated or not with the distal inferior tooth and/or with the mandibular canal"*.[5] Any canal that met this definition, regardless of its width, was considered as retromolar.

The orientation of the third molars was assessed to search for a relation between the presence of a retromolar canal and the position of the third molar in the mandible. For this assessment, 3D reconstruction of the imaging data was done. The following classification was used: not present, vertical axis orientation, mesioangulation or distoangulation of third molar. Lastly, the number of teeth present in each hemimandible was noted. Descriptive statistics were used for all assessed parameters during macroscopic and radiographic evaluation.

Results

7.1. Presence of retromolar foramina macroscopically

Of a total of 89 mandibles, 73 showed uni- or bilateral presence of foramina on macroscopic evaluation, with 49 showing bilateral foramina. Thirteen mandibles showed a foramen only on the right side, 11 only on the left side. The total number of retromolar foramina was 122. The results can be seen in Figure 7.2.

7.2. Presence of retromolar canals during CBCT evaluation

Of 89 mandibles, 64 showed uni- or bilateral presence of a retromolar canal during CBCT assessment, with 34 showing bilateral canals. Twenty-seven mandible showed unilateral presence of a retromolar canal, 20 on the right side and 7 on the left (Figure 7.2). The total of canals was 101. Forty-nine foramina turned into a retromolar canal on the right and 34 on the left. In 19 mandibles (both sides), retromolar foramina and canals were absent. In 57 hemimandibles, macroscopic and radiographic observations did not match, either because the macroscopic evaluation showed a foramen and the CBCT did not show a canal, or vice versa.

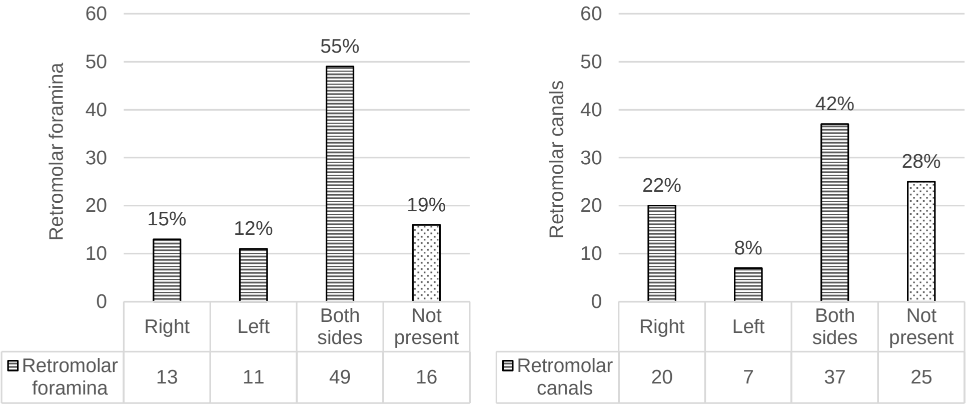

Figure 7.2. *Presence of retromolar foramina observed macroscopically (left) and retromolar canals found on CBCT (right), and side distribution in a total of 89 mandibles.*

7.3. Relation between third molar orientation and the retromolar canal

In total, 112 hemimandibles contained a third molar, 58 of which also showed presence of a retromolar canal. In the other 54 hemimandibles, no retromolar canals were detected (Figure 7.3). The most retromolar canals were observed in the presence of a vertically orientated third molar (n=41). However, the data showed no relation between third molar orientation and the presence of a retromolar canal (Figure 7.3). The prevalence of detected canals was similar for both third molar orientations: 52% for vertical (41/79) and 52% for mesial (17/33).

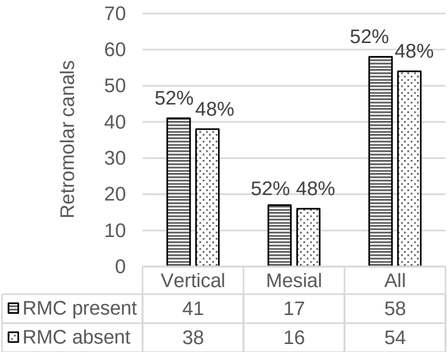

Figure 7.3. *Presence of retromolar canals according to the orientation of the third molar. Analysis of 112 hemimandibles with third molar present. RMC = retromolar canal.*

Discussion

The retromolar trigone and its anatomical variations such as the retromolar foramen and retromolar canal can be important when it comes to the extraction of third molars, treating mandibular angle fractures, performing orthognathic surgery and/or any other procedure in this area. Local complications have been reported, including anesthetic failure[2,3,10,15,17], hemorrhage[3,17] and neurosensory disturbances in the retromolar area[3,10,17], such as paresthesia after the extraction of a lower third molar, as already reported by Singh back in 1981.[18] That patient experienced numbness of the gingiva from the buccal sulcus to the canine when compared with the contralateral side.[18] The present study aimed to assess the prevalence of retromolar canals and foramina in dry mandibles, and to evaluate the potential relation of the presence of a retromolar canal with the orientation of the ipsilateral third molar.

The high number of retromolar foramina during macroscopic observation could be attributed to the inclusion of all foramina in the triangle, irrespective of their diameter. Gamieldien and Van Schoor (2016) reported a retromolar foramen prevalence of 8%, calculated in 885 dry mandibles.[4] They considered a foramen to be *"any perforation in the retromolar area that allowed the passage without resistance of a needle of 1 mm in diameter"*. As far as retromolar canals are concerned, the results showed that 64 mandibles showed presence of at least one retromolar canal, totaling 101 canals in 178 examined hemimandibles. Even the smallest diameter (<1mm) was considered, although Oliveira-Santos et al. (2012) reported that the width of the retromolar canal should be at least 2mm to be clinically relevant.[19] The reason for not considering a smaller diameter is that a smaller caliber canal would contain a smaller neurovascular bundle, so its clinical complications would not be significant.[4] It is possible that because of different diameter cut-off values, the evidence for complications reported being associated with the retromolar canal is contradictory. Gameldien and Van Schoor (2016) concluded that there is limited evidence that the retromolar canal and foramina are responsible for anesthetic failure. Additional bleeding may occur in this area, but can be easily controlled.[4]

We would like to stress that our sample contained less than 100 mandibles, so that the reported percentages in the figures are to be considered carefully. Though, reporting of the percentages is necessary to be able to compare the present study with existing publications. The reported prevalences of retromolar canals and foramina vary widely among sample types, ethnicities and ages.[3,20] Studies on cadaveric mandibles usually concentrate on the retromolar foramen rather than the retromolar canal. Athavale et al. (2013) included dry ossified mandibles and adult cadavers, but excluded edentulous mandibles and the ones from which third molars had been extracted or had a resorbed third molar socket.[9] A retromolar foramen was found in 10 mandibles out of 71 studied (14%), and it was found to be located 1cm from the posterior border of the wisdom tooth. Kawai et al. (2012) established the presence of this structure by counting the number of foramina per hemimandible (27%).[14]

Similar to our direct anatomical observations, Schejtman et al. (1967) studied and dissected 18 heads, of which 72% showed a single retromolar canal, and 27% bilateral ones.[1] They confirmed that these canals arose from the mandibular canal and in many cases contained a neurovascular bundle branch. However, they did not record the width of the canal and foramen. Another study was conducted by Patil et al. (2013), who described a retromolar canal prevalence of 75% observed on CBCT, all diameters included.[12]

Similar to our findings, Kawai et al. (2012) found a relatively high prevalence (52%) of the retromolar foramina.[14] Ninety sides of 46 cadaveric mandibles of unknown gender were evaluated through CBCT to confirm the presence of a retromolar canal and foramen. The retromolar foramina were lingually located from the mandibular canal, with a prevalence of 52%.[14] This high number seems to confirm that it is not an unusual anatomical structure. A similar conclusion was reached in a retrospective study by Sisman et al. (2015).[16]

The prevalence of retromolar canals and foramina found in patient populations is generally lower than in dry mandibles. Lizio et al. (2013) used a sample of 233 CBCT images from 187 patients with a mean age of 46 years.[7] The relatively low prevalence (16%) found in this study, as also in the paper by von Arx et al. (2011) (26%), can be explained by restricted inclusion criteria (minimal diameter).[15] The limits were set based on earlier studies that considered only widths between 1.5–4.4mm as clinically relevant.[10] On the other hand, Kang et al. (2014) analyzed CBCT images from patients with an age range from 16 to 57 years, and found that 53% of the bifurcations in the mandibular canal were retromolar canals.[21]

It is widely agreed that CBCT is the examination method of choice when identifying retromolar canals. Because of their limited width, it is difficult to detect the presence of accessory canals on panoramic radiographs. In addition, the superimposition of anatomical structures in this technique might hamper the observation of accessory canals. Von Arx et al. (2011) found 31 canals in 121 sides using CBCT, where only 7 of these canals could be seen on panoramic radiographs.[15] Fakumi et al. (2012) reported that spiral CT was not very effective for the assessment of this structure either, because the discrimination between the trabecular bone and the canal was not clear.[22]

Most of the research into retromolar canals and foramina is about incidence, characteristics of anatomical variations and the clinical implications of their presence. The present study evaluated the relation of the orientation of the third molars and the presence of a retromolar canal. Figure 7.4 shows a dry mandible with a large retromolar canal. Although the connection with the third molar follicle can clearly be seen, no relation could be deduced from the present data.

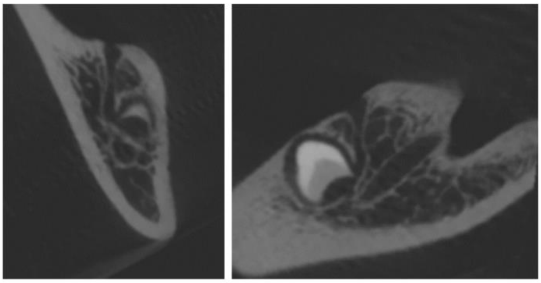

Figure 7.4. *Coronal (left) and sagittal (right) view of a dry mandible showing a retromolar canal. The relation with the third molar follicle can clearly be seen.*

Another interesting topic of research is the link between the retromolar that emerges through the retromolar foramen, and the gubernacular cord. This might be the reason why some authors described the distance between the foramen and the lower third molar.[4,12] The gubernacular cord is a structure of connective tissue surrounded by a bony wall known as the gubernacular canal.[23] This structure was first described by John Hunter in 1778 as a canal that connects a tooth in formation with the gums.[24] It is said that the cord is derived from the fragmented remains of the dental lamina and contains connective tissue that includes nervous, vascular and lymphatic portions, as well as epithelial remains.[25] Cahill and Marks (1980) studied the role of the gubernaculum during tooth eruption. Despite the small sample, they concluded that this structure could play a role in the eruption process, but its absence does not prevent it from happening.[26] If the retromolar canal is a histological vestige of gubernacular canal of the third molar, we should probably have found a higher frequency of the canal in relation to third molars with dental malpositions such as mesioangulation, or impacted or rotated teeth. More histological and morphological studies will be necessary to verify this hypothesis, as well as to assess the specific role of the gubernaculum in relation to third molar orientation and the appearance of a retromolar canal.

Conclusions

In the present study, the prevalence of the retromolar canal was higher than in previous studies. It can be concluded that this anatomical structure is more frequently present than thought. No relation was found between the presence of the retromolar canal and the orientation of the ipsilateral third molar (or its gubernacular cord). In any case, the retromolar canal should be considered when performing surgical procedures in the retromolar area to avoid the occurrence of intra- and postoperative complications such as bleeding and neurosensory disturbances, most importantly in case of a wider diameter. Further studies are needed to assess the prevalence of retromolar canals and foramina, also considering their diameter, and their clinical relevance.

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CHAPTER 8

Do anatomical variations of the mandibular canal pose an increased risk of inferior alveolar nerve injury after third molar removal?

Vranckx M.[1]

Geerinckx H.[1]

Gaêta-Araujo H.[1,2]

Ferreira Leite A.[1,3]

Politis C.[1]

Jacobs R.[1,4]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

[2]Department of Oral Diagnosis, Division of Oral Radiology, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, Brazil.

[3]Department of Dentistry, Faculty of Health Sciences, University of Brasília, Brasília, Brazil.

[4]Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden.

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Abstract

Purpose: The present study aimed to assess whether anatomical variations of the mandibular canal are associated with neurosensory disturbances of the inferior alveolar nerve (IAN) following mandibular third molar removal.

Methods: Two observers evaluated 402 panoramic and CBCT images of 201 patients undergoing third molar removal in context of the M3BE study. Assessed parameters were third molar orientation, root-nerve relation and presence of bifid mandibular canals (BMC) and/or retromolar canals (RMC). Potential neurosensory disturbances of the IAN were surveyed ten days after third molar removal. Fisher's Exact was performed to correlate presence of anatomical variations to postoperative neurosensory disturbances of the IAN. Positive and negative predictive values (PPV, NPV) and likelihood ratios (LR+, LR–) were calculated.

Results: CBCT was superior in visualization of anatomical variations of the mandibular canal, compared to panoramic radiography. Prevalence of BMC was 14% on CBCT and 7% on panoramic radiographs. Incidence of (temporary) postoperative altered sensation of the lower lip was 6.5% (n=13), with 2 of these patients having mandibular canal bifurcations on the ipsilateral side of the injury. Fisher's Exact showed that the studied mandibular canal variations were not related to postoperative IAN neurosensory disturbances. In both imaging modalities and for all parameters, PPVs were low (0.04–0.06) and NPVs were high (0.92–0.98).

Conclusion: The assessed mandibular canal variations had limited predictive value for neurosensory disturbances of the IAN following third molar removal. While a close relation between the third molar and the IAN remains a high risk factor, mandibular canal variations do not pose an increased risk of postoperative IAN injury after mandibular third molar removal.

Key words: bifurcations, inferior alveolar nerve, mandibular canal, neurosensory disturbances, retromolar canal, third molar

Introduction

While third molar removal is one of the most commonly performed procedures by dentists and oral and maxillofacial surgeons, as with any type of surgery, per- and postoperative, complications can occur. One of the possible complications following mandibular third molar (M3) removal is damage to the inferior alveolar nerve (IAN), resulting in temporary or permanent disturbance in sensory function. These injuries translate as numbness (dys- or paresthesia) of the lower lip and chin or even complete loss of sensory function (anesthesia).[1] Although in literature the reported incidence of (especially permanent) injuries of the IAN following third removal is comparatively rare, third molar removal is still the main cause of this trigeminal neuropathy.[2–4] Caution for risk factors of postoperative IAN injury is therefore vital, listed among which are surgeon's inexperience, age of the patient, surgical instruments causing direct injury, and most importantly, the anatomical relation of the third molar roots and the mandibular canal. This relation can be radiographically assessed using panoramic radiography (PAN), and in cases of suspected risk, additional cone-beam computed tomography (CBCT) imaging.[4]

Another risk factor that is often disregarded in radiographic assessment is the presence of anatomical variations of the IAN, defined as bifurcations of the mandibular canal (BMC) (such as side branches and loops), and retromolar canals (RMC).[5–8] Analysis of the contents of the canals showed that they contain a neurovascular bundle coming from the IAN, innervating the oral mucosa and gums in the lower molar and premolar regions.[5,9,10] Given this neurovascular content, anatomical variations of the mandibular canal might be of clinical relevance during dental procedures.[9,11–14] However, little research has been done on the potential correlation between mandibular canal variations and the occurrence of postoperative IAN injury after third molar removal.

Therefore, the primary aim of the present study was to investigate a potential relation between mandibular canal variations and neurosensory disturbances of the IAN following mandibular third molar removal. As a subobjective, it was assessed whether CBCT enabled enhanced risk prediction in terms of IAN injury, as compared to PAN.

Materials and Methods

Patients were selected from the M3BE database (Chapter 4), a Belgian prospective epidemiological study in which patients undergoing third molar removal were followed up until 10 days postoperatively. The study was approved by the Ethics Committee Research of the University Hospitals of Leuven (Belgium) (B322201525552), and was carried out according to the ICH-GCP principles and the Declaration of Helsinki (2013). Patients had to be ≥18 years, undergoing mandibular third molar removal, and as part of diagnosis and surgical planning, PAN and CBCT images were acquired on the same day.

Two experienced and calibrated oral radiologists evaluated the two sets of radiographs. PAN were acquired using the VistaPano S Ceph device (Dürr Dental, Bietigheim-Bissingen, Germany) and CBCT using the Newtom VGi evo (QR, Verona, Italy). Training sessions were organized prior to the start of the observations in which a random selection of radiographic images from the M3BE database were collectively examined. Exclusion criteria were: poor resolution or poor-quality images, supernumerary teeth, bone pathology associated with the third molar area (e.g. odontomas, tumors, bone metabolism disease), and other lesions that could modify the path of the mandibular canal.

Four radiographic variables were evaluated:

- Third molar orientation: vertical, mesial, horizontal, distal or buccolingual (Appendix A);
- Close relation of third molar roots with the mandibular canal (yes/no) based on the presence of Rood & Shehab markers (Appendix A);
- Presence of bifurcations (BMC) of the mandibular canal (independent of width);
- Presence of retromolar canals (RMC).

The course of the BMC, when present, was further classified on CBCT into RMC (BMC in retromolar area), BMC in mandibular corpus (with or without confluence), BMC in mandibular ramus (with or without confluence). The course of the RMC was further classified according to von Arx (2011): vertical (with or without accessory canal), oblique, or horizontal (with or without accessory canal).[7] The anatomical variations were scored by means of a Likert five-point scale: definitely present (1), probably present (2), uncertain (3), probably absent (4), definitely absent (5), which was made binary for further analysis. Moreover, to be able to account potential non-detection of anatomical variations to poor visibility of the mandibular canal, the cortical borders of the canal were assessed as continuously visible, intermittently visible (interruption of one cortical border) or not visible (interruption of two cortical borders on PAN; and canal not traceable from mandibular foramen to mental foramen on CBCT).

After third molar removal, neurosensory disturbances were prospectively surveyed on day 10 postoperatively. Questions inquired after:

- Presence of altered sensation in the lower lip;
- On which side (left or right);
- Type: numbness, tingling, altered feeling upon touch, other;
- Constant or episodical nature of these symptoms.

Data were analyzed in MedCalc Statistical Software version 19.1.6 (MedCalc Software Ltd, Ostend, Belgium). Interobserver reliability was calculated using Cohen's kappa. The percentage of agreement between observations in both imaging modalities was determined. The number of false positives and false negatives on PAN was calculated, with CBCT considered as the reference standard.

The relation between the presence of a BMC and/or RMC and postoperative neurosensory disturbances of the IAN was checked using Fisher's Exact. P-values <0.05 were considered significant. For each PAN and CBCT assessed parameter, the positive predictive value (PPV) for prediction of a postoperative neurosensory disturbances was calculated as true positives (TP) divided by the sum of true and false positives (FP). This means the number of teeth with risk factor and postoperative neurosensory disturbance divided by the total number of teeth with risk factor. The negative predictive value (NPV) was calculated as true negatives (TN) divided by the sum of true and false negatives (FN), meaning the number of teeth without postoperative neurosensory disturbance and without risk factor divided by the total number of teeth without risk factor.

To assess the odds that a neurosensory disturbance actually occurred if a given parameter was observed on PAN and/or CBCT, positive likelihood ratio

(LR+=sensitivity/(1–specificity)) was calculated. To assess the likelihood of a patient reporting post-op neurosensory disturbances when a priori diagnosed without a risk factor, the negative likelihood ratio was calculated (LR–=(1–sensitivity)/specificity). The higher LR+, the better the risk factor in estimating postoperative neuropathy, and the lower the LR–, the better absence of a risk factor rules out the neuropathy.

Results

8.1. Radiographic assessment and agreement PAN vs. CBCT

In total, 357 third molars were removed in 201 patients (83 males; 118 females; mean age 26.4 (± 8.6) years) during 226 surgeries. Accordingly, 357 hemimandibles were evaluated (181 left and 176 right). Table 8.1 shows the agreement of observations on PAN and CBCT. Hemimandibular prevalence of total BMC (including RMC) was 7.5% on PAN and 14.2% on CBCT (n=50). Hemimandibular prevalence of RMC was 6.5% on PAN and 7.9% on CBCT (n=28).

Table 8.1. *Detection of variables on panoramic radiographs and CBCT. Agreement ranged between 80.1% and 89.4%. (n=357 hemimandibles)*

	PAN		**CBCT**		**Agreement**	
Orientation	N	%	N	%	**307**	**86.0%**
Vertical	123	34.5	121	33.8		
Mesial	184	51.4	189	52.8		
Horizontal	40	11.1	44	12.2		
Distal	10	2.7	1	0.3		
Buccolingual	2	0.4	4	1.0		
Relation M3–IAN					**319**	**89.4%**
Yes	344	96.4	313	87.7		
No	13	3.6	44	12.3		
Bifurcations					**286**	**80.1%**
Yes	26	**7.5**	50	**14.2**		
No	321	92.5	301	85.8		
Retromolar canal					**315**	**88.1%**
Yes	23	**6.5**	28	**7.9**		
No	329	93.5	325	92.1		

PAN = panoramic radiography; CBCT = cone-beam computed tomography; M3 = third molar; IAN = inferior alveolar nerve; Numbers for bifurcations and retromolar canals do not add up to n=357 because of some unclear observations.

Detected canals were further classified according to their appearance on CBCT: 5 BMCs in corpus (1 with confluence, 4 without); 17 BMCs in ramus (2 with confluence, 15 without); and 28 RMCs (17 vertical, 7 oblique and 4 horizontal). The visibility of the mandibular canal was compromised in 40% of the PAN images, with interruption of one cortical border in 34.5%, and interruption of two cortical borders in 5.5%. On CBCT, these numbers diminished to 29.7% and 0.6%, respectively.

The interobserver reliability was on average 0.73, with values ranging from 0.24–0.74 on PAN and 0.81–1 on CBCT. In particular, agreement was low for detection of mandibular canal variations on PAN (0.24).

False positive and false negative observations on PAN are displayed in Table 8.2. Values were low for M3-IAN relation, but were high for detection of anatomical variations. In total, 64.1% and 62.4% of BMC and RMC observations were falsely positive. On the other hand, 72.9% and 68.6% of BMC and RMC observations were falsely negative, meaning that they remained undetected on PAN (Figure 8.1).

Table 8.2. *False positive and false negative detections on panoramic radiographs. 62.4% to 64.1% of the observed anatomical variations of the mandibular canal were falsely positive, and 68.6% to 72.9% of variations remained undetected (false negative).*

	False positive	False negative
Relation M3–IAN	35	3
%	10.1	1.0
Bifurcations	17	37
%	64.1	72.9
Retromolar canal	14	19
%	62.4	68.6

Figure 8.1. *Panoramic radiograph of a patient with a clear retromolar canal on the left side, confirmed by CBCT (circle close-up). The retromolar canal on the right side can be overlooked.*

8.2. Postoperative neurosensory disturbances in relation to the radiographic findings

Thirteen patients reported neurosensory disturbances in the lower lip on day 10 after surgery (4 right; 7 left; 2 bilateral), totaling 15 mandibular sides. Accordingly, the incidence of self-reported neurosensory disturbances in the lower lip was 6.5% of patients and 4.2% of hemimandibles. Numbness was reported 6 times, whereof 2 times in combination with tingling. One patient reported sole tingling and one patient experienced sensory disturbances upon touch. Six of these sensory disturbances were reported being of constant nature, 2 were episodical. In 5 patients, details on nature of the altered sensation were missing. All 13 patients had a close relation of the third molar roots with the IAN. Two patients suffering postoperative neurosensory disturbances had an anatomical variation of the mandibular canal in the ipsilateral side of the injury (Figure 8.2). However, Fisher's Exact showed that nor root-nerve relation, nor anatomical variations of the mandibular canal (BMC and RMC) were significantly associated with postoperative neurosensory disturbances of the IAN (p-values 0.41–0.62).

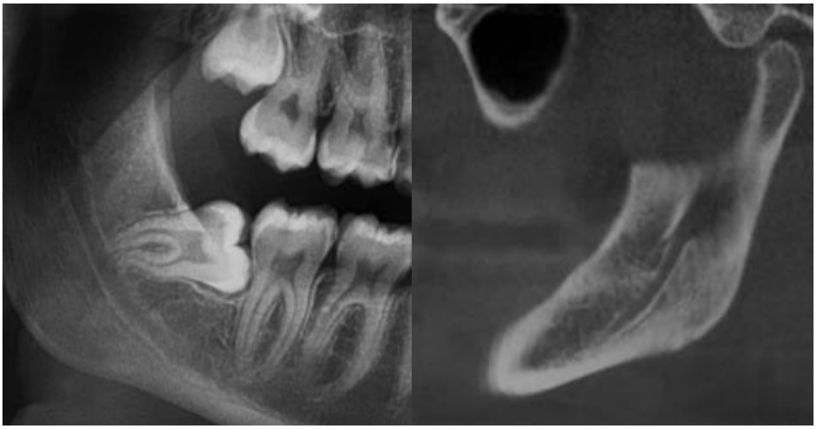

Figure 8.2. *Panoramic radiograph (left) and CBCT image (right) of a patient presenting with postoperative neurosensory disturbances in the right lower lip and chin area. CBCT shows a retromolar canal in the ipsilateral side of the injury, that remained undetected on the panoramic radiograph.*

To determine the predictive value of PAN and CBCT assessed parameters on the occurrence of postoperative IAN injury, PPVs and NPVs were calculated (Table 8.3). In both imaging modalities, PPVs were low (0–6%) and NPVs were high (92–98%). LR+ were around 1, resulting in little to no diagnostic value. LR– ranged from 0.53 to 1.90.

Table 8.3. *Positive and negative predictive values of the assessed risk factors for suffering IAN injury. Positive predictive values (PPV) of the assessed risk factors were low, meaning that having the risk factor is limitedly predictive for suffering IAN injury. Negative predictive values (NPV) were high, meaning that not having the risk factor is predictive for not suffering IAN injury. The higher LR+, the better the risk factor in estimating postoperative neuropathy, and on the contrary, the smaller the LR–, the better the absence of a risk factor rules out a postoperative neuropathy.*

Predictive values for IAN injury for the risk factors assessed on		
	PAN	**CBCT**
Relation M3–IAN		
PPV (LR+)	4% (0.97)	4% (1.07)
NPV (LR–)	92% (1.90)	98% (0.53)
Bifurcations		
PPV (LR+)	0% (0)	6% (1.43)
NPV (LR–)	95% (1.09)	96% (0.93)
Retromolar canal		
PPV (LR+)	0% (0)	0% (0)
NPV (LR–)	95% (1.07)	95% (1.09)

PAN = panoramic radiography; CBCT = cone-beam computed tomography; M3 = third molar; IAN = inferior alveolar nerve.

Discussion

The present study aimed to assess the relation between mandibular canal variations and neurosensory disturbances following mandibular third molar removal. High heterogeneity exists among reported prevalence rates, with values for BMCs ranging from 2.0% to 8.3% on PAN, and 9.8% to 65% on CBCT.[8,15–17] Similarly, reported ranges for RMCs are generally lower on PAN (3.1–5.8%) compared to CBCT (14.6–43.1%).[7,12,18,19] The present data showed a (hemimandibular) BMC prevalence of 7.5% on PAN and 14.2% on CBCT; and a (hemimandibular) RMC prevalence of 6.5% on PAN and 7.9% on CBCT. Varying results among studies can be attributed due to a number of factors, such as ethnic differences in study samples, variations in sample size and characteristics (ex vivo or in vivo), and the expertise of the observers.[5,20] Moreover, the imaging modality, the image settings and image quality are probably the most important contributors to these varying numbers. Prevalence of PAN-detected BMC range from 1% in earlier studies to 8% in later studies, due to improved quality of devices over time.[16,21] With the 2D rendition of 3D facial structures, PAN images are obviously subject to effects of magnification distortion, superimposition of structures and patient positioning.[12] CBCT, on the other hand, is a 3D representation of the skull, providing an accurate and reliable visualization of anatomical structures, including location, shape and relationship with adjacent structures.[5,22]

Interobserver reliability was excellent for CBCT (0.81–1) and substantial for PAN (0.60–0.74). However, interobserver reliability for detection of variations on PAN was low (0.24). From the higher number of detected variations on CBCT (n=50) and the low level of interrater agreement on PAN, we can conclude that CBCT was the most sensitive technique in detecting anatomical variations. In addition, PAN-based assessments resulted in high numbers of false positives and false negatives (Table 8.2). False positive assessments of BMCs on PAN might arise from the imprint of the mylohyoid nerve on the internal mandibular surface.[17,23] Moreover, BMCs can remain undetected on PAN because of diminished corticalization of the mandibular canal in areas where bifurcations often occur. The results showed that the visibility of the mandibular canal was diminished in 40% of PAN images, which could have paved the way for false negative observations.

Overall, the mean agreement between PAN and CBCT findings was high (80.1 to 89.4%), with the highest agreement observed in the assessment of root-nerve relations. PAN detected 96.4% root-nerve relations, of which 87.7% were confirmed on CBCT (Table 8.1). From this we can conclude that Rood & Shehab's markers are reliable for determining presence of root-nerve relation, however in selected cases, PAN leaves room for misinterpretation, so that root-nerve relation can most precisely be evaluated on CBCT.[24] This is in line with other studies' findings, and is the very reason why, in cases of suspected risk, preoperative protocols advocate additional CBCT assessment.[1,10,19,25] While PAN is the first-line imaging modality in the preoperative assessment, its principle merit with regard to root-nerve relation evaluation is ruling out a relationship between third molar roots and the IAN, more so than confirming it. Importantly, subjects fitting the inclusion criteria had undergone both PAN and CBCT in context of third molar removal, resulting in a sample of patients with moderate to high risk of root-nerve relation.

The incidence of (temporary) neurosensory disturbances of the IAN (6.5% of patients; 4.2% of hemimandibles) fell within reported ranges (0.35–8%).[26,27] The results showed that the presence of anatomical variations of the mandibular canal was not significantly related to the occurrence of IAN injuries. It is important to notice that patient outcomes were self-reported, and surveying might not be ideal for correctly assessing posttraumatic trigeminal neuropathies (PTTN). The method of measurement might influence the incidence, so a clinical diagnosis of PTTN could have resulted in lower numbers of PTTN.[28] However, since this study was performed on a subsample of the M3BE study, we had to adhere to its methodology.

To assess the diagnostic power of PAN and CBCT assessed variables on the occurrence of postoperative IAN injury, PPVs and NPVs were calculated (Table 8.3). In both modalities and for all parameters, PPVs were low (PAN 4%; CBCT 4–6%) and NPVs were high (PAN 92–95%; CBCT 95–98%). While the former means that only 4% to 6% of patients diagnosed with M3-IAN relation will develop PTTN, the latter means that in the absence of a root-nerve relation or anatomical variation, more than 9 out of 10 patients did not experience IAN neurosensory disturbances. LR+ were generally higher in CBCT, compared to PAN, whereas the LR– were lower. This means that a positive detection in CBCT (slightly) increased the odds of developing PTTN, while a negative diagnosis (slightly) reduced the odds of developing PTTN.

Nevertheless, evidence is mounting that preoperative CBCT imaging does not reduce the incidence of IAN neurosensory disturbances after third molar removal. While some put forward the better visualization of the mandibular canal, it is to date not proven that CBCT results in more accurate prediction of intraoperative IAN exposure, let alone reduces the prevalence of iatrogenic nerve damage.[4,5,28] Guerrero et al. (2012) demonstrated that use of CBCT does not show a significant reduction in post-op complications compared to PAN.[1] Likewise, Matzen et al. (2019) concluded that preoperative CBCT assessment does not affect postoperative outcome in terms of IAN injuries.[28] Factors that do have an impact on the risk of IAN neurosensory disturbances are duration of the surgical intervention and surgical technique.[3] This does not detract from the fact that surgeons can precisely plan the procedure based on 3D data (buccolingual view and number and position of roots), eventually resulting in shorter surgical time, and reduced postoperative discomfort and risk of complications. Still, it is challenging to clearly distinguish the effects of preoperative imaging and surgical performance.[3]

Borgonovo et al. (2017) reported that because of the relatively small diameter, a lesion of the RMC is not often related to a clinically relevant loss of sensibility.[6] It is generally accepted that variations >2mm are important to consider.[29,30] However, also after injury of a RMC with limited diameter, hypoesthesia of the buccal gingiva in the lower molar region has been reported.[6,10] Therefore, it remains advocated to take mandibular canal variations cautiously into consideration when planning and performing mandibular third molar removal.[6] Although current data seems to suggest that presence of a RMC and/or BMC is not significantly related to increased risk of IAN neurosensory disturbances following mandibular third molar removal, it does not exclude the possibility of intraoperative complications such as insufficient anesthesia and hemorrhage.

Conclusions

In the present study, CBCT was superior in visualization of anatomical variations of the mandibular canal, as compared to PAN. However, in both imaging modalities, the assessed anatomical variations had limited predictive value for IAN neurosensory disturbances following third molar removal. While a close relation between the third molar and the mandibular canal remains a high risk factor, canal variations did not pose an increased risk of postoperative IAN injury after mandibular third molar removal.

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CHAPTER 9

General discussion, conclusions and future perspectives

Vranckx M.[1]

[1]OMFS-IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium.

General discussion

Third molar removal is one of the most commonly performed oral procedures among oral and maxillofacial surgeons. Considering the often-prophylactic nature of the intervention, it is important to carefully consider the risks and benefits associated with it. As a matter of fact, the clinical management of third molars differs across countries, with some treatment guidelines discouraging prophylactic removal of asymptomatic impacted third molars[1,2], while other guidelines advocate an interventional approach as soon as it is clear that the third molars will be of low functional value in the mouth.[3,4] In the current atmosphere of ongoing disagreement, clinicians largely rely on their own expertise and beliefs in their clinical decision making.[5,6] As a result, great variation continues to exist between clinicians regarding their evaluation of the need for third molar removal.

The main objectives of this doctoral thesis were to provide clear view on the common practice of surgical third molar removal and the indications and morbidity associated with this type of oral surgery. In addition, it was aimed to identify patients at risk of impeded third molar eruption and patients vulnerable for persistent morbidity after removal. In this chapter, the main results are discussed and the methodological flaws are critically debated.

Early prediction of the third molars' eruption potential would be the first and ideal step in estimation of the (future) functional value of the third molars and, consequently, in a timely and appropriate treatment decision. In **Chapter 2**, we investigated the third molars' pre-eruptive rotational changes and eruption chances based on angulation measurements on orthodontic panoramic radiographs. We observed that **third molars are not static in development**. **However, the rotational changes were not sufficient to improve the eruption chances of the teeth**. Daily clinical practice also shows us a critically low number of functional third molar eruptions in fully dentate jaws. A critical angle of 27° was identified. More than half of the patients in the sample (63%) had third molars that exceeded this critical angle and were estimated to fail eruption. The results were in line with findings by Nance et al. (2006), revealing a third molar angulation greater than 35° to be unfavorable for eruption.[7] Over a follow-up period of 2.2 years, only 3% of the third molars exceeding 35° erupted to the occlusal plane.

More research has been done on the prediction of third molar impaction and eruption. Ventä et al. (1997) developed a transparant impaction prediction device to overlay panoramics[8], and Begtrup et al. (2013) combined cephalometric and panoramic measurements to calculate the probability of eruption.[9] A prediction formula was suggested combining the hemimandibular arch length from ramus to incisors with the mesiodistal width of the lower second molar. Measurements of the available retromolar space for eruption were not included in our study set-up. Aberrant third molar orientation is only one of the factors paving the way for impaction. In addition, the retromolar eruption space can be insufficient to properly accommodate the third molars. This factor is considered at least as important as the third molar's orientation.[10,11] Sufficient retromolar eruption space is defined as a retromolar space of at least the maximal width of the third molar crown. Still, it was shown by Hattab et al. (1997 and 1999) that 17% of third molars with adequate retromolar space failed functional eruption.[10,11] It is the combination of favorable orientation and sufficient space posteriorly in the dental arch that is key to functional third molar eruption. Future eruption prediction models should ideally combine the two modalities: prediction of favorable angulation changes and measurements of the available retromolar space. Furthermore, Chapter 2 revealed that fully developed impacted third molars are at increased risk of being in close relationship with the mandibular canal, containing the inferior alveolar nerve (IAN), as compared to fully developed erupted third molars. This means that **not only does a great angulation result in minimal eruption chances, it also increases the risk of iatrogenic nerve complications in case of extraction**. We therefore concluded that third molars that will fail to erupt into functional position can better be timely removed, at early development stage and stage of least risk of mandibular nerve injury.

In order to be of daily clinical ease-of-use, it is important that eruption prediction is fast, accurate and consistent, and of little burden for the dental practitioner. Therefore, in **Chapter 3**, we developed and validated an Artificial Intelligence (AI)-driven tool for automated measurements of the molar angulations on dental panoramic radiographs. The angulation measurements of Chapter 2 were automated with 80% to 98% accuracy. The network jointly predicted the molars' segmentation maps and orientation lines, and can ultimately be implemented in standard image viewing software in the dental or orthodontic practice. This would allow for easy and fast prediction of third molar eruption at adolescent age during or at the end of orthodontic treatment. Although, the ultimate goal is to develop a fully automated prediction tool, in the current work, small manual refinements to the network's segmentations and orientations were sometimes needed. Manual adjustments to the estimated orientations were often the result of the observer's interpretation of the 3D anatomical relation of the third molars to the neighboring elements and bony structures. So far, this human analysis of the anatomical structures on a panoramic radiograph, taking the overall clinical picture and treatment needs into account, cannot be mimicked by a convolutional neural network (CNN). Yet, it is readily clear that **AI will steadily and progressively gain ground in assisting and complementing the dental practitioner in the daily dental workflow**.

If the third molars will not erupt into a functional position in the dental arches, the ideal time for removal should be identified: the stage of least risk of postoperative morbidity and complications for the patient. In **Chapter 4**, we aimed to investigate the effect of increasing age and symptomatic indications on the patient's recovery after third molar removal. The starting point was that, if we would adhere to the conservative treatment approach advocated by the KCE third molar report (2012), we would only operate on impacted third molars with signs or symptoms of disease. It was hypothesized that two factors could be risk indicators for problematic postoperative recovery and persistent morbidity after third molar removal: symptomatic indications for removal and increased age. The results showed that increasing age was associated with more and persistent morbidity (pain, trismus and swelling), though, symptomatic indications were not. Even on the contrary, on day 3 after surgery, people with pre-existing symptoms reported less postoperative morbidity, which we think was due to subjective feelings of relief that the potential cause of preoperative pain and discomfort was removed. On day 10 after surgery, an effect of indication was no longer observed. In this respect, **waiting for symptoms or pathology to arise before proceeding to extraction would not compromise patient recovery**. However, it was shown by Vandeplas & Vranckx et al. (2020) that the incidence of symptoms and pathology climbs with increasing age of the patient.[12] Consequently, **only removing third molars when signs or**

symptoms of disease arise would probably cause a shift in the mean age of patients at time of admission to the OMFS department, and then the effect of age comes into play. In the past, a similar phenomenon was shown by McArdle et al. (2012) in a report that evaluated the effects of the NICE guidelines in a 10-year period after implementation.[13]

Third molar removal is also one of the first oral procedures performed by (supervised) surgical residents in their training in Oral and Maxillofacial Surgery. It is important that the associated postoperative morbidity remains within limits and proportional to the invasiveness of the procedure. In **Chapter 5**, we evaluated the effect of surgeon's inexperience on the patients' recovery after prophylactic third molar removal in a supervised setting. Although our findings contradicted with some earlier records[14,15], **the effects of surgical inexperience were limited in our sample**. Postoperative recovery was shown to be more dependent on intraoperative factors like the number of extractions and surgical method, rather than on the surgeon's level of experience.

In **Chapter 6**, we investigated the potential relation between radiographic information retrieved from the preoperative panoramic radiographs, and the postoperative patient recovery reports. We aimed to identify radiological risk indicators for persistent postoperative morbidity after third molar removal. The results showed that deep impactions and difficult extractions were related with more and persistent morbidity. Moreover, presence of pericoronal pathology and resorption compromised the postoperative recovery process. It can be debated that this information did not add much to the state-of-the-art in terms of "innovation", yet, it is important to keep considering the individual anatomical characteristics during the preoperative consultation with the patient. Patient satisfaction depends largely on complete and customized information about the oral intervention and the anticipated postoperative sequelae. With the information presented in Chapter 6, clinicians may better inform patients at risk for persistent postoperative discomfort following third molar removal. Patients who are well-informed about their recovery process will be less worried when particular postoperative symptoms linger. **The results can help in translating preoperatively diagnosable tooth-related factors into certain levels of morbidity, and in retrieving the maximum of**

information from panoramic radiographs, before potentially proceeding to CBCT.

It is interesting how the method of statistical analysis can influence certain results and outcomes. In Chapter 4, clear differences were observed in the effects obtained by the univariate and multivariable analyses. In order to disclose the real predictive effects of certain patient- and surgery-related factors on the patient's postoperative recovery after third molar removal, it is important to carefully consider potential confounding by covariates. The univariate analysis in Chapter 4 demonstrated significant effects of symptomatic indications for third molar removal on the postoperative morbidity reported on day 3 and day 10 after surgery. Also a multivariable model was constructed to assess the relation between patient- and surgery-related variables and postoperative morbidity. In consideration of potential confounding by covariates, it was shown that symptomatic indications for removal showed a significant reducing effect on immediate postoperative morbidity (day 3) such as pain, trismus and swelling; yet, on day 10, the effects did not stand (except for trismus). **It is thus likely that the observed univariate effect of symptomatic indications on persistent morbidity was confounded by other factors contributing to postoperative sequelae**. Likewise, Chapter 6 showed univariate effects of pre-existing pathology, in particular the presence of pericoronal pathology and resorption, on the occurrence of persistent postoperative pain and painkiller intake. Because of the univariate nature of this analysis, it should be emphasized that the observed effects in Chapter 6 could have been confounded by intraoperative events, such as extensive osteotomy, the number of extracted third molars in one surgical session, or the duration of the surgical intervention. Intraoperative difficulties could have affected the clinical outcomes in this study, and may have masked the predictability of certain of the considered radiological markers. Consequently, univariate associations can be deceiving to some extent and should therefore be interpreted with caution. Many earlier records reported results of univariate analyses. The multivariable model in Chapter 4 of the present work confirmed some of the earlier univariate findings, but contradicted others, e.g. the effect of anesthesia and surgeon's inexperience.[16–18]

The risk of iatrogenic injury to the IAN and lingual nerve (LN) is one of the reasons why certain legislators and authorities have discouraged prophylactic third molar removal in their latest treatment guidelines. The impact on the patient's quality of life is significant, and the risk of legal claims against practitioners is real. The results in Chapter 2 showed a significantly higher chance of close root-nerve relations in case of severely angulated impacted third molars. In addition, Chapter 4 showed that, if removal is postponed until older age, the probability of iatrogenic nerve injury increases from 0.9% and 1.8% in adolescence and early adulthood (≤16 and 17–25 years, respectively) to 4.6% and 5.8% at age 26–35 and 36–55 years. This means up to a 5-fold increase in the probability of detrimental nerve complications if third molar removal is delayed until later age.

In **Chapters 7 and 8**, we aimed to identify additional risk factors for nerve complications following third molar removal by exploring the anatomical variations of the mandibular canal in the (retro)molar area. Side-branches of the mandibular canal, containing neurovascular bundles coming from the IAN, are important to consider during third molar extraction. The surgical consequences could be significant. However, the data in Chapter 7 failed to reveal a potential link between third molar orientation (e.g. mesioangulation) and the presence of retromolar canals. In addition, Chapter 8 showed **no effect of the presence of mandibular canal bifurcations or retromolar canals on occurrence of (temporary) IAN injury after third molar removal**. **Still, anatomical variations of the mandibular canal might be more frequently present than thought** (Chapter 7). It is important to note that the study protocols in Chapters 7 and 8 did not include cut-off values for the detection of variations and no measurements of the widths of the canals were done. Despite showing no evidence that the variations were related to an increased risk of posttraumatic trigeminal neuropathies (PTTN), the retromolar canal is in the surgical field when performing third molar extraction, and neurosensory disturbances of the gums in third molar area have been reported postoperatively.[19] Therefore, it remains important to carefully consider anatomical variations of the mandibular canal, particularly when they are wider than >2mm diameter, in order to reduce the risk of neurosensory disturbances.

Clinical evaluation of postoperative neurosensory disturbances would have been preferred over patient self-reports. Clinical neurosensory testing in patients presenting with PTTN can be done by two-point discrimination, sharp-blunt discrimination, light touch and moving-point discrimination, and response testing to hot and cold stimuli.[20] Since PTTN was not the main topic of this doctoral research, we adhered to the methodology of the M3BE protocol. Nevertheless, the topic is highly valued and studied within our department.[20,21] To insure the patient's quality of life, immediate and appropriate medical action is required in order to minimize the risk of permanent neurosensory dysfunction. Research investigating the surgical consequences of anatomical variations of the mandibular canal and incisive canal following other oral interventions, e.g. implant placement, remains of high interest and daily clinical relevance.[22,23]

All in all, a close third molar root-nerve relation remains the highest risk factor for neurosensory disturbances of the IAN after mandibular third molar removal, especially when the nerve is positioned lingual or interradicular. In Chapter 8, the **Rood & Shehab markers (Appendix A) were confirmed to be reliable in ruling out root-nerve relations on panoramic radiographs, but were of little to no value for the prediction of iatrogenic IAN injury**. Studies have shown that the extent of overlay or superimposition of the third molar roots on the mandibular canal on 2D panoramic radiographs might be more suited to determine the risk of nerve injury.[24,25] A larger contact area between the third molar roots and the mandibular canal would pose a higher risk of intra- and postoperative damage to the IAN. For the assessment of the exact 3D anatomical relation between the third molar roots and the mandibular canal, CBCT is most suited. However, the CBCT-based assessment in Chapter 8 focused mainly on the anatomical relationship in the sense of direct contact (loss of cortical border) between the molar and the mandibular canal, without considering the position or course of the IAN relative to the third molar roots. Neither did we specifically evaluate if the nerve was being enclosed by the roots or not. However, these two situations are important as they interfere with the standard surgical protocol, which on its turn can influence the postoperative recovery of the patient.

Based on the results of 4 years of epidemiological and radiological research on the surgical removal of third molars, the following **evidence-based treatment approach** is suggested based on the patient's age at the time of admission to the hospital:

- **≤ 16 years:** An **estimation of the third molars' eruption chances** can be made based on the patient's panoramic radiograph(s) acquired during or at the end of orthodontic treatment (Chapters 2 and 3). The critical angle for eruption is 27°. Prophylactic removal at this age is associated with higher odds of immediate (day 3) postoperative swelling and trismus (Chapter 4). At this age, third molars are frequently bony impacted so that extensive bone removal might be required during extraction, resulting in significant postoperative discomfort (Chapters 4 and 6). The probability of IAN injury is at its lowest level: 0.9%.
- **17–25 years:** This is the **reference age for third molar removal**. Patients will suffer the least postoperative sequelae at this age (Chapter 4). Also cost-implication-wise, this age is considered most beneficial (school leave over work leave). Healthy patients are expected to recover smoothly and within reasonable time, with low risk of iatrogenic nerve complications. The probability of IAN injury is 1.8%.
- **26–35 years:** This age category is considered a **grey zone** with regard to third molar treatment decisions. Shortly after extraction (day 3), no significant differences in recovery are to be expected, compared with patients in the reference age category (Chapter 4). However, patients are at higher risk of persistent pain, trismus and swelling (morbidity lingering until 10 days after surgery). **In case of (recurrent) complaints, further delaying third molar removal is not recommended, better proceed to extraction**. Symptomatic indications will not compromise the patient's recovery, but aging will (Chapter 4). The probability of IAN injury is 4.6%.
- **36–55 years:** Shortly after surgery (day 3), no significant differences in recovery are to be expected, compared with patients in the reference age category (Chapter 4). However, **patients are at higher risk of persistent pain, trismus and swelling** (morbidity lingering until 10 days after surgery). Moreover, the probability of IAN injury is the highest in this age category:

5.8%. Treatment of patients in this age category represents the highest socioeconomical cost, both in time and money (risk of complications, extra control visits etc.). A trade-off should be made between the costs of retention vs. extraction, considering the risks of pathology in case of retention (Chapter 1), the risks of persistent postoperative morbidity in case of removal (Chapter 4), and the associated socioeconomic costs. It might be recommended to only operate in case of clinically urgent indications.

- **> 55 years:** An **individual case-by-case approach** is recommended. A clear clinical or radiological indication for removal should be present before proceeding to extraction. The probability of IAN injury is 5.6%.

It is crucial to include the patient's individual needs and preferences in the treatment decision, as he/she should always be the center of care. Shared decision making contributes to patient satisfaction. In addition to this suggested treatment approach, other considerable and generally justified surgical indications - independent of the patient's age - are extractions prior to chemo- or radiation therapy, third molar removal in the context of orthodontic or prosthodontic treatments, third molar auto-transplantation to replace a missing element, or third molar extraction in preparation of orthognathic surgery.

Methodological limitations

Research on the topic is generally prone to limitations inherent to the nature of the procedure. It remains difficult to obtain a total picture of the need for third molar removal in the entire population. Most studies are subject to a certain degree of **selection bias**, because samples are selected in the OMFS department or dental practice. Studies in non-patient samples (volunteers, military people, etc.) do exist; however, none of them included Belgian subjects.[26–31] Consequently, it remains hard to get clear view on the current volume of prophylactic third molar treatments in Belgium and the associated socioeconomic costs and resource expenditure.

The main concern regarding the applied methodology is the **validity of surveying data with regard to the proper assessment of postoperative morbidity**. Surveys or self-reports are highly subjective, yet, this strategy allowed us to collect data on more than 6000 subjects in 5 centers. Surveys were the method of choice to perform epidemiological research on this large scale, because of the minimal burden and effort for both patients and clinicians. Fixed control appointments to clinically evaluate the patients' postoperative morbidity at two points in time would mean a very high cost (in both time and money) for the patient, for the OMFS department, and for society; especially when considered relative to the invasiveness of the surgical procedure. Accordingly, such study set-up was considered infeasible in the present extensive sample.

Studies dependent on surveying data rely mainly on good and clear communication between the researcher or medical professional and the patient. To minimize subjectivity, elaborate explanation and instructions were given prior to inclusion of every patient. **Bias in postoperative pain measures** were minimized by use of a visual analogue scale (VAS) scale ranging from 0 'no pain' to 10 'unbearable pain'. Still, gender and ethnicity seem to inevitably introduce some level of bias in pain reporting.[32,33] It is likely that the reporting of postoperative trismus and swelling was subject to certain levels of bias as well. Other factors contributing to postoperative recovery that were hard to control and could have influenced patient outcome were e.g. oral hygiene, smoking, postoperative patient compliance in terms of aftercare and medication use (mouth rinse, NSAIDs, antibiotics, corticosteroids, etc.).

Because the recovery assessment was self-reported, **clinical diagnosis of postoperative complications, such as alveolar osteitis or dry socket, infection, hemorrhage, oroantral communications and fractures fell outside the scope of our research**. These complications have been topic of many earlier studies though. **Alveolar osteitis or dry socket** is the most commonly observed postoperative complication.[34,35] Dry socket occurs when the blood clot inside the tooth socket dissolves prematurely, leaving the underlying bone exposed. Reported incidences vary from 0.5 to 11.9%, ranging up to 30% in some records.[35,36] It is reported that females are more likely to suffer from alveolar osteitis, which might be attributed to the use of oral contraceptives.[37] Other contributing factors to the occurrence of dry socket are smoking habits, oral hygiene, and systemic diseases including diabetes mellitus, blood clotting disorders and bone pathologies.[35] Furthermore, it has been reported that diseased third molar extraction sites are prone to postoperative complications, e.g. a **postoperative infection** can be the result of an unresolved pericoronitis.[38,39] In line with this, Chapter 6 showed longer pain and painkiller intake in case of periocoronal pathology, although it could not be further identified if the persistent pain was the result of a postoperative complication such as dry docket or infection. The effect of symptomatic indications on the occurrence of postoperative complications can ideally be investigated in a sample of patients who reconsult the clinician on one or more postoperative control appointments, so that postoperative complications can be clinically diagnosed.

In line with the observed effect of age on postoperative discomfort (Chapter 4), several studies have shown that the **risk of complications also rises with increasing age of the patient**.[40–42] Older patients have a higher risk of **alveolar bone fractures**[43] (mandible or maxillary tuberosity) and per- and postoperative **hemorrhage**, especially when they are on anticoagulant therapy.[44]

Moreover, pre- and postoperative complications do not exclusively occur in the third molars. Also the **second molar's health** can be compromised as a result of third molar impaction and/or removal. Research has shown that the recovery of the second molar's periodontal health is significantly better in case of early removal of the adjacent third molars.[45,46] The risk of permanent periodontal ligament damage, clinical attachment loss and periodontal bone defects distal to the second molars is higher at greater age.[3] Pre-existing intrabony defects and plaque accumulation serve to these adverse outcomes. Deteriorating periodontal conditions can also extent further anteriorly. Elevated bacterial counts have been reported in first and second molar region in patients with partially erupted third molars.[27,29,47] Partially erupted impacted third molars are prone to pericoronitis. When not properly treated, the inflammation of the mucosa and gingiva in the third molar region, accompanied by bacterial invasion, can progress into periodontitis, a chronic inflammation of the periodontal tissues, which can eventually lead to loss of elements. Furthermore, third molar impaction has been associated with the risk of **intraoperative bone perforations**. In the maxilla, deeply impacted third molars, reaching into the maxillary sinus, can cause **oroantral perforations** following extraction with the risk secondary sinusitis.[48,49] In the mandible, extraction of deeply impacted and/or aberrantly orientated (e.g. transversal) third molars can result in **lingual or vestibular alveolar bone perforations**.[50]

Although the current work was performed on a highly inclusive sample of patients with all kinds of third molar eruption and impaction levels (exclusion criteria were limited to patients with supernumerary teeth and patients undergoing additional coinciding oral interventions), the **uni- and multivariable analyses in Chapters 4 and 5 did not include anatomical features or surgical difficulties as potential risk factors for prolonged recovery**. The radiological study in Chapter 6 did evaluate the effects of anatomical characteristics such as impaction status and third molar orientation on the occurrence of postoperative morbidity; however, the analysis was univariate. In order to achieve a complete and highly accurate prediction model for postoperative morbidity after third molar removal, it is important that the potential confounding effects of anatomical variables are considered in the estimation of the postoperative outcome.

Therefore, it would be interesting to further evaluate the anatomical and pathological third molar characteristics on the available preoperative panoramic radiographs of all of the M3BE patients, and **implement this radiographic information in a multivariable model assessing the probability of postoperative morbidity** (Chapter 4). By consideration of all of these contributing factors, and in consultation with the patient and his/her individual preferences, one can proceed with the most appropriate and adequate treatment strategy. In general, third molars in vertical orientation and with adequate space in front of the anterior border of the ramus might deserve a chance to erupt into functional occlusion, provided that the oral hygiene posteriorly in the mouth can be maintained. On the other hand, partial third molar eruptions and soft tissue impactions with communication to the oral cavity generally ask for intervention. Finally, complete bony impactions without the risk of damaging adjacent structures (e.g. second molar roots) might be better left untouched.[51]

The studies presented in this doctoral thesis were able to identify several risk factors for persistent morbidity after third molar removal; however, it is apparent that many other pre-, peri- and postoperative factors contribute to patient outcome. Other considerable factors that were outside the scope of our research but are highly interesting to implement in future studies are the duration of the surgery, surgical flap designs, intraoperative lingual retraction, aftercare measures, etc.

Conclusions

No discussion exists as to the removal of third molars with signs or symptoms of disease; however, the management of impacted third molars when free of pathology (prophylactic removal) has been debated for many decades. It is evident that an appropriate treatment decision should be based on the clinician's expertise, on the individual needs of the patient, and on the best available research. However, it is also evident that the scientific literature, so far, has not been able to provide clear answers on the questions raised in the ongoing debate. Consequently, we believe that a regular need exists to update prevailing positions in accordance with the most recent findings and latest insights.

Our findings enabled reliable estimation of the eruption chances of developing third molars, and give insight into the recovery of the patient after third molar extraction. All things considered, the clinical and radiological findings in the current work direct the treatment decision towards timely removal of impacted third molars, preferably between the ages 17–25 years, particularly to avoid persistent morbidity and nerve complications.

The results of this doctoral thesis broaden our knowledge about the ongoing but debated practice of prophylactic third molar removal and address the gap in large-scale prospective data on the topic. The results may serve as a welcome directive for dental practitioners, maxillofacial surgeons and orthodontists in the treatment decision process concerning third molar removal, and may ultimately form an evidence base for updated treatment guidelines on the management of third molars.

Future perspectives

To date, no systematic approaches exist to make satisfactory predictions on third molar disease development taking impaction status, the patient's oral hygiene and the overall clinical picture into account. No straightforward approach to obtain satisfactory answers on the questions raised in the ongoing debate about the justification of prophylactic third molar removal exists either. Unfortunately, the nature of the intervention does not allow randomized controlled trials to compare the effects of prophylactic third molar removal vs. retention of the teeth on the patient's quality of life.[52] There is an **evident need for well-designed longitudinal trials that compare the effectiveness of extraction versus retention over a patient lifetime**. Yet, such study set-ups are prone to attrition bias (loss of participants). Long-term follow-up studies are hard to perform because many retained third molars are eventually removed at some point in the patient's life, because of pathologies associated with the retention of these teeth.[53,54] Still, healthcare institutions and policy-makers, as well as the dental practitioners and maxillofacial surgeons, would clearly benefit from transparent numbers on the frequently performed practice.

Furthermore, **several AI applications are lurking around the corner to facilitate the routine dental workflow**. Not only can deep learning networks be of use in third molar eruption prediction; currently, CNNs are already deployed in disease detection and staging, treatment planning, and dental age estimation.[55–57] Moreover, CNNs will possibly be able to accurately classify third molar root-nerve relations on panoramic radiographs by differentiating between buccal, interradicular and lingual position of the IAN relative to the third molar roots based on 2D data. This would mean that in case of mere 2D radiological superimposition of the roots and the IAN on panoramic radiographs - but no actual relation in 3D reality - additional CBCT can be avoided. In compliance with the As Low As Reasonably Achievable (ALARA) principle of radiation protection, CNNs will allow us to extract the maximum of information out of first-line 2D radiographs, before proceeding to 3D imaging modalities.[58] Nevertheless, the ultimate goal is the development and implementation of several AI-driven treatment planning and prediction tools in 3D, as CBCT is the most commonly used imaging modality in the preparation of several oral and maxillofacial procedures. Accurate detection, labeling and segmentation of anatomical structures on CBCT will always be the first and most challenging step in the preoperative planning process.[59] CNNs can complement clinicians in this very time-consuming and tedious task. Replacing this operator-dependent task by a deep learning network will also avert the interobserver variability of manual image manipulations.[60–62]

Further advancements in digital innovations such as automated segmentation of third molars, the mandibular canal and other adjacent structures by CNNs will eventually lead towards fast and highly accurate 3D reconstructions, and visualization of anatomical relations. If combined with augmented reality in the surgery room, where the 3D reconstruction can be projected onto the patient during surgery, these technologies might ultimately be the key to an actual reduction of iatrogenic nerve injuries following third molar removal. Future advancements in augmented reality and image-guided surgery will enable real-time visualization of the surgical manipulations of the tooth and roots that would stretch or damage the IAN. If supplemented with tactile feedback in surgical instruments, direct injuries would become highly unlikely. In the next few years, AI will become more and more implemented in the daily workflow. It will lead to **ever-increasing diagnostic accuracies and will maximize treatment effectiveness.**

From a biomedical scientist point-of-view, it is highly interesting to further investigate the possibilities of the use of **third molar stem cells in regenerative medicine**.[63] Mesenchymal dental stem cells, isolatable from the third molar follicle, have been the topic of extensive research. Owing to their multilineage differentiation potential, dental pulp stem cells are of high interest in tissue engineering.[64] In order for regenerated tissues to be viable, adequate vascularization and innervation is crucial. Dental stem cells have this angiogenic and neurogenic differentiation potential. Currently, dental stem cells are already employed in periodontal tissue regeneration and dental socket healing after extraction.[65] It is plausible that in a few decades, we could routinely harvest the stem cells from extracted third molars and employ them for differentiation into several tissues with the ultimate goal of patient-customized organ breeding, hard tissue regeneration (e.g. for reconstruction of the craniofacial skeleton), and in the treatment of (oral) cancers.[66]

Third molars are vestigial teeth, teeth that have lost most of their ancestral function. While they once were a necessity for our early human ancestors to chew and grind uncooked food and plant foliage, it is likely that over several centuries, they will go completely missing as a result of evolution. It would be interesting to further deepen our knowledge in the **genes responsible for dental agenesis**, and in particular third molar agenesis. Several genes mutations have been identified in hypodontia and oligodontia (e.g. PAX9 and MSX1), and it is plausible that more genes contributing to these phenotypes will be identified in the future.[67,68] Currently, the worldwide rate of third molar agenesis is found to be 22.6% (95% CI 20.6–24.8%), with the percentage of patients presenting with at least one agenetic third molar ranging up to 56.0%.[69] Third molar agenesis is highly dependent on biologic factors and geographic profiles, and is more likely to occur in the maxilla than in the mandible.[69] The entire debate on prophylactic third molar removal would be off-topic when third molars would become completely agenetic. But until then, **it is imperative that clinicians are well acquainted and equipped with proper diagnostic criteria and evidence-based treatment guidelines, and have thorough insight into the risk–benefit ratio of the oral intervention, so that the highest level of care can be ensured for the patient.**

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SUMMARY

Lack of space in the jawbones often leads to difficulties for the last teeth, the third molars or wisdom teeth, to erupt into their natural functional position. Compromised third molar eruption can result in impaction, a state in which the third molars are impeded from eruption by adjacent teeth, dense bone, or an overgrowth of soft tissue. Impaction is frequently associated with pain, discomfort and pathology. Although general agreement exists that third molars should be removed when signs or symptoms of disease are present, consensus is lacking about how to proceed in the absence of clear signs of pathology (prophylactic removal).

As a result, the clinical management of impacted third molars differs across countries, with some treatment guidelines discouraging prophylactic removal of asymptomatic impacted third molars, while other guidelines advocate an interventional approach as soon as it is clear that the third molars will be of low functional value in the mouth. Given the socioeconomic costs involved, it is understandable how the validity of prophylactic third molar removal has been called into question over the last decades. However, in the current atmosphere of disagreement, clinicians largely rely on their own expertise and beliefs in their clinical decision making. As a result, great variation exists regarding the evaluation of the need for third molar removal.

Treatment guidelines should be based on the best available research, but in the striking lack of large-scale prospective and/or longitudinal data on the topic, drafting evidence-based treatment guidelines is easier said than done. For this

reason, the main objectives of this doctoral thesis were to provide clear view on the common practice of surgical third molar removal and the indications and postoperative morbidity associated with this type of oral surgery. In addition, it was aimed to identify patients at risk of impeded third molar eruption, and patients vulnerable for persistent morbidity and nerve complications.

In **Chapter 1**, the overarching debate on prophylactic third molar removal is positioned, and the risks associated with retention of impacted third molars are reviewed. The international differences in the management of third molars are highlighted, and the socioeconomic costs involved with prophylactic removal are described.

Early prediction of the third molars' (future) functional value in the mouth would be the first step in a deliberate treatment decision process. In **Chapter 2,** we investigated the third molars' pre-eruptive rotational changes and eruption chances based on angulation measurements on panoramic radiographs of 1011 adolescent patients. We demonstrated that third molars were not static in development; however, the pre-eruptive rotational changes were not of such extent that they improved the eruption chances of the third molars. A third molar angulation of 27° relative to the second molar was identified, from which functional eruption becomes highly unlikely. In **Chapter 3**, we developed and validated an Artificial Intelligence (AI)-driven tool for automated molar angulation measurements on dental panoramic radiographs with the purpose of wisdom tooth eruption prediction. The angulation measurements of Chapter 2 were automated with 80% to 98% accuracy. The AI network jointly predicted the molars' segmentation maps and orientation lines, and allowed easy and fast prediction of the third molars' eruption potential at adolescent age.

If the third molars will not erupt into a functional position in the dental arches, prophylactic third molar removal might be advocated. In **Chapter 4**, we aimed to investigate the effect of increasing age and symptomatic indications on the patient's recovery after third molar removal. In total, 6010 third molar patients were followed up at four time points during their treatment, and 15357 third molars were extracted. It was shown that there are convincing patient- and surgery-related factors that favor timely third molar removal, preferably before the age of 25.

Increasing age at the time of surgery significantly increased the risk of persistent postoperative morbidity and nerve complications. Symptomatic indications for removal were most common in patients over age 25 years, but pre-existing pathologies did not compromise the postoperative recovery process.

Third molar removal is one of the first oral interventions performed by (supervised) surgical residents in their training in Oral and Maxillofacial Surgery. It is important that postoperative morbidity remains within limits and proportional to the invasiveness of the procedure. In **Chapter 5**, we showed that the effects of surgical inexperience were limited in our sample (2560 patients and 8672 third molars). Postoperative recovery was shown to be more dependent on intraoperative factors like the method of extraction and the number of extractions.

Panoramic radiography remains the most commonly used method for diagnosis and preoperative planning of third molar surgery. Therefore, in **Chapter 6**, we aimed to identify radiological risk indicators for persistent postoperative morbidity in 1009 patients undergoing third molar removal, for both mandibular and maxillary third molars (n=2825). The results showed that deep impactions and difficult extractions were related to persistent postoperative morbidity (pain, trismus and swelling). Moreover, presence of pericoronal pathology and resorption compromised the postoperative recovery process. Based on the studies in Chapters 4, 5 and 6, clinicians may better inform patients at risk for persistent postoperative discomfort after third molar removal.

The most severe complication associated with third molar surgery is iatrogenic nerve injury of the inferior alveolar nerve or lingual nerve. Injury to these mandibular branches of the trigeminal nerve can cause temporary or lifelong paresthesia of the ipsilateral lower lip or tongue, respectively. Although these injuries are relatively uncommon and mostly transient in nature, they severely affect the patient’s quality of life. In **Chapters 7 and 8**, we aimed to identify additional risk factors for nerve complications following third molar removal by exploring the anatomical variations of the mandibular canal in the (retro)molar area. Side-branches of the mandibular canal, containing neurovascular bundles coming from the inferior alveolar nerve, could be of clinical relevance during third molar extraction. The most important mandibular canal variation in third molar area is the retromolar canal. Although anatomical variations of the mandibular canal were more present than expected, the presence of bifurcations or retromolar canals was not associated with a higher risk of inferior alveolar nerve injury following third molar removal.

In **Chapter 9**, the main results are discussed and the methodological flaws are critically debated. In conclusion, the clinical relevance of all of these findings are highlighted and future perspectives are outlined.

SAMENVATTING

De wijsheidstanden of derde molaren zijn de laatste tanden die doorbreken in de mond. Dit gebeurt meestal rond de leeftijd van 17–25 jaar. Vaak is er te weinig ruimte in de mond, waardoor de derde molaren niet goed passen. Bijgevolg blijft de tand ingesloten of ‘geïmpacteerd’. Ingesloten derde molaren kunnen uiteenlopende problemen en ongemakken veroorzaken, waardoor er vaak voor gekozen wordt om deze tanden (preventief) te verwijderen. Het verwijderen van wijsheidstanden is dan ook één van de meest uitgevoerde ingrepen in de Mond-, Kaak- en Aangezichtschirurgie. Hoewel de ingreep over het algemeen erg veilig is, brengt het verwijderen van wijsheidstanden, zoals elke chirurgische interventie, een risico op intra- en postoperatieve complicaties met zich mee.

Momenteel bestaat er geen consensus over het al dan niet preventief ingrijpen bij asymptomatische geïmpacteerde wijsheidstanden. Sommige experten opteren voor preventieve verwijdering om problemen en pathologie in de toekomst te vermijden. Anderen zijn van mening dat de voordelen van een preventieve verwijdering niet opwegen tegen het risico op intra- en postoperatieve complicaties die de ingreep met zich meebrengt. Zo kunnen pijn, zwelling en trismus optreden of kan de nervus alveolaris inferior of de nervus lingualis beschadigd raken, waardoor de patiënt, tijdelijk dan wel permanent, gevoelsstoornissen in de onderlip of tong kan ervaren.

Het onderwerp is veel beschreven in de wetenschappelijke literatuur. Toch is de kwaliteit van de meeste studies ondermaats, de patiëntengroepen te klein of is de follow-up periode te beperkt. Er bestaat tot op heden dus onvoldoende evidentie om te kunnen besluiten dat de voordelen van de preventieve verwijdering van wijsheidstanden opwegen tegen de risico's die ermee gepaard gaan. Er bestaan wel aanwijzingen dat het behoud van wijsheidstanden zelden een ziektevrij verloop kent. Een goede risico-batenanalyse dringt zich dus op. Met dit doctoraatsonderzoek werd nagegaan welke patiënten gevoelig zijn voor impactie of onvolledige doorbraak, hoe patiënten herstellen na het verwijderen van hun wijsheidstanden en wie gevoelig is voor langdurige ongemakken en (zenuw)complicaties zodat in de toekomst de behandeling hier nog beter op kan afgestemd worden.

In **Hoofdstuk 1** wordt het debat rond de preventieve verwijdering van wijsheidstanden geschetst. Door middel van een systematic review van de bestaande literatuur werd onderzocht wat het risico is op het ontstaan van pathologie bij geïmpacteerde wijsheidstanden. De internationale verschillen in behandelrichtlijnen worden beschreven en de socio-economische kosten verbonden aan een (preventieve) chirurgische interventie worden uitgelegd.

Het zou erg nuttig zijn indien we de functionele doorbraak of eruptie van derde molaren op relatief jonge leeftijd zouden kunnen voorspellen, zodat in geval van impactie in deze patiëntengroep sneller kan worden overgegaan tot verwijdering. In **Hoofdstuk 2** gebruikten we hiervoor de panoramische radiografieën van adolescente patiënten tijdens en na hun orthodontiebehandeling. Aan de hand van de hoek die de derde molaren maken t.o.v. de andere molaren in de onderkaak hebben we de eruptiekansen van de wijsheidstanden geëvalueerd. Derde molaren met een hoek van 27° of meer t.o.v. de tweede molaar bleken deze hoek tijdens de ontwikkeling verder te vergroten en daardoor zelden functioneel te kunnen doorbreken in de mond. Om het risico op langdurige ongemakken en zenuwcomplicaties te beperken, is in deze patiëntengroep een tijdige ingreep vaak aangewezen. In **Hoofdstuk 3** presenteerden en valideerden we een eruptiepredictie-tool gebaseerd op artificiële intelligentie. Deze softwaretool segmenteert automatisch de mandibulaire molaren op een panoramische radiografie en bepaalt op basis van de segmentatiemap de oriëntatie van de tanden. De hoekmetingen uit hoofdstuk 2 werden op deze manier geautomatiseerd met 80% tot 98% accuraatheid. Artificiële intelligentie zal meer en meer een plaats krijgen in de dagelijkse praktijk wat zowel de clinicus als de patiënt ten goede zal komen.

In **Hoofdstukken 4 en 5** trachtten we een overzicht te verkrijgen van de huidige praktijk inzake de chirurgische verwijdering van de wijsheidstanden. Met een prospectief epidemiologisch onderzoek in vijf Belgische ziekenhuizen werd onderzocht wat de klinische indicaties zijn voor de verwijdering van wijsheidstanden en welke patiënten gevoelig zijn voor (langdurige) postoperatieve ongemakken en complicaties. De hypothese was dat de verwijdering van symptomatische derde molaren meer morbiditeit en complicaties met zich meebrengt t.o.v. een preventieve ingreep bij asymptomatische derde molaren, en dat het risico op langdurige ongemakken en complicaties toeneemt met de leeftijd van de patiënt. Er werden verschillende parameters geïdentificeerd die kunnen wijzen op de voordelen van tijdige interventie (voor de leeftijd van 25 jaar), voornamelijk om het risico op postoperatieve ongemakken en zenuwcomplicaties te verminderen.

Panoramische radiografieën zijn onmisbaar in de preoperatieve diagnostiek en bij de voorbereiding van de ingreep. De beelden kunnen de chirurg wijzen op verschillende intra- en postoperatieve risico's. In **Hoofdstuk 6** zijn we nagegaan welke radiologische kenmerken kunnen duiden op een moeilijk of langer postoperatief verloop. Zo kunnen chirurgen en tandartsen de patiënt preoperatief nog beter inlichten i.v.m. zijn/haar individueel herstel. Diep geïmpacteerde en moeilijk gepositioneerde wijsheidstanden kunnen aanleiding geven tot langdurige postoperatieve ongemakken. Bovendien werd de preoperatieve aanwezigheid van pericoronaire pathologie en resorptie in verband gebracht met een langer postoperatief herstel.

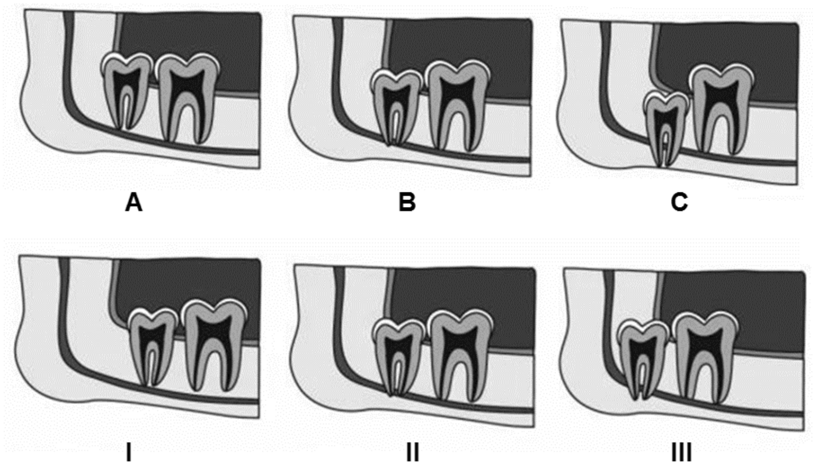
In **Hoofdstukken 7 en 8** gingen we op zoek naar risicofactoren voor letsels van de nervus alveolaris inferior, een ernstige complicatie die kan optreden bij de verwijdering van wijsheidstanden. Deze complicatie kan gevoelsstoornissen in de onderlip en kin veroorzaken, wat een enorme impact heeft op de levenskwaliteit van de patiënt. Een nauwe anatomische relatie van de wortels van de wijsheidstanden met de nervus alveolaris inferior behoort tot één van de grootste risicofactoren voor deze complicatie. Daarnaast kunnen anatomische variaties van de zenuw een bijkomend risico vormen bij chirurgie in de derde molaarregio. De meest voorkomende variaties zijn bifurcaties van het mandibulaire kanaal, dat de nervus alveolaris inferior omvat. Omdat deze anatomische variaties in het chirurgisch veld kunnen liggen bij het verwijderen van wijsheidstanden is het belangrijk om de risico's goed in te schatten. Op basis van de gegevens in Hoofdstuk 8 werd er geen relatie gevonden tussen het voorkomen van deze zenuwvariaties en een verhoogd risico op postoperatieve gevoelsstoornissen in de onderlip en kin.

Tot slot worden in **Hoofdstuk 9** de resultaten van alle studies kritisch bediscussieerd, de methodologische limitaties worden besproken en de klinische relevantie van de resultaten wordt benadrukt. De resultaten worden in een breder toekomstperspectief geplaatst zodat ze een basis kunnen vormen voor evidence-based behandelrichtlijnen en verder onderzoek.

APPENDICES

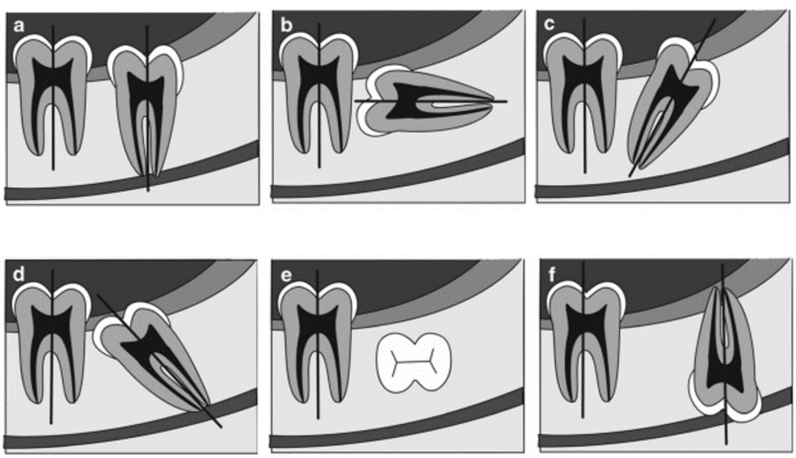
Appendix A: Third molar classifications

Figures (with permission) from Miclotte A, Grommen B, De Llano Perula MC, Verdonck A, Jacobs R. The effect of first and second premolar extractions on third molars: a retrospective longitudinal study. *J Dent.* 2017;61:55–66. And by Marijke Beckers (Boundless Graphix).



Pell & Gregory classification for third molar eruption:

A, B, C: vertical eruption levels; I, II, III: horizontal eruption classes.

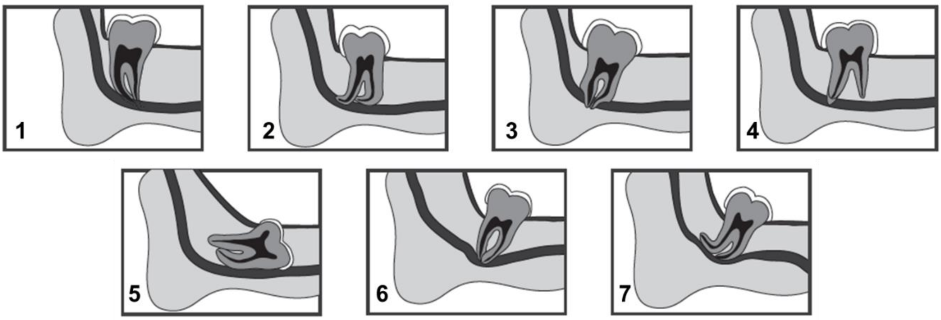


Winter's classification for third molar orientation:

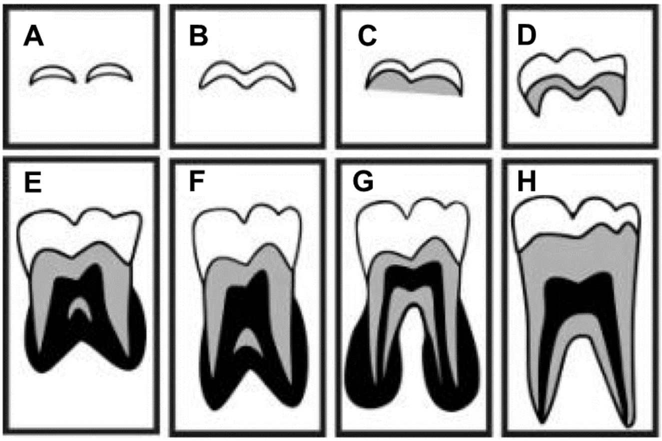
(a) vertical; (b) horizontal; (c) distoangular; (d) mesioangular; (e) transversal or buccolingual; and (f) inverse.

Whaites' classification for root-nerve relation:

(1) superimposition of roots and canal; (2) loss of cortical border of the mandibular canal; (3) narrowing of the canal; (4) deviation of the canal; and (5) radiolucent band across the roots.



Rood & Shehab classification for root-nerve relation:
(1) root darkening; (2) root deflection; (3) root narrowing; (4) bifid root apex/apices; (5) canal interruption; (6) canal diversion; and (7) canal narrowing.



Demirjian's classification for molar development:

A–D no roots; E starting bifurcation; F–G roots equal of greater than crown height; and H fully developed, apices closed.

Appendix B: M3BE surveys

Consultation

Name: ……………………………………………………………

Patient number: ………………………………………………

Date of birth (dd/mm/yyyy): …………………………………

Gender: ❑ male ❑ female

Patient sticker

Type of referral?
- ❑ I am not referred.
- ❑ I am referred by a dentist.
- ❑ I am referred by an orthodontist.
- ❑ Other: …………………………………………

What is the reason of your visit?
- ❑ I have (had) symptoms.
- ❑ I don't have any symptoms, but there was found an abnormality.
- ❑ I don't have any symptoms, but I am referred in the context of another treatment.

Do you have any symptoms at this moment?

Multiple options are possible
- ❑ I don't have any symptoms.
- ❑ Pain
- ❑ Swelling of the cheek(s)
- ❑ Fever (> 38°C)
- ❑ It is difficult to open my mouth.
- ❑ I experience altered sensation of the lip or tongue.

Do (did) you have orthodontic treatment (in the past)? ❑ Yes ❑ No

Length (m): ………………………………..

Weight (kg): ………………………………

Do you smoke? ❑ Yes, ………………… cigarettes per day
❑ No

Birth country of father: …………………………………

Birth country of mother: ……………………….............

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Do you suffer from other medical conditions? Multiple options are possible	❑ None ❑ Lung disease ❑ Allergy: ……………………… ❑ Heart or vascular disease (including hypertension) ❑ Diabetes Mellitus ❑ Connective tissue disease ❑ Immune system diseases (e.g. Rheumatoid Arthritis, Sjogren, Systemic Lupus Erythematosus) ❑ Other: ………………………
Are you on medication at this moment?	❑ No ❑ Oral contraceptives ❑ Blood thinners ❑ Corticosteroids ❑ Bisphosphonates (e.g. in context of bone cancer) ❑ Antibiotics at this moment ❑ I don’t use any of the abovementioned drugs.

Surgical report

Patient sticker

Part 1 Preoperative

Initials surgeon: ....

Initials supervisor: ....

	Indication for extraction, based on ICD-10	**18**	**28**	**38**	**48**
Impaction	Orientation	❑	❑	❑	❑
	Lack of space	❑	❑	❑	❑
Caries & Acute discomfort	Caries	❑	❑	❑	❑
	Pericoronitis	❑	❑	❑	❑
	Periapical pathology e.g. **abscess**	❑	❑	❑	❑
	Periodontitis	❑	❑	❑	❑
	Resorption of M3 or neighbouring element(s)	❑	❑	❑	❑
	Cysts/tumors	❑	❑	❑	❑
	Tooth fracture	❑	❑	❑	❑
Other treatment	Orthodontics, orthognathic surgery	❑	❑	❑	❑
	Medical indication e.g. bisphosphonates, chemotherapy, radiotherapy, osteomyelitis	❑	❑	❑	❑
Prophylaxis	Infectious prophylaxis, hard to maintain hygiene	❑	❑	❑	❑
Afunctional	Malocclusion, no antagonist	❑	❑	❑	❑

Type anaesthesia ❑ Local anesthesia ❑ Procedural sedation ❑ General anesthesia

Diagnostics ❑ Panoramic radiograph < 6 months old ❑ CB-CT < 6 months old
❑ Panoramic radiograph > 6 months old ❑ CB-CT > 6 months old

Is there an **increased risk of nerve damage**: ❑ no ❑ 38 ❑ 48 ❑ n.a.

Is there **inflammation** present at the time of the surgery? ❑ Yes ❑ No

Part 2 Postoperative

Duration ❑ Shorter than average
❑ Average
❑ Longer than average → Which element was the cause? ❑18 ❑28 ❑ 38 ❑ 48

Was the inferior alveolar nerve **visualized** during surgery? ❑ Yes ❑ No ❑ n.a.

Use of lingual nerve **protection**? ❑ Yes ❑ No ❑ n.a.

M3	**Non-surgical** *luxation and elevation*	**Surgical: no osteotomy** *soft tissue impaction*	**Surgical: with osteotomy** *bony impaction*	**Sectioning crown/roots**	**Coronectomy**
18	❑	❑	❑	❑	❑
28	❑	❑	❑	❑	❑
38	❑	❑	❑	❑	❑
48	❑	❑	❑	❑	❑

Deviation from surgical protocol? ❑ No ❑ Yes, because.............................

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Survey **3 days** after surgery

Name: ……………………………………………………………

Patient number: ……………………………………………….

Date of birth (dd/mm/yyyy): …………………………………

Gender: ❑ male ❑ female

Side of tooth extraction? ❑ left ❑ right ❑ both sides

*These questions concern your health status **today**.*

Are you in pain because of the surgery? Please circle the representative number on the pain scale:

0	1	2	3	4	5	6	7	8	9	10
No pain		A little		Moderate pain		Severe pain		A lot of		Unbearable

If yes, where is it located?

- ❑ Top left
- ❑ Bottom left
- ❑ Left, unclear top or bottom
- ❑ Left in front of ear
- ❑ Top right
- ❑ Bottom right
- ❑ Right, unclear top or bottom
- ❑ Right in front of ear

1 Not at all
2 A little
3 Quite a bit
4 Very much

Did you sleep poorly last night?	❑ 1	❑ 2	❑ 3	❑ 4
Do you have trouble eating?	❑ 1	❑ 2	❑ 3	❑ 4
Do you have trouble opening your mouth?	❑ 1	❑ 2	❑ 3	❑ 4
Are your cheeks swollen?	❑ 1	❑ 2	❑ 3	❑ 4

Do you experience altered sensation in your **lip**? ❑ **yes** ❑ **no**

- If yes, which side? ❑ left ❑ right ❑ unclear
- If yes, what type of altered feeling? ❑ numb feeling ❑ stabbing pain ❑ tingling ❑ pain at touch/eating ❑ other type of pain: ……….......................................
- Is this altered feeling: ❑ constant ❑ in episodes

Do you experience altered sensation in your **tongue**? ❑ **yes** ❑ **no**

- If yes, which side? ❑ left ❑ right ❑ unclear
- If yes, what type of altered feeling? ❑ numb feeling ❑ taste ❑ tingling ❑ other type of pain: ……….......................................
- Is this altered feeling: ❑ constant ❑ in episodes

Do you still need painkillers? ❑ yes ❑ no

Are you active in the house? ❑ yes ❑ no

Have you resumed your work/study activities? ❑ yes ❑ no ❑ different circumstances: ………………………………..…………

Survey 10 days after surgery

Name: ……………………………………………………………

Patient number: …………………………………………………

Date of birth (dd/mm/yyyy): …………………………………

Gender: ❑ male ❑ female

Side of tooth extraction? ❑ left ❑ right ❑ both sides

*These questions concern your health status **today**.*

Are you in pain because of the surgery? Please circle the representative number on the pain scale:

0	1	2	3	4	5	6	7	8	9	10
No pain		A little		Moderate pain		Severe pain		A lot of		Unbearable

If yes, where is it located?
- ❑ Top left
- ❑ Bottom left
- ❑ Left, unclear top or bottom
- ❑ Left in front of ear
- ❑ Top right
- ❑ Bottom right
- ❑ Right, unclear top or bottom
- ❑ Right in front of ear

If yes, how did the pain evolve over time?
- ❑ I still have pain, but it has decreased over the past 10 days.
- ❑ I still have pain, and the pain increased in the last couple of days.

1 Not at all
2 A little
3 Quite a bit
4 Very much

Did you sleep poorly last night?	❑ 1	❑ 2	❑ 3	❑ 4
Do you have trouble eating?	❑ 1	❑ 2	❑ 3	❑ 4
Do you have trouble opening your mouth?	❑ 1	❑ 2	❑ 3	❑ 4
Are your cheeks swollen?	❑ 1	❑ 2	❑ 3	❑ 4

Do you experience altered sensation in your **lip**? ❑ **yes** ❑ **no**
- If yes, which side? ❑ left ❑ right ❑ unclear
- If yes, what type of altered feeling? ❑ numb feeling ❑ stabbing pain ❑ tingling ❑ pain at touch/eating ❑ other type of pain: ………...
- Is this altered feeling: ❑ constant ❑ in episodes

Do you experience altered sensation in your **tongue**? ❑ **yes** ❑ **no**
- If yes, which side? ❑ left ❑ right ❑ unclear
- If yes, what type of altered feeling? ❑ numb feeling ❑ taste ❑ tingling ❑ other type of pain: ………...
- Is this altered feeling: ❑ constant ❑ in episodes

Please proceed to the next page

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- After how many days did you resume your daily activities in the house?
  ………………………. (Day of surgery is day 0)

- How many days after surgery did you resume your work activities?
  ………………………. (Day of surgery is day 0)
  If not possible due to other circumstances (e.g. holidays, (chronic) illness, retirement, unemployment), please let us know: ……………………………………………………………

- On which day did you take the last painkillers?
  ………………………. (Day of surgery is day 0)

- Did you revisit a physician due to symptoms? ❑ Yes ❑ No
  If yes, on which day ……………………………………… (Day of surgery is day 0)

  If yes, what was the reason for the visit?
  ❑ Pain
  ❑ Bleeding
  ❑ Swelling
  ❑ Fever
  ❑ Altered sensation in lip or tongue
  ❑ Other: ……………………………….

Were you prescribed **antibiotics**? ❑ Yes ❑ No

- By whom? ❑ Treating surgeon/hospital
  ❑ General Practitioner
  ❑ Dentist
  ❑ Other: ………………………

- What was the name of the drug: ……………………………………

- On which day did you start taking it?
  …………………………………………… (Day of surgery is day 0)

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PERSONAL CONTRIBUTION

The author, Myrthel Vranckx, conceived the projects, collected and managed the clinical and radiological data, analyzed the data and wrote the (peer-reviewed) research publications by scientific support of her promotors Prof. dr. Reinhilde Jacobs and Prof. dr. Constantinus Politis, and all of her co-authors. Accordingly, Myrthel Vranckx is first author of all of the thesis chapters and corresponding research papers, except for Chapter 7, of which she is deserving second author. The project in Chapter 7 was conceived before her start at the OMFS-IMPATH research group, but was soon transferred and adapted to her PhD topic. Consequently, she was involved from the moment of data collection, and not from conception.

CONFLICTS OF INTEREST

The author, Myrthel Vranckx, has no conflicts of interest to declare with respect to publication of this work.

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CURRICULUM VITAE

The author, Myrthel Vranckx, graduated in 2016 as MSc in Biomedical Sciences with a Master's thesis on the use of CT imaging in Forensic Medicine (Faculty of Medicine, KU Leuven). She was a PhD researcher in the OMFS-IMPATH research group from October 2016 to December 2020 with Prof. dr. Reinhilde Jacobs and Prof. dr. Constantinus Politis as her scientific promoters (Department Imaging and Pathology, Faculty of Medicine, KU Leuven). Her PhD research was focused on third molar pathology and postoperative morbidity associated with third molar surgery. She coordinated a multicenter research project at the Department of Oral and Maxillofacial Surgery in five Belgian hospitals. She was involved in multiple radiological studies with regard to third molar pathology and anatomical variations of the mandibular canal. She combined her PhD training with Postgraduate Studies in Advanced Medical Imaging (Faculty of Medicine, KU Leuven), from which she graduated in June 2020. Within both of these trainings, she explored the possibilities of the use of artificial intelligence in dentomaxillofacial radiology and oral surgery.

List of Publications

<u>Publications part of the PhD thesis:</u>

Vranckx M, Fieuws S, M3BE research group, Jacobs R, Politis C. Prophylactic vs. symptomatic third molar removal: effects on patient postoperative morbidity. *Under review*

Vranckx M, Fieuws S, Jacobs R, Politis C. Surgeon's inexperience has limited effect on postoperative morbidity following third molar removal. *Under review*

Vranckx M, Lauwens L, Moreno Rabie C, Politis C, Jacobs R. Radiological risk indicators for persistent postoperative morbidity after third molar removal. *Under review*

Vranckx M, Geerinckx H, Gaêta-Araujo H, Leite AF, Politis C, Jacobs R. Do anatomical variations of the mandibular canal pose an increased risk of inferior alveolar nerve injury after third molar removal? *Under review*

Vandeplas C, **Vranckx M**, Hekner D, Politis C, Jacobs R. Does retaining third molars result in the development of pathology over time? A systematic review. *J Oral Maxillofac Surgery.* 2020;S0278-2391:30588–7. (shared first-authorship)

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Collaborator of Dimitra Research Group:

Belmans N, Gilles L, Vermeesen R, Virag P, Hedesiu M, Salmon B, Baatout S, Lucas S, Lambrichts I, Jacobs R, Moreels M, **DIMITRA Research Group**. Quantification of DNA Double Strand Breaks and Oxidation Response in Children and Adults Undergoing Dental CBCT Scan. *Sci Rep.* 2020;10:2113.

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Contributions to (inter)national conferences

16/11/2019 – Najaarsvergadering KBVSMFH, Zaventem (Belgium)
M3-Observatorium: 4 years down the line

22/08/2019 – IADMFR Conference, Philadelphia (USA)
Radiological prediction of postsurgical recovery after wisdom tooth removal – Awarded with 3rd prize Research Award

17/05/2019 – VVT-MKA Congres, Antwerpen (Belgium)
Wisdom teeth: to extract or not to extract

14/06/2018 – EADMFR Conference, Lucerne (Switzerland)
Eruption prediction and angulation changes of developing wisdom teeth

18/03/2017 – Voorjaarsvergadering KBVSMFH, Zaventem (Belgium)
M3-Observatorium preliminary results

03/02/2017 – VVMKA Congres, Lommel (Belgium)
M3-Observatorium preliminary results

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The author,
Myrthel Vranckx,
graduated in 2016 as MSc in Biomedical Sciences (Faculty of Medicine, KU Leuven). From 2016 to 2020, she was a PhD researcher in the OMFS-IMPATH research group with Prof. dr. Reinhilde Jacobs and Prof. dr. Constantinus Politis as her scientific promoters (Department Imaging and Pathology, Faculty of Medicine, KU Leuven, and Department of Oral and Maxillofacial Surgery, UZ Leuven). She combined her PhD training with Postgraduate Studies in Advanced Medical Imaging (Faculty of Medicine, KU Leuven), from which she graduated in 2020. Her research was mainly focused on third molar eruption prediction, pathology and surgery, with specific interest regarding the full exploitation of panoramic radiographic information.

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Lack of space in the jawbones often leads to difficulties for the last teeth, the third molars or wisdom teeth, to erupt into their natural functional position. Compromised third molar eruption can result in impaction, a state in which the third molars are impeded from eruption by adjacent structures and tissues. Impaction is frequently associated with pain, discomfort and pathology. Although general agreement exists that third molars should be removed when signs or symptoms of disease are present, consensus is lacking about how to proceed in the absence of clear signs of pathology (prophylactic removal). Due to this atmosphere of disagreement, clinicians largely rely on their own expertise in their clinical decision making. As a result, great variation exists in the management of (impacted) third molars across countries and among specialists. The main objectives of this doctoral thesis were to provide clear insight into the current practice of surgical third molar removal, to identify patients at risk of persistent postoperative morbidity and nerve complications, and to predict the third molars' eruption chances during development. Our findings revealed several patient- and surgery-related factors that favor timely third molar removal, preferably before the age of 25, in order to avoid persistent (postoperative) sequelae and nerve complications later in life. The present thesis may serve as a directive for clinicians and may ultimately form an evidence base for updated treatment guidelines.